# Table of Contents

- Introduction .................................................. 3
- The Environment ............................................. 4
- Ethical Considerations ..................................... 6
- Where to from here? .........................................
  - The importance of Patient Involvement ............. 8
  - What can we learn from the UK? ................. 9
- Transparency .................................................. 10
- National Rare Disease Plan .............................. 11
- Ring-fenced funding & managed entry .......... 11
  - Patient Registries ...................................... 12
  - Clinical Trials .......................................... 13
- Costs .............................................................
  - Cost of medicines ...................................... 14
  - Cost of services ........................................ 14
  - Cost efficiencies ....................................... 15
- Conclusions .................................................... 15
- Appendix 1: Speaker Biographies ....................... 16
- Appendix 2: Contributors ................................. 18
Introduction

This Outcomes Report arises from the IPPOSI Round Table Meeting, ‘Orphan Drugs: Access in Ireland’, which was held on 26th February 2015 in Dublin.

At this meeting, the listed speakers and contributors each took a turn to express their views, concerns and hopes for access to orphan drugs in Ireland, and when they were finished — and following some facilitated discussion between these contributors — the discussion was widened to include the membership of IPPOSI in attendance that day.

In all, and including IPPOSI staff and nominated contributors, more than 100 people attended an interesting and lively meeting that incorporated views from right across the health sector — from decision-makers and payers, to clinicians, patients, academia and industry.

These views were recorded for the purpose of writing this report, however readers should note that the attributed comments that follow may not have occurred in the order that they appear here. For the sake of coherence, this report begins with a description of the orphan drug environment in Ireland and Europe, before briefly examining the ethical situation that informs this environment.

Thereafter the report is broken into the sections outlined in the table of contents.

IPPOSI would like to thank everyone who took part in this meeting for their time and contribution.

Eibhlin Mulroe

CEO IPPOSI
The Environment

There is a stark difference between the ideal of care for people with rare diseases in Ireland and the reality of the services and treatments that exist. Even then, accessing the services or treatments that do exist is a significant challenge, even where approved medicines are concerned, as we shall see. This document is a description of the various ideas, challenges and models of care that occur in Ireland, the UK and Europe. But we must begin with the patient perspective. Anne Marie O’Dowd of Cystinosis Ireland outlined some of the challenges:

“I represent one of those small organisations with almost no resources, so sometimes we have a little voice… it was suggested that society is based on need, well it’s not in Ireland, it’s who shouts loudest and it’s wrong that people feel they have to compete with each other for treatments or services. We have to look at the bigger picture – firstly, how society prioritises what it funds. Will social needs be given equal rating to economic needs? Secondly, that in relation to funding for things like Orphan Drugs, I think we need to remember that patients have put a lot into R&D in rare diseases – they have given their bodies over to it, and in the condition that I represent many of the patients have been on drug trials. When you talk about stakeholders, they are the real stakeholders, so it’s looking at the big picture”.

That ‘big picture’ is of particular concern to patients, as we shall see in the pages to come – questions of funding, of society’s priorities, a refusal to accept that there are limited resources for this corner of healthcare when resources are found — or are extracted — for other controversial government policies.

Nevertheless, while still far from satisfactory, the situation for people with rare diseases has improved in Ireland, and in Europe over the last fifteen years, and Fred Doherty of Genzyme explained why when he outlined the European framework for orphan drugs:

“We know that in 2000 the EC enacted the European Orphan Medicines Product Regulation. … prior to that incentive there were only eight products approved in Europe for orphan diseases, and post that EU Regulation, 70 new treatments have been made available, so legislation has been very successful at encouraging R&D and access to treatments.”

“The EC also made the point that, ‘patients suffering from rare conditions should be entitled to the same quality of treatment as other patients – it’s therefore necessary to stimulate the R&D and bringing to market of appropriate medicines by the pharma industry’, and they called on member states to support R&D and availability to orphan drugs.”

But while this drove some progress, Mr Doherty also noted that:

“There was a European analysis published in Orphanet in 2013 that analysed the cost of orphan drugs right across Europe, and significantly it differentiated orphan drugs by therapeutic class. Not surprisingly 70% of those medicines are in the oncology space, and the cost of those oncology drugs are not any more expensive than non-orphan oncology drugs. So the challenge in reimbursement decisions really occur in the 30% of non-oncology Orphan drugs that target chronic degenerative and very often ultra-rare conditions.”

Responding to the argument that orphan drugs might have a high budget impact, Mr Doherty suggested that:

“The cost of orphan drugs across the EU is estimated to peak in 2016 at 4.6% of total pharmaceutical expenditure. The actual impact of orphan drugs in the five major EU markets 2004-09 was 1.7% of pharma expenditure. So I think fears of unsustainable cost escalation to orphan drugs or ultra-orphan drugs is probably not justified. Particularly now as we start to see the early orphans coming off patent. And the introduction of generic alternatives which will further reduce the cost burden. But despite that, people continue to experience challenges with access and a GRDO survey done here in 2012 64% identified challenges accessing treatment.”

Referring to the environment in Ireland, Dr Roisin Adams of the National Centre for Pharmacoconomics (NCPE) pointed out that:

“From the point of view of the orphan drugs that we (NCPE) have assessed — all orphan drugs, not UOD — so in 2012 it was 1, in 2013 it was 5, in 2014 it was 9, so it is increasing. Almost all of those (9) have been reimbursed – even though none of them proved cost effective within the threshold that we were given, which isn’t a special threshold for orphan drugs, it’s the same one that applies across every drug. This confirms that aspects other than cost effectiveness are being considered by decision-makers.”

However, even with a positive recommendation from the NCPE, and a positive decision from the HSE Drugs Committee, we know that access remains a major issue for patients seeking orphan drugs due to local budget decision making in different hospitals. This issue is addressed in...
more detail in the next section of this report.

