New Medicines for Serious Conditions: Weighing the Risks and Benefits

The Verdict of a Jury of Patients

A project supported by Genetic Alliance UK and facilitated by the Welsh Institute for Health and Social Care.
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A project supported by Genetic Alliance UK and facilitated by The Welsh Institute for Health and Social Care, University of Glamorgan

The Jury took place between September and December 2011. This report was finalised in March 2012.

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The Jury

Duncan Batty, Suffolk
Mark Bostock, Bristol
Mary Carter, Penarth
Jean Collingwood, Hull
Samantha Evans, London
Natalie Fernandes, London
Carlee Gilbert, Merseyside
Pat Linck, Bangor
Elizabeth Littlewood, Cambridge
Rea Mattocks, London
John Thomas (accompanied by Anne Cameron), London
Paul Warren, Bridgend

This report was drafted by Amy Simpson and Professor Marcus Longley on behalf of the Jury, and approved by the jurors.

This document is available to download at www.geneticalliance.org.uk/docs/citizens-jury-report.pdf
Genetic Alliance UK

Genetic Alliance UK is the national charity of 154 patient organisations supporting all those affected by genetic conditions. We aim to improve the lives of people affected by rare genetic conditions by ensuring high quality services and information are available to all who need them. We provide a united voice for all those affected by rare genetic conditions, enabling us to work together towards a common goal of making life better for patients, their families and carers.

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

- The Risks and Benefits project. The project has involved providing jurors with the knowledge and understanding that they need to undertake an informed critique of existing regulatory and risk analysis systems, enabling them to comment on which aspects of these systems adequately reflect their perspective and which aspects do not. This critique has been used to develop a practical framework of recommendations that can be applied to existing systems.
- Rare Disease UK, a multi-stakeholder group working together to inform and influence health departments and the NHS to develop a plan for rare diseases, which includes the information and support they require under the management of their care.
- Route Maps for Rare Conditions, a project involving ten of our small member groups developing a practical and cost-effective framework for improving information, access and coordination of health and social care services for individuals and families with a wide range of rare genetic conditions.

Genetic Alliance UK is a registered charity in England and Wales (no.1114195) and in Scotland (no.SC039299). A company Limited by Guarantee (no. 05772999).

The Welsh Institute for Health and Social Care at the University of Glamorgan

The Welsh Institute for Health and Social Care in the University of Glamorgan was established in 1995, and works across a range of health and social care policy areas. It focuses on applied research, using rigorous methods to help address issues of immediate and practical concern. It has for many years worked on aspects of pharmaceutical regulation, and has developed and evaluated new ways of involving patients, service users and the public more generally in the development of policy. For the last 15 years it has used Citizens Juries, together with a range of other deliberative processes, to involve lay people in complex policy issues, in the belief that everyone can engage in these vital issues, given sufficient information, time and support.

Acknowledgements

The Project Team would like to express their enormous gratitude to all those who helped in this work, including the jurors, the Steering Group, witnesses, and all those who advised on the project as it developed, including the clinicians who helped write the case studies.
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Summary

This is the report of the discussions and verdict of a Jury which met over a total of five days between September and December 2011.

Focus of the Jury

No medicine is 100% safe. So, regulators need to decide whether the advantages outweigh the disadvantages of taking the medicine and whether the side effects are acceptable before they grant marketing authorisation. This analysis of the risks and benefits associated with new medicines is very complex – what risks and benefits are we talking about, and how should they be weighed? Where the condition is serious and/or rare, these decisions can be even harder. The Jury was designed to be a structured and in-depth study into how patients with serious and/or rare conditions perceive risks and benefits, and how effectively current regulatory decision making reflects their preferences. The discussions of the Jury were focused on the following questions:

1. How do patients with rare and/or serious conditions perceive the risks and benefits of new medicines?
2. To what extent should regulators be more permissive in their marketing authorisation decisions?
3. How should patients be involved in the assessment of risks and benefits, and regulatory decision making?

Citizens’ Jury Method and Process

The Citizens’ Jury is a participatory research method. Drawing upon aspects of a legal trial by Jury, a small group of individuals form a Jury over a few days, to learn about and deliberate a particular issue in depth. They weigh the evidence presented, discuss it amongst themselves, and reach a ‘Verdict’. They also often make other observations and recommendations relevant to the matter in hand.