Turning now to the wider European and global orphan drug settings, Nigel Nichols of BioMarin had the following points to make:

“The bigger picture I wanted to look at is the fact that people talk about the cost of orphan drugs, and I think Fred painted a really good picture to the fact that even though we’ve had this orphan drugs (EU) regulation from 2000, there are only 70 (treatments) and I think it is a hallmark of progress, but to me its woeful that we still have 7,000-8,000 orphan diseases and only this limited number of treatments - and you could then ask the question, ‘how come there aren’t many more companies involved in it?’ Because in any other marketplace you look at – cars, computers – any industry, if this marketplace is so profitable there would be more entrants.”

“There have been many articles in BMJ about orphan drugs being a licence to print money, if that was the case, I would proffer to people that there should be many more companies and I would actually advocate that that would be a good thing because when there is competition it does drive down prices, but it is really difficult to do research, because of the small patient numbers, lack of registries and knowing how many patients there are and because some patients don’t want to take part”.

In summary and as the EC Directive states, there is an imperative to treat people with rare diseases as we would any other patients, and thus R&D for orphan drugs has been incentivised. Industry argues that the cost burden is much less than that feared by payers, but while many more treatments have been developed, these are not as commercially attractive to industry as has been suggested by the medical community – as evidenced by the lack of companies developing orphan drugs.

Against this, the NCPE in Ireland has assessed and recommended a growing number of orphan drugs for use in Ireland, in spite of these treatments not conforming to the incremental cost effectiveness ratio (ICER) of €45,000 – and that these recommendations have even been supported by the ultimate decision maker, the HSE Drugs Committee. The problem for patients is that these decisions are not supported at a local level – and patients cannot access orphan drugs, even where they have been approved.

Before turning to these and other discussion points raised during the meeting there is a brief examination of the ethical situation underpinning the environment described above.
In the course of his contribution on ethics, Dr David Smith described four elements that should be present in ‘The Accountability of Reasonableness’ (Daniels & Sabin, when a decision is made about priority setting of a drug). Bearing in mind that ‘The Accountability of Reasonableness’ assumes the existence of a rights-based approach to health decisions (as per Rawls’s Rule of Rescue), the rationale for the decisions should be:

1. Publicly accessible: why was this decision made?
2. The decision about meeting healthcare needs must be contextually relevant to fair-minded people (they don’t define who the fair-minded people are);
3. Allowances should be made for appeals so that previous decisions can be reconsidered in the light of new evidence or arguments.
4. And that there must be a process of enforcement to facilitate the implementation.

Three of these four elements arose in discussion several times during in course of the meeting, and are paraphrased here as 1) Transparency; 3) Appeals; and 4) enforcement. With respect to Transparency, the issue arose so frequently that it merits its own section in this report, which you can find on page 10. Regarding point three and appeals, the question does not arise in the Irish context because there are no formal appeals. In relation to element number four, enforcement, Mr Fred Doherty of Genzyme made this contribution.

“One of the challenges in Ireland I think is that we do not have a dedicated process for Orphan Drug assessment, and one of the difficulties is that even where we get a positive recommendation, either from the NCPE, but particularly from the HSE, where those products are administered in hospitals there is no allocated budget to administer them, so while we receive a positive reimbursement, patients who try to access treatments in individual hospitals experience long delays and significant discrimination across the country as they try to access them out of existing hospital budgets that haven’t been given any consideration for the impact of that decision on them locally.”

We can immediately see there is a tension between the theoretical rights-based approach and the reality of a system that tries to do the most good for the greatest number of people, i.e. takes the utilitarian approach. If we acknowledge that the utilitarian approach is the principle that guides most, though perhaps not all, health budget decisions, then there is no question of Rawls’s ‘Rule of Rescue’ applying, however desirable that might be – except in relation to one of its three attributes: opportunity costs. (The other two, non-applicable attributes being Endangered Lives, and Identifiable Individuals).

Without a robust ethical philosophy in place therefore, the question becomes one of allocating resources, and this, as Dr Smith pointed out, is a political matter. This gives rise to clientelism, as the high number of public representatives and their relative accessibility to the citizens of Ireland makes political interference a potentially effective tool for patients and carers desperate to access orphan drugs and the associated services. In the absence of any transparency, or credible alternative, two patient representatives identified this political option as one that patients can and must keep in their arsenal until alternatives exist. Furthermore, they fundamentally rejected the terms of any discussion that presupposes a limited or fixed health budget.

Mr Damien Peelo, CEO of COPD Ireland and EUPATI Patient Expert Trainee said:

“If we buy into that (process) I think we’re buying into something that I think is a mistake. We know that politically money can be found when it needs to be found and there’s a decision politically about where the resources go and about how the money is distributed, so you have corporations that don’t pay taxes but yet you’re making these very difficult decisions about people that need access to drugs. So I think that’s something that should be considered, because when we buy into it I think we’re agreeing with the system.

“In my experience, often what people think is that the role of the patient group is to become involved in the process like HTA and understand how complex the system is, and then therefore they’ll just be part of that ongoing struggle trying to get a little slight change here and a slight change there, because we have a finite budget and in the end of the day it’s going to be tough – but I don’t think that’s the role of the patient organisation. I think the patient organisation comes in there to redefine the way that we make those decisions and redefine how those budget allocations are made, and I do think we have to come from a rights based approach to our healthcare.... the patient isn’t just there to be educated on the complexities of the process, so that we understand the decisions being made. If you really serious, weight that patients voice in a higher way than the economic arguments, so when you’re coming into the HTA process, the patient voice (a collective not individual voice) has greater credence than maybe some of the other things in there.”
In this context, Damien expressed a reluctance to shy away from the proven tactics, until the patient voice is really embedded and changing the current system, — working with politicians; using the media – if they get patients access to the treatment they need as it can be so frustrating and high risk for the patient to wait for systematic change.

Mr Nigel Nichols of BioMarin said that:

“When we look at ethical issues, because I really like the professor’s points about the positive discrimination (Rule of Rescue) that needs to occur. It’s around lifestyle diseases and the societal choices that we make. The question should we be positively discriminating for orphan diseases where 80% or more are caused by genetic conditions — patients have been born into that condition as opposed to lifestyle conditions and where there are currently few treatments available?”

But as we read in Dr Adams’ comment on page 4, the NCPE and the HSE Drugs Committee have approved nine treatments for rare diseases in spite of their not being cost effective. Thus Ireland has a system that tacitly applies a utilitarian approach, while on an ad hoc basis managing requests for treatment that might be driven by patients, politicians and that will not be cost-effective, but which may nevertheless be approved for reimbursement — only for local payers to choose in many cases not to make these treatments available to patients.

In the face of this rather informal situation, patients are reluctant to let go of any levers be they in media or politics, that can potentially drive access to treatments. These then are the contradictions that exist in Ireland with respect to accessing orphan drugs, and the associated services, and this is relevant as we look to the UK and their system for assessing and deciding upon medicines.
The importance of Patient involvement

Patient involvement is the cornerstone of IPPOSI’s work and its importance with respect to accessing orphan drugs was highlighted by Ms Katie Murphy, R&D Officer with CF Ireland. Ms Murphy has CF herself, and has benefitted from an orphan treatment for her condition, as she explains:

“This issue is close to my heart as person who has benefitted quite substantially from a high tech innovative therapy which was incredibly expensive. And we had issues in trying to get it approved initially – IVACAFTOR is the (generic) name of the drug – and I don’t want to get into too much detail about this one specific example, but I think it’s important to look at how we as an organisation, and patient representatives, did engage in the conversation around the approval of the treatment.

“It was a good example of how patients should be at the fore of these discussions. I think the main thing that patients can bring to these types of discussions is emphasising the importance of looking past the current assessments of HTA, and try and have a more holistic view how these new and innovative therapies can really change a person’s life – looking at quality of life rather than just the clinical benefits.

“For example with IVACAFTOR we saw huge improvement in lung function, which is a marker in disease progression in CF. But when you actually speak to people who are on the drug, and I can vouch for that myself, people aren’t talking about the improvement in their lung function, they’re talking about how they have gone back to employment and education, and they’re able to live independently from their parents, and these are the kinds of things that aren’t captured in the current assessments but really are incredibly valuable to patients themselves, and I think that goes right across many disease groups not just cystic fibrosis.

“And when we’re looking at orphan drugs, it’s a very positive development that we’re having these discussions because it means there are finally some treatments out there for patients who have maybe never had access to drugs that target the underlying cause of their illness. So again it leads to another limitation with the current assessments in that there may be no comparators for these assessments to be carried out effectively.

“But if you speak to patients you can compare it to their current standard of living versus their post-standard of living. And I think there is a lot of ways we can capture that data and use it effectively because in rare diseases there may not be a huge amount of people on the trial so therefore we can gather extra data from them and use this in the assessments.

“So we know that there are a lot more drugs coming in the pipeline and that this is something that we’ll come up against time and time again; it’s to try and get these through as smoothly as possible. You have to consider the anxiety of patients with CF waiting for these wonderful drugs that are in the pipeline. Equally we don’t want patients to be used like pawns in the media or anything like that.

“But we want patients to very much understand why we need to do these assessments we need to get good prices for these drugs, because we are citizens of this country as well as patients, but we also need to ensure people don’t become so anxious about getting these life-saving drugs – and that they feel there’s an understanding of why it’s so important that they are approved.

“And I think central to this are patient views, I definitely think patients should be at the centre of conversations about accessing these new therapies, and I think this is a really good start. Like Eibhlin (Mulroe), I think it’s a really good start in assessing wider societal perspectives, and the benefits of those drugs when we do assessments. So in closing, just to emphasise the importance of patient involvement, we need to establish the burden of disease, quality of life, and the current assessments really aren’t strong enough in Ireland.”

The next speaker, Dr Roisin Adams (NCPE), described the NCPE experience of approving the drug to which Ms Murphy had referred. Dr Adams said:

“From an NCPE perspective, we believe that IVACAFTOR was handled well because we knew it was coming, and that was because patients knew it was coming long before we did – they had all the information and they were able to come to us and give us that information. And we engaged with the patient group, people like Ms Murphy, and we met with them and discussed the issues that would arise, that we were going to have difficulty, that it is a really expensive technology. We could tell them that this was possibly not going to be cost effective, however that is not the final decision, and in turn they were able to feedback to the patients in their group and keep...
people informed.

“It was the same with clinicians – we spoke to them so that they could feedback to their patients that the final decision is not made on the NCPE non-recommendation and that this will be looked at by decision-makers. That afforded the HSE time to agree a fair price with manufacturers, and that was useful to do without the glare of media lights and other factors that are interfering with that process. So it worked very well.

“There are lots of examples where it didn’t work well, and I think we’re learning all the time. I think that parts of the process are working well, I think the NCPE are adapting their processes to engage more with patients and bring that engagement to the decision-making table.”

Referring to the fact that not all people with rare diseases have a patient organisation like CF Ireland – or indeed one at all – to represent them, Dr Adams said:

“The groups with more funding are the people who are heard – that’s a problem, currently we’re trying to do that a little bit more through IPPOSI by highlighting the drugs that we’re going to be reviewing (on www.ipposi.ie) in order to raise awareness so that patients have a platform to bring relevant information forward.”

Nevertheless Dr Adams made the following commitment:

“We will try and meet anyone if they have something that can contribute to a good (HTA) decision being made – if they can, well then they should be listened to. Also the fact that they can come in and have an active role in that, is really beneficial for the patient, but also for society in general. We will meet with people – and this may help them understand the kind of information that we want to tease out, and about those uncertainties we have. We can then use this information and put it into our report. That is a way of getting things to the table, insofar as we haven’t got a process at the moment where the patient is at that table. We can do something to just get the information there at least and that’s what we (NCPE) can do and I will give my commitment that we will try and meet people that want to come and meet with us.”

Later in the meeting Ms Helen Byrne of the HSE also expressed her support for patient involvement. She said:

“I think that it is crucial that patient advocates are involved as they bring real experience in how services can be improved.”