The twelve jurors were either patients with serious and/or rare conditions, or were the family members of someone with a serious and/or rare condition. The Jury met for a total of five days between September and December 2011. During this time, Jurors explored the risks and benefits of hypothetical case studies and heard from a number of expert and advocate witnesses about how the regulatory system currently works, its strengths, and its potential weaknesses. The jurors deliberated two opposing arguments: a) Making a case for change (regulators should be more permissive) and b) Defending the status quo (regulators should not be more permissive).

The Verdict: Summary of Jury’s Recommendations

After considering the evidence and debating the issues amongst themselves, the jurors concluded that:

1. Regulators should include psychosocial factors in their decision making.
   Jurors argued that insufficient weight is given to psychosocial factors in the evaluation of medicines for licensing. Applications for new medicines are judged primarily upon biomedical evidence and clinical outcomes. For patients, there are likely to be psychological and social factors that are equally as important. Jurors would like to see regulators broadening the range of issues which they consider when deciding whether to approve a new medicine, with greater weight placed on the psychosocial aspects of serious and/or rare conditions, and on the potential for new medicines to alleviate (or exacerbate) them. Jurors have generated a list of 25 psychosocial factors that are important to them, to be included in the assessment of risks and benefits of new medicines.
2. Regulators should be more permissive for those treatments for people with rare and/or serious conditions.
Patients affected by serious and/or rare conditions often have few or no effective treatments available to them. Because of their unique circumstances, such patients may well be willing to take greater risks than the system currently allows, and should be given that choice. Key questions for regulators in their marketing authorisation decisions are ‘do the advantages outweigh the disadvantages of taking the medicine?’ and ‘are the side effects acceptable?’ In the case of serious and/or rare conditions, regulators should lower the threshold of what they consider to be acceptably safe, giving more weight to psychosocial benefits and involving patients in the decision making.

3. Patients should be more involved in all stages of the process, from setting the research agenda, to post-marketing authorisation decisions.
Patients’ experiences and preferences should be represented in all the processes which lead to the development of new medicines, from the initial determination of research priorities, right through to the regulatory processes which grant and remove marketing authorisation. This would ensure that the benefits which really matter to patients, and the levels of risk they are prepared to tolerate are considered in the decisions. This is particularly important for serious and rare conditions, where the stakes are so high. Patient representatives (such as patient group members) should be supported as joint decision makers, alongside clinical experts, throughout the process.

4. Patients should be better supported to make their own decisions.
Patients wish to decide which medicines they take, reflecting their individual circumstances, beliefs and preferences. The result of Recommendations 1-3 above will be that patients with serious and/or rare conditions will in future be faced with more choices, as more medicines are made available to them. Such decision-making is challenging, but possible for most patients. But people need help from their clinical team, and from a variety of other sources, including relevant, credible and understandable information about the potential risks and benefits of the new medicines. Jurors welcomed work to improve the way in which such risks and benefits are communicated, and also generated a list of questions to help guide patients when deciding on their own treatment options. Tools such as these should be used by clinicians and patients to aid a shared decision making or a partnership approach to prescribing practices.
How the jury went about its work

The Risks and Benefits Citizens’ Jury was a Genetic Alliance UK project, delivered and facilitated by Professor Marcus Longley and Amy Simpson of the Welsh Institute for Health and Social Care, University of Glamorgan. The project began in September 2010, with the Citizens’ Jury events taking place in Birmingham in September, November and December 2011.

This report outlines the background to the project and the jurors findings in relation to the following questions:

1. How do patients with rare and/or serious conditions perceive the risks and benefits of new medicines?
2. To what extent should regulators be more permissive in their marketing authorisation decisions?
3. How should patients be involved in the assessment of risks and benefits, and regulatory decision making?

Context

All new medicines must be approved, and given marketing authorisation, by the regulatory bodies before they can be prescribed to patients.¹ This is crucial protection for patients who might otherwise suffer serious harm from potentially ineffective treatments or potentially harmful treatments.

Over the past ten years there have been several high profile cases which have clearly demonstrated the difficulties that regulators, as well as pharmaceutical and biotechnology companies, have in measuring and balancing the risks associated with new therapies against the potential benefits they may offer patients. It might be inferred that public and media reaction to the cases has induced both an increasingly cautious approach to the approval of new products, and the prioritisation of risk avoidance over innovative research. It is possible to argue that people living with serious and/or rare conditions would be willing to take much greater risks than those deemed acceptable by regulators, because the stakes are so much higher for them than for the rest of society.