It is clear then that there is consensus for improved / accelerated patient involvement in this space. So what exactly might that look like, and what models can we adopt from other jurisdictions?

What can we learn from the UK - and Is Ireland different?

In England, patients are involved at every stage of the process, as Ms Josie Godfrey of NICE outlined in her description of the process and its origins:

“I was asked to talk about NICE work, and how we involved patients – the AGNSS (model) hasn’t existed since March 2013, but for those who know, it’s spirit lives on. Number 1: NICE has put in place robust, transparent and independent processes for assessing the cases for new drugs. Independence is really important – it’s not just the responsibility of one stakeholder, be it money, industry, patients; we’re trying to represent all of those views and be independent in making those decisions.”

“Number 2: It is worth noting, in this forum, in England we don’t distinguish between orphan drugs and everything else, but we do distinguish between ultra-orphans, for want of a better phrase, and everything else. So there isn’t a nice neat legal definition of what we mean by Ultra Orphan Drugs (UOD) unfortunately. But that also has benefits in that there’s flexibility about what we consider. So I’m responsible for the topic selection process and that’s how we determine whether a new project should sit within our technology appraisals programme, which has the capacity to look at about 45 topics a year or the highly specialised technologies (HST) programme which has capacity for three. And the HST programme is what the UOD are put through.

“The processes are fairly similar they’re based around a manufacturer’s submission and an industry/academic critique of that submission, but there’s also a fundamental role for patients, clinicians and other stakeholders who contribute evidence.

“So we start by trying to decide should we even be looking at this topic, have we got the right questions, do we know what it is we are being asked to consider? And that’s called the ‘topic selection and scoping’ process and straight away there are opportunities for patients to be involved. So alongside clinicians, payers, and industry, they are invited to comment on a draft scope and to attend a scoping workshop. We found that it’s absolutely fundamental in saying what is important about this disease, and the impact it has on their whole life; what is the outcome that they want – the benefits they’re hoping for – so it really helps us make sure we get the question right.”

“Then we move into the phase of getting the submissions in and there’s a slight difference there between the Technology Appraisal programme and the highly specialised (approach), because for those rarer conditions we are probably more proactive in making sure we get strong patient engagement – we’re actually going out and finding patient groups, working with them, supporting them in

http://www.ipposi.ie
terms of understanding the kind of evidence the committee would find helpful, and how they might go about that, so particularly encouraging surveys of their members e.g. thinking about the kinds of questions they might ask. This is really central to the evidence base for decision making.”

“We then also invite patients to attend as expert witnesses so we have patient organisation representatives actually sitting at the table in the public session of committee discussions able to answer questions and clarify uncertainties. We also have lay members on the committee for the Highly Specialised Technology programme: that’s three who are committee members out of a group of only 13-14 people, so quite a substantial proportion, and they are fundamental to the decision-making, to interpreting what we’re seeing and being able to speak with that holistic perspective. Patients also have an opportunity to comment on preliminary recommendations – a public consultation, i.e. that’s patient groups and anyone who wants to participate. And then (there is) the option to comment and appeal on the final decision, so they really are embedded through both those processes.”

“The real difference is probably how proactive we are in the highly specialised technology programme, and the fact that we’re asking broader questions for the highly specialised technology programme. So it does have a more holistic approach, taking more of a societal perspective. It looks less at a traditional notion of cost effectiveness and looks at total budget impacts and cost and benefits not just health benefits but wider societal benefits to families and carers. It tries to grasp how innovative a product is, what potential it might have both within that disease area and beyond, and the possibilities for future research, to name but a few things.”

“As you can imagine in cases of these very rare diseases where data is so challenging, without the patient and clinician input we really would not be able to make appropriate decisions.”

“By trying (in England) to have a process that is robust, that is transparent, that is appealable, that involves people, that meets those requirements for accountability for reasonableness. That is how we get the (political) support. The Ministers in England want to protect the system because they think the system is meeting those requirements and there’s far less inclination to look at individual drugs, and individual people, because they want to protect what they see as a robust system. And that’s the same with other stakeholders; the process, by being transparent, people understand what goes into it and what comes out of it by being able to sit and watch the public part of meetings - not the final decision part - but to understand the issues that are playing out, the kind of questions people are asking of experts, (it) means there’s that understanding of the process and that hopefully means that even when people don’t like the decision at least they understand how we got there.”

In summary, the UK and NICE enjoy a robust system that is transparent, and appealable, and which makes patient involvement central to the process. As attractive as this system might be to Irish patients, there are some structural impediments here, most obviously the difference in population sizes. With more than 40m people in the UK, NICE are better able to find more patients with the same rare disease, and possibly an organisation representing their interests. It should be noted however that where such an organisation does not exist in the UK, there is a record of bigger organisations guiding unrepresented patients through the process.

Another key difference is resourcing – NICE are able to proactively seek patients with a given rare disease if and when a suitable treatment comes under review. In Ireland, the NCPE simply do not have this resource.

**Transparency**

This issue was the most common cause of frustration for meeting attendees, whether they were patients, academics or from industry. Everyone acknowledged that transparency is good when the NCPE are in control of the process, and Dr Adams outlined how assessments worked there:

“I lead NCPE assessment group – we are tasked by the HSE to do a review of evidence submitted by manufacturers to support reimbursement of their products. That involves a full review of the evidence around efficacy – does this drug work; and we look at a lot of the adverse effects, we’ll look at how that will translate into the population in Ireland; we do look at other factors like the cost of the drug, but also the costs that this drug might prevent over time in relation to onset of the diseases, savings included.”

However, the NCPE can only make a recommendation for the potential approval of a treatment. The final decision on approval rests with the HSE’s Drugs Committee, and here the process is not transparent. IPPOSI’s Eibhlin Mulroe raised this point with Ms Helen Byrne of the HSE:

“The decision-making process is the real issue for a lot of the patients involved in trying to access new treatments; the HTA is generally done by the NCPE, it’s up on their website it’s very clear whether it’s a yes or no, and then its passed onto the drugs committee – and that’s where the time gap is, that’s where you’re getting the parliamentary questions – and I know every patient organisation in this room; nobody wants to go down that road, when you’re ill or have an ill child, the last thing you want to be doing is talking to a politician.

“To take that out of the equation we need more communications, and I suppose the drugs committee – we talked about how in England how it’s public, there’s a public hearing – so can you take this back to the powers that be – that if they really want to solve that issue they’re going to have to start communicating.

Ms Byrne replied:

“Everything everyone is saying makes sense and I agree that it has to be transparent.”

Professor Greg Pastores, Consultant in Metabolics at the
Mater Hospital said:

“I think when the whole process is transparent then there will be less people who feel disgruntled and excluded, and I think there are challenges there, and this (meeting) perhaps is a start of bringing up what the issues are and somebody has to set priorities.”

IPPOSI’s Eibhlin Mulroe put the issue of transparency (and patient involvement, and a separate system of assessment) to Mr Oliver O’Connor the Chief Executive of the industry representative body IPHA. She asked:

“Can you see a specialist system for the NCPE for accessing orphan drugs in terms of how they assess orphan drugs, and secondly, patient involvement within the assessment, but also we were talking a lot here about transparency in decision making, is that an issue for your members as well?”

Mr O’Connor responded:

“I don’t have a sign off on a negotiating mandate, the talks have not begun, so with that caveat, let’s say an agreement with the state and Pharma industry should cover all areas of mutual interest, and engagement between the two, and any agreement should be a question of mutual commitments, so if there is a subject that the two can make a commitment about, then it should be in an agreement, and why would you not cover these areas, would be my question?

National Rare Disease Plan

Though the National Plan for Rare Diseases was published in July 2014, and supported by the Department of Health, provision for its funding was initially missing from the HSE Service Plan, which caused distress among the rare disease community. Subsequent efforts by the Rare Diseases Taskforce and others saw the National Office for Rare Diseases going back into the Service Plan, however it was only at this round table meeting that IPPOSI members learnt for certain that the Office was definitely going to open this year.

Anne Lawlor of GRDO had this to say in the aftermath of the Office being confirmed:

“I’m so relieved to get official confirmation of the National Office, at the same time I’m alarmed because that plan was published last July (2014) and we’ve had to wait until now for official confirmation - I can also speak as a patient rep because I have a daughter with a rare disease. Full implementation of the National Rare Disease Plan for Ireland will mean that what we went through will not happen to others. And I know there are others, there are hundreds and hundreds of people like me and my daughter whose lives would be changed for the better”.

Meanwhile Professor Eileen Treacy, Clinical Lead for the Rare Diseases Clinical Programme (NCPRD) indicated that while the Rare Diseases Clinical Programme is separate to the HSE Drugs Committee and the Lead or Programme has no current role in the HSE Drugs Committee or Management Team, she has worked on the HSE Steering Group which developed the Rare Diseases National Plan which includes the recommendations to enhance access to rare drugs and technologies and she is fully supportive of the recommendations of this plan to improve the access to these medications, and the need for a Working Group to bring forward the appropriate decision criteria for reimbursement which is transparent; that patients and providers know what drugs are being reimbursed; what are the arguments put forward; that there is equity and consistency and every patient gets the same access; sensitivity to the values, to the economic evaluations etc.

At the time of this meeting, the Working Group mentioned above had not yet been established, but it since came into being as the National Rare Disease Plan Oversight Committee, which met for the first time on March 24th, 2015. It is tasked with supervising the plan’s implementation, which is something Ms Sian O’Neill of Shire echoed the call for:

“I think if the HSE can prioritise the implementation of the plan and centralise management and funding that there’s going to be more patients treated and more cost efficiencies as well.”

Ring-fenced funding managed entry and patient expectations

In the absence of enforcement, and with local payers sometimes choosing not to provide orphan drugs to patients, meeting attendees expressed the desire to have funding ring-fenced for rare diseases, in line with the recommendations of the National Rare Disease Plan.

Professor Greg Pastores said:

“I think it might be interesting to look at models where budget is ring-fenced and the process is transparent and equitable, because these are conditions that require expertise from both the patients and the physicians. Probably having a committee where some of these discussions are held in a town hall fashion, will hopefully make it clear to all that we are hoping for patients to gain access to treatments, albeit expensive, and which will really translate into meaningful benefits.

“Not just ‘get on a drug because it’s available’. And that’s easier said than done. In my experience I feel like baseline disease severity does influence outcome and unfortunately when a drug is new, patients will be at different stages of their disease and the question is: do you grant access to everybody and how do you arrive at that decision? So I think it’s a big challenge, and without a registry of patients we cannot properly plan for the future.
“(We should look) at models of managed entry agreements, where there is active engagement of the patient in any decisions made with respect to going on a therapy.”

Mr Fred Doherty of Genzyme said:

“We see other areas where we have ring-fenced national dedicated budgets such as in our oncology programme, our haemophilia programme, and they work extremely well based on the principles of money follows the patient. So we don’t need to reinvent the wheel to find a model that works, we have them very close to home. Mike Drummond (Professor of Health Economics, University of York), in a recent article, suggested that people with rare diseases are a minority group based on their genetic make-up and they should be discriminated against positively, which is an interesting concept.

Professor Treacy cautioned that any budget, ring-fenced or otherwise must not only be used for treatments, but the services that match the treatments. She gave the example of the UK:

“(it is) imperative also that the required resources to deliver the appropriate care and monitoring are put in place for the monitoring not just the costs of the medication. In 2005, the UK NSCAGS Commissioning Body not only provided the Budget for reimbursement of Lysosomal Storage Disease High Cost Enzyme Replacement Therapies, but also provided and commissioned centres of expertise to provide the appropriate monitoring and outcome analysis including the use of Registries. Likewise, in Ireland, we cannot just pay for the high-cost medications, we need to consider the budget also for the expert staff, registries, etc. to deliver the service”.

Ms Josie Godfrey of NICE, England supported this point (on paying for services as well as treatments).