The analysis of the risks and benefits associated with new medicines is a complex subject. The Jury was designed as a structured and in-depth study into how patients with rare and/or serious conditions (and their families) perceive this balance, and how effectively current regulatory and other mechanisms reflect their preferences. Based on a Citizens’ Jury model, the project involved 12 such people in deliberative dialogue on this issue over five days, informed by the evidence.

Defining Serious and Rare

The twelve jurors were either patients with serious and/or rare conditions, or were the family members of someone with a serious and/or rare condition.² Hence, the primary focus of the jurors’ discussions and recommendations were regulatory processes for serious and/or rare conditions.³ Although the terms are used together throughout the report, it is important to note that they are not interchangeable. The recommendations outlined in this report are important for common serious conditions, as well as rare serious conditions. All patients with a serious condition (common or rare) will share a similar set of circumstances, which is likely to affect their perception of risks and benefits. The two terms are defined in more detail below.

Serious

Although there is no official definition, there are a number of factors which could be associated with a serious condition. A serious condition is significantly life limiting or life threatening. Its symptoms are likely to affect a patient’s normal daily life, and they are likely to be highly dependent on medical care. Most serious diseases are incurable, but the symptoms may be managed or alleviated through various treatments. A serious disease might be common (such as breast cancer), or rare (see below).
Rare
A rare disease has been defined by the European Union as one that affects less than 5 in 10,000 of the general population. Currently, there are approximately 7,000 known rare diseases, but new rare diseases are frequently added to this list. 7% of people at some point in their lives will have a rare disease. Collectively, they affect 30 million people across Europe. Rare diseases are likely to have a genetic component to them, and they are often chronic and life-threatening illnesses. For example, 30% of rare disease patients die before their fifth birthday. Well known rare conditions include cystic fibrosis and huntington’s disease. 4

Aims and Objectives
The Risks and Benefits Citizens’ Jury was an examination of how patients with rare and/or serious conditions perceive the balance between the risks and the benefits of new medicines. The project set out to generate informed opinion and identify what patients consider to be the key factors in defining an acceptable balance between risk and benefit for a new therapy.

The objectives of the project were to:

- Systematically examine how patients with rare and/or serious conditions perceive the balance between the risks and benefits of new therapies.
- Enable patients to frame recommendations to be used as a practical tool by policy makers and regulators.
- Generate informed opinion and provide evidence on the patient perspective of this issue that will contribute to debate about the management of health interventions, the planning of clinical trials and the practices of regulators, pharmaceutical companies and clinicians.
- Empower patients to validate the inclusion of their perspective into analysis of risk and benefit.
- Engage the general public and the media in this debate and increase understanding of the complex decision-making process involved in this issue.

Citizens’ Jury Method
The Citizens’ Jury is a participatory research method. Drawing upon aspects of a legal trial by Jury, a small group of individuals form a Jury over a few days, to learn about and deliberate a particular issue in depth. They weigh the evidence presented, discuss it amongst themselves, and reach a ‘Verdict’. They also often make other observations and recommendations relevant to the matter in hand. 5

The approach is based on the premise that ordinary people, given enough time, support and resources, are eminently capable of arriving at complex decisions about complex issues. Citizens’ Juries may take a number of different forms, but they have the following in common:

- Time - Several days to consider the question
- Information - As much evidence as possible in the time available
- Scrutiny - Opportunity to cross examine, call for more evidence/witnesses
- Deliberation - Opportunity for discussion amongst themselves and with witnesses
- Independence - The Jury is independent of the organising body
- Authority - Findings carry a weight of authority derived from independence and integrity

Steering Group and Project Team
The project was overseen by a Steering Group, whose role was to ensure the robust, fair and transparent running of the project. Its terms of reference were to:

- Maintain awareness of the relevant evolving political, social and health service environments.
- Represent the views and needs of a wide range of stakeholders both from its own resources and through its network of contacts.
- Provide expert advice on relevant aspects of the project work
- Approve and monitor all the key aspects of the project process, specifically the focus and questions to be addressed, methods, juror selection and the programme of witnesses, as well as any other relevant aspects.
- Ensure the appropriate quality of work.
- Provide support in the dissemination of the project findings.

A full list of Steering Group members for this project can be found at Appendix i.

The project was led by Professor Marcus Longley and Amy Simpson of the Welsh Institute for Health and Social Care (WIHSC), University of Glamorgan, with assistance from Teresa Neate MBE on the Jury sessions in September and November 2011. The WIHSC team have previous experience in designing and facilitating Citizens’ Jury projects, focusing on complex healthcare issues.

Colleagues in Genetic Alliance UK, particularly Alastair Kent and Celine Lewis, provided invaluable assistance throughout, as did colleagues in WIHSC.

Funding
Funding for the project has been provided by six pharmaceutical companies: Novartis, Roche, Shire, AstraZeneca, GlaxoSmithKline and Pfizer. All six donations were made in line with clause 23 (Relationships with Patient Organisations) of the ABPI Code of Practice for the Pharmaceutical Industry 2008. The project also received financial support from The Wellcome Trust.

Ethics
The project was approved by the appropriate Ethics Committee in the University of Glamorgan.

Recruitment
The recruitment process began in May 2011. The jurors were recruited in three stages:

Stage 1
An initial explanatory email was sent to Genetic Alliance UK member groups in early May, and a further email was sent to Rare Disease UK members in mid May, inviting people with serious and/or rare conditions to express an interest in being a juror. A wide range of material, including a more detailed document and a short video clip were provided via a web link. In total, 72 individuals registered their interest between May and July. A full breakdown of those who registered their interest is outlined in Appendix ii.

Stage 2
In the second stage of the recruitment process, each of the original respondents were contacted and told a bit more about what would be involved. Following this, if individuals still wanted to be considered for a place on the Jury, they were asked to provide further information to the project team in a second survey. The purpose of the survey was to identify any personal requirements, which would need to be taken in to account in order for them to be able to participate fully in the Jury. The aim was to make the process as inclusive and accessible as possible. In total, 51 responded to the second survey.

Stage 3
Initially, 16 jurors were selected from the 51 respondents. The focus of the selection process was to find a Jury that was as diverse as possible in terms of gender, age, ethnicity, and condition. Where possible, jurors were selected on the basis that they were within 2.5 hours travelling time from Central Birmingham. By November 2011, 4 jurors withdrew from the project due to other (unforeseeable) commitments. 12 jurors took part in the two Citizens’ Jury weekends.
The Jury

Table 1: A Profile of the Jurors

<table>
<thead>
<tr>
<th>Gender</th>
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<tr>
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</tr>
<tr>
<td>Female</td>
<td>8</td>
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</tbody>
</table>

<table>
<thead>
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<th>Age</th>
<th></th>
</tr>
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<tr>
<td>28-37</td>
<td>2</td>
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</tr>
<tr>
<td>48-57</td>
<td>4</td>
</tr>
<tr>
<td>58-67</td>
<td>3</td>
</tr>
<tr>
<td>68+</td>
<td>1</td>
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</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>White - English/Welsh/Scottish/Northern Irish/British</td>
</tr>
<tr>
<td>Any other White background</td>
</tr>
<tr>
<td>Any other Asian background</td>
</tr>
<tr>
<td>Other ethnic group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Religion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Religion</td>
</tr>
<tr>
<td>Christian</td>
</tr>
<tr>
<td>I’d rather not say</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

The Programme

Schedule

The Jury met for an initial planning and orientation day in September 2011, and then over two long weekends in November and December. The programme for the Citizens' Jury was developed over a number of months with the Steering Group. The final programme is shown in Appendix iii.

Planning

In addition to the jurors' own reflections (individually, in small and larger groups), the programme included two main types of sessions: case study focused sessions, and expert or advocate witness sessions. The case studies were developed by Longley and Simpson, in conjunction with clinical experts relevant to the different conditions depicted. A list of the case studies is shown in Appendix iv. Expert witness biographies are shown in Appendix v. The findings section below provides further detail.