“We’ve always seen that the services and the drugs need to go hand in hand – these are very expensive drugs for very rare diseases, these are not drugs you’d want every clinician in the country to be able to prescribe, so you want to manage that entry and now that’s become quite a formal part of the NICE recommendations – that there be a national expert centre; that there would be a registry; that there would be research into outcomes; so increasingly formalise that part but it’s always been – we’ve had the luxury in the UK of having sufficient patients and sufficient experts to be able to create centres of excellence for all of these disease areas.”

Helen Byrne of the HSE also supported ring-fencing, and the use of budget for services as well as treatments, and she highlighted what can happen when budget isn’t allocated in this way.

“I think it (budget) does have to be ring-fenced like cancer drugs and that allows for the budget which is finite to be monitored and used for the intended purpose.”

Along with ring-fenced budgets, patient registries are another key provision of the Rare Disease Plan and many patient organisations have set about establishing them. As Professor Pastores outlined in his comments on page 11, without patient registries, we cannot plan for future needs, and there was widespread support for the development of more patient registries provided this was executed in a useful way. This sentiment was best captured by Dr Adams of the NCPE:

“The key with registries is what don’t we know and what are we trying to find out? The danger is that we enter registries and gather all this data and it’s not actually answering any question that we don’t know, so it’s really important to know ‘what is our problem here?’ What’s the missing piece of information, before we start investing money.”

And significant money at that. Dr Dmitri Wall of the Irish Skin Foundation said that the budget required to establish a successful, standards compliant and sustainable registry can be far greater than expected, potentially exceeding one million euro, depending on the scope. He also cautioned against viewing them as a Holy Grail:

“My focus over the last two years has been registries, I’m a doctor but I’ve got a big interest in health informatics, and I don’t know if this is going to surprise you, but registries are not the answer – not in the way that we know registries at the moment anyway.”

“From what I hear, a lot of the problems we’re seeing here (today) are from information deficits; information silos, information that comes in drips, and we try and adopt plans to take the little bits of info and use that to push things forward, and I suppose the way registries have been developed up to this point is not supportive of that. One of the best registries in the country, alongside the cancer registry, is the CF registry and they have had to evolve to meet changing demands.

“What we really need are linked information systems. Why registries have been successful is because they are one of the few information systems that look at the objectives they want to achieve at the very, very start and then try to meet those with their solution. If people keep going and creating registries that don’t have any ability to interlink with each other, we are going nowhere and there will be a massive difference in quality between the best registries and the poorest ones. If we can change our strategy to work collaboratively and with a big picture in mind, registries can play a major part in a successful solution for healthcare delivery in Ireland.”

IPPOSI’s Eibhlin Mulroe responded to this and sought to explain potential state reluctance to invest in this area:

“I think in general though we’d like to see an overarching body that sets standards which patients, clinicians, industry, can talk to so we’re all using the same platform...”
and software (for registries), and I think it goes back to expenditure, and government — they’re afraid of investing in anything to do with technology in the Department after some debacles that have happened in the past, and I think that’s one of the reasons we’ve been so slow with e-learning, and registries.”

Mr Oliver O’Connor of IPHA was very supportive of registries:

“Personally I like very much the issue about registries, and the more we can do to build them and support them would be excellent, and build up that infrastructure in Ireland which is very necessary on the wider point about health economics.”

Ms Caitriona Dunne of Fighting Blindness said:

“We’re working in Fighting Blindness to build our own registry – we’re an organisation that has put a lot of resources into this, and we have the capacity to do that, and we’re finding that it’s a very slow process, a very long process, and we’re finding it hard to find patients, so I would have concerns I guess about how small organisations would have the capacity to do things like that – it’s a great idea and I know it’s really important, but we have the capacity and we know the difficulties involved so.”

Professor Mark Little of Trinity College said:

“I would like to reiterate the clarion call for registries as a means of supporting all this. The reality is that we’re not going to have clinical trials for all these medications and it’s the post-marketing surveillance that’s really going to determine how we use them and their benefit. For example with Botox and Viagra; that was all post marketing surveillance that showed us what other ways these drugs could be used.”

“So I believe that the portal for using these medications, or being allowed to provide them to patients, must include registration in a registry. So that has to be part of the door which is pushed to allow us to use these medications, and also that the cost of running this registry is part of the overall cost that the supposed ring-fenced budget for these medications includes.

“Finally I want to make the point that the technology is now there to allow the patient to be the central part of the registry – it’s very straightforward now to capture patient reported outcomes as a key measure in the registry, so we can measure the important things, such as how I feel on a day to day basis. Stuff that we are really, really bad at measuring as doctors and scientists. You can put an app on a phone quite easily and have people check in a couple times a day to say this is how I feel on this medication, and that allows you to measure what we are doing and we must measure what we do so that we can go back and say look what we did, and use it as a basis for getting further advances. In terms of finding the patients – we must inextricably link being on the registry with the therapy. So it’s part of the contract you have with society and the doctor that’s treating you – that you register on the registry – if you want the therapy.”

Declan Noone of the Irish Haemophilia society said:

“I think Mark’s point about patients engaging in the registry is very important. I don’t necessarily think that if you don’t give your information you shouldn’t get treatment, but the patient has a huge role and responsibility – not just for getting this drug, but for getting better drugs down the line – identifying side effects, tolerability, cohorts of patients treatment works the best for – we introduced an app recently and we record all of our treatments, I take the treatment, I scan the box, I send it through. If it is a significant bleed or a bleed that should have stopped, within 24 hours I will get a phone call saying, we noticed you had a significant bleed or a bleed – the registry constantly updates itself and flags up any issue predetermined by the clinic as an issue and informs the haemophilia team.”

Dr David Smith was concerned with the automatic patient sign-up approach however:

“I was interested in Mark’s point, if you don’t agree to be part of the registry you don’t get the treatment, but I think people also have a right to not be signing up.”