“When I initially read through the case studies, I’d found them rather daunting...it was encouraging...to discover that in the course of exposition and discussion, the density of the information was diminished, the questions and issues were unpacked and became clearer and more manageable, and that like most other members of the group I was able to make a judgement and form an opinion in which I could have some confidence”

Process

During the first Jury weekend, jurors discussed four of the case studies in depth. The final two case studies were discussed in December. Jurors were asked to explore the risks and benefits of each case,
and whether they thought the treatment should be available to patients. The case study discussions helped inform the first question:

1. How do patients with rare and/or serious conditions perceive the risks and benefits of new medicines?  

Using audio recordings of the discussions, contemporaneous notes and flip chart summaries, and jurors’ own individual reflections, Simpson and Longley produced a summary document (after the first weekend) of the emerging themes and issues. Jurors were presented with the themes, and were asked to explore them further in the second weekend. From this, jurors created a series of lists of important factors to consider in the risk and benefit calculus. Jurors drew upon their own experiences of being affected by, or caring for someone with a rare and/or serious condition. (See recommendation one). Exploring the jurors’ perceptions of risk and benefit also provided a valuable insight into the risks they might be willing to take in order to gain potential benefit.

The Jury also focused on current research and regulatory processes and systems. Jurors heard from a number of expert and advocate witnesses about how the system currently works, its strengths and its potential weaknesses, in order to consider the following:

2. To what extent should regulators be more permissive in their marketing authorisation decisions?  
3. How should patients be involved in the assessment of risks and benefits, and regulatory decision making?

On the final Saturday, jurors put to use everything they had learnt during the process. They did this by partaking in a debate, with the support of expert coaches. The jurors explored and debated two opposing arguments: a) Making a case for change (regulators should be more permissive) and b) Defending the status quo (regulators should not be more permissive).

On the final day, jurors discussed their conclusions and recommendations. The jurors’ findings are outlined below, and have been framed around four key recommendations. The first three addressed the specific questions put to the Jury; the fourth reflected the jurors’ own desire to improve the system for patients.6

Data Collection  
Data was collected in a variety of ways during the process including:

- Each discussion session was audio-recorded  
- Key points were captured in note form on flip charts by the facilitators  
- Jurors kept reflective diaries throughout the process  
- Jurors completed questionnaires at the end of each meeting (September, November and December)  
- Jurors took part in voting exercises

“Meeting new people and listening to their experiences, and being able to share those experiences, was comforting and at the same time thought provoking”
New Medicines for Serious Conditions: Weighing the Risks and Benefits

Recommendations

Recommendation One | Regulators should include psychosocial factors in their decision making

Jurors argued that insufficient weight is given to psychosocial factors in the evaluation of medicines for licensing. Applications for new medicines are judged primarily upon biomedical evidence and clinical outcomes. For patients, there are likely to be psychological and social factors that are equally as important. Jurors would like to see regulators broadening the range of issues which they consider when deciding whether to approve a new medicine, with greater weight placed on the psychosocial aspects of serious and/or rare conditions, and on the potential for new medicines to alleviate (or exacerbate) them. Jurors have generated a list of 25 psychosocial factors that are important to them to be included in the assessment of risks and benefits of new medicines.

Summary of Patient Preferences

One of the primary objectives of the Citizens’ Jury project was to create a useful list (or ‘toolkit’) for those involved in the regulation of new medicines, to ensure that factors important to patients are addressed and given appropriate weighting in the risk benefit calculus. Figure 1 on page 15 summarises these factors. They are discussed in detail below.

Biomedical Factors | A Patient’s Perspective

Jurors recognised that currently regulators focus primarily on the biomedical aspects of new treatments in their decision making, and that in general, they carried out this aspect of their task appropriately. Jurors identified a number of questions relating to the biomedical aspects of a medicine/condition that they considered important in determining the appropriate risk/benefit calculus. These have been ranked by their relative importance. Although each of the questions were considered important to the group, the effectiveness of the treatment was regarded as the most significant thing to patients, and the frequency of side effects was ranked as the least. The top five important biomedical factors are included in figure 1.

1. How effective is the treatment?
2. Are the side effects treatable?
3. How long term are the side effects?
4. How severe are the side effects?
5. How credible is the data?
6. How serious is my condition?
7. What are the limitations of the data?
8. What is the excess mortality rate?
9. Will I maintain the capacity to make decisions about treatments in the future?
10. How common are the side effects?

The discussion below further expands on the lists above:

Effectiveness of the treatment

‘Effectiveness’ is the product of a range of factors, most of which were explored throughout the Citizens’ Jury process. Jurors were particularly concerned that improving the quality of life should be given as much weight as extending the length of life:
“My condition isn't life limiting....what treating my condition