Clinical trials / Patient appetite for involvement

Whether or not patients wish to, or might be obliged to sign up to registries, many are extremely keen to do everything they can to improve their condition, including going on clinical trials. IPPOSI’s Eibhlin Mulroe said:

“Somebody asked whether people with rare diseases would be interested in clinical research – people with rare diseases, life threatening chronic debilitating rare diseases, will do anything to save their child or themselves, and sometimes you have to protect yourself and the patient in that environment.”
Cost of services

As we know, the cost, and cost-effectiveness of new treatments in the orphan drugs space are a major issue, but this did not preclude a discussion of costs across Europe, where medicine prices in certain continental European countries can be lower than in Ireland. Dr Ina Knerr of Temple St CUH said:

“I trained and worked in Germany and I think it’s quite striking that there are large discrepancies between official prices and actual cost, and I think there is a need for a European price for the very expensive orphan drugs. I know that for certain drugs in Germany we pay the minimum price or average price (100%) of the EU, and I know that in Ireland the price can be up (e.g. 150-160%) and I’d like to ask Nigel or Fred (i.e. company representatives) if there’s any way we could establish a European price for the very expensive orphan drugs in the longer term.”

Eibhlin Mulroe of IPPOSI added:

“I know price in Germany is different to price here, and maybe that’s why we’re so slow to make decisions on access here, because our country knows that (i.e. Germany pays less) but then the other side of that coin is how are those specialist services in Germany, and how are the people who are needed to provide the treatments who are they? I know in Ireland sometimes they’re from the company and that’s not the case in other countries so there are lots of issues, and again it goes back to the fact that it’s not transparent. We don’t know what the issues are (for decisions on new treatments) so this is a big debate, and a debate that needs to happen between companies at a global level because this isn’t going to go away.”

BioMarin’s Nigel Nichol said:

“Normally I think most companies try to operate a fairly narrow window across most countries in Europe because they don’t want parallel trading, or a grey market, so there does tend to be a fairly transparent published price. In order to invest in the next set of orphan drugs companies obviously need to recoup their investment from very much smaller patient numbers than is present in mainstream pharma.”

“You could then ask the question, ‘how come there aren’t many more companies involved in it?’ Because in any other marketplace you look at – cars, computers – any industry, if this marketplace is so profitable there would be many more entrants.”

EUPATI trainee and COPD Ireland CEO, Damien Peelo said:

“We really need to think about what Pharma’s role in this is, are they prepared to look at this is terms of their profits nationally and internationally. It’s a case of saying what ways can we change how we go about this system and I think looking at an EU wide price or a global price for drugs could really help in terms of country by country because each country has its own inequalities, some can afford to pay a lot more than others so we really need to look at how we can bring this across not just Europe but the globe really.”

“I’d be interested to know if there are many drugs that are ready to go to market but haven’t gone there because of the economic argument, is it because well look we’re not able to afford that or is it that the drug doesn’t add any additional value to what’s already out there, and I’d be interested to know how many drugs don’t get there because of the pure economic argument.”

Professor Pastores remarked:

“I learned as a clinician a long time ago that what should be done is linking access to value, and I think the concept of a ring-fenced type inter-service provision may be one consideration, to achieve the best governance, and address where there may be cost efficiencies, that then will allow you to have more patients gain access to available treatments.

“But there is a lot in the press about more and more therapies but in fact the benefits are not necessarily the same, and unfortunately for the type of diseases that I deal with there usually is only one therapeutic option and no room for bargaining, and so I think as I understand what was raised earlier, the burden for setting the price for a drug or finding a mechanism for paying for it, should not be on the patient, and ironically, although there should perhaps be affirmative action, the question becomes when you have 50 or 100 rare diseases, who gets to be first in line.”
Cost efficiencies

Mr Declan Noone of the Irish Haemophilia Society described in detail the work and experience of his organisation around cost efficiencies.

“In relation to haemophilia, it has been mentioned already by Fred Doherty in relation to the process around the way the purchases (are) at the moment. There are significant differences in price across Europe, we recently did a survey, and the same product ranges from €0.28 to €1.05 and that’s a stark, stark difference. And a lot of that is to do with cost efficiencies.

“Professor Treacy talked about the need for services as well as paying for drugs well, in haemophilia, we have a product selection board that meets 6 times a year. There are three haematologists, two patient reps, a blood safety expert, a virologist, a member from DOH and a procurement specialist, all working together choosing the products, examining what are the values of the patients and clinicians.

“That has resulted in significant price reductions and significant price efficiencies over the last few years, in 2002 when it was set up, we were paying 26% over the EU average and we are now paying over 36% under the EU average for the same product types. This type of organisational structure requires buy-in from both patients and clinicians, and we were talking about ring-fenced funding already, it does make significant difference. It’s not just the cost of the drug. We work with colleagues across Europe and with the patients being in the room it makes a difference. In the UK at the start of the tender process, there was a realisation through discussion with all in the room of how the product is mostly used and the commissioners realised that it may was possible to deliver it directly to the home and make an additional saving as well as improving the service for the patient. It’s a win-win.

“These are the sort of efficiencies and needs that patient involvement is necessary for because little things like that can drive efficiencies across the service. I think I was at an NCPE training day last year and the analogy used was that if people were choosing a car for a population to get around, the majority of people might need a Ford Fiesta – some people will need a Ferrari. If we sit down with patients and identify their needs, some patients will be able to get away with a Ford, and provide a driver and you’re still providing a better, more cost-efficient service as well as dealing with the patient needs. We need to work those things out together rather than ‘paying for drugs’ and ‘paying for services’ separately – that connection needs to be made very, very strongly as soon as possible…”

“… I think a lot of what we are talking about here is going to be seen in the new EU procurement directive in relation to negotiated or competitive dialogue tenders where there may only be one or two products on the market and additional items like registries and home care and other services will be attached. There are a number of aspects where those negotiations need to stop being just about price (for the treatment) but become about an overall package that benefits the payers and the patients…”

Referring to live registries, Mr Noone said:

“When we’re talking about this it’s also about cost efficiencies, and in haemophilia with this sort of active registry, they were able to remove a huge amount of stock that was going out of date or coming close, so now with stock rotation around the 32 hospitals, wastage is significantly minimized – patients sometimes get drugs at home and they go in the fridge and they’ll go to the back of the fridge, and the system will in place will remind patients to use older stock first.”

“These are the sort of things that make a really big difference when it comes to reducing the overall cost, and looking at what is the best way of taking your treatment. We need to take the treatments that we have well, and when we do and work together to optimise, treatments and services, then we start to see real efficiencies in care for patients.”

Based on the discussion that unfolded at the Round Table meeting in February, and guided by the provisions of the National Rare Disease Plan for Ireland 2014-2018, this report concludes that patients must be involved in the decision-making process, and furthermore that the decision-making process should be public and transparent.

Conclusions

Ireland must also develop a resource in the NCPE similar to the NICE model that can proactively find patients to involve in the assessment of pertinent orphan drugs. More generally, Irish patient training in health technology assessments must continue to grow.

Finally, this report concludes that there is a need to establish an implementation group that examines Orphan Drugs assessments in Ireland. In summary:

1. Increased patient involvement in Orphan Drug decision-making
2. Transparent and public decision-making
3. Development of a resource in NCPE similar to NICE model that can proactively seek patient input on rare diseases irrespective of whether patient organisations exist or not
4. Training patients in Health Technology assessment
5. Establishing an Implementation Group that examines the process of Orphan Drugs assessment in Ireland
Appendix 1: Speaker biographies

Katie Murphy has worked with Cystic Fibrosis Ireland since Jan 2012 working as both a Regional Development Officer and more recently Research & Development Officer. She has a degree in Psychology and a Masters in Health Promotion. As well as working as a researcher at the Health Promotion Research Centre in NUI Galway she also has taught on the postgraduate course in Health Promotion. As a person with Cystic Fibrosis (PWCF) Katie also acts as a patient advocate, with a particular interest in promoting patient involvement in, research, health technology assessment, policy development and the development of clinical care standards and practices. Other areas of interest include, availability of new therapies, exploring the patient experience in the health care system, information provision and patient/family support.

Josie Godfrey, Associate Director-Highly Specialised Technologies and Topic Selection, NICE UK. Josie Godfrey is Associate Director at NICE with responsibility for the new Highly Specialised Technologies and Topic Selection programmes. She is leading work to establish a programme which will issue guidance to the NHS in England about the use of new highly specialised technologies. Before joining NICE, Josie helped establish the Advisory Group for National Specialised Services (AGNSS). She developed a decision-making framework to support AGNSS in making recommendations to health ministers and developed the process for considering highly specialised services, drugs and technologies. Josie has worked in health policy development and implementation for the NHS in England at a national and local level.

Dr. Roisin Adams, MPharm, MSc., PhD is Deputy Head of the National Centre for Pharmacoconomics. She was awarded a PhD for her work on the cost effectiveness of biologic agents in inflammatory rheumatological disease. She is a graduate of the Robert Gordon University, Aberdeen and trained in Ninewells Hospital, Dundee. In 2003 she was appointed Chief II pharmacist in St. James’s Hospital where she specialised in palliative care and rheumatology. Roisin completed her MSc. in Clinical Pharmacy at Queens University, Belfast. She leads the review group for pharmaceutical technologies at the NCPE. Her areas of interests include methods for preference elicitation and methodology of indirect comparisons for evidence synthesis.
**Speaker biographies**

**Gregory M. Pastores MD** is a Consultant with the Adult Metabolic Service/Department of Medicine/National Centre for Inherited Metabolic Disorders at the Mater Misericordiae University Hospital. He is also a Visiting Professor with the Department of Medicine, Yale University School of Medicine, USA.

He graduated from the University of Sto. Tomas in Manila (1983). He has extensive clinical and research experience in the diagnosis and management of patients with the lysosomal storage disorders and other inborn errors of metabolism. He was also engaged in the development and testing of treatments for Gaucher, Fabry, MPS I, IV and VI, Pompe disease and a late (adult)-onset form of Tay-Sachs disease (G_{M2}gangliosidosis).

He has published over 200 papers, 20 book chapters and two textbooks.

**Fred Doherty, Genzyme Therapeutics.** Fred has worked as a healthcare professional for 10 years before joining the pharmaceutical industry where he has worked for the last 28 years. Since 2010, he has been responsible for market access and government affairs for Genzyme Therapeutics and prior to that he held several senior management positions in Bristol Myers Squibb.

Fred has a Masters in Business Administration, is a member of the Marketing Institute and, has a Dip in Public Relations and is an RGN and RPN. He is an external lecturer in the UCD Medical School and has a particular interest in developing partnership initiatives between healthcare stakeholders.

**Prof. David Smith, B.Phil., B.D., S.T.L., M.A., S.T.D.** David Smith is Associate Professor of Healthcare Ethics in Royal College of Surgeons, Ireland and Director of the MSc in Healthcare Ethics and Law in RCSI. He lectures on Healthcare Ethics in TCD, UCC, UCD, the Royal College of Physicians of Ireland and Hibernia College. He is an Ethics Consultant to a number of Healthcare Systems in Ireland. He was a member of the Irish Council for Bioethics. He is currently a member of the National Advisory Committee on Bioethics Ethics, the National Council of the Forum on End of Life in Ireland, the Ethics Working Group of the Irish Association of Palliative Care Consultants, the advisory committee on Research Ethics Committees in Ireland established by HIQA, among many other groups.
Appendix 2: Contributors

- Ms Helen Byrne, HSE
- Ms Rachel Foley, Irish Cancer Society
- Mr Declan Noone, Irish Haemophilia Society
- Mr Nigel Nichols, BioMarin
- Ms Sharon Thompson, EUPATI Trainee
- Mr Damien Peelo, COPD, EUPATI Trainee
- Ms Sian O’Neill, Shire Pharmaceuticals
- Prof Eileen Treacy, Temple Street CUH
- Prof Mark Little, TCD
- Ms Anne Marie O’Dowd, Cystinosis Foundation Ireland
- Dr Ina Knerr, Temple Street CUH

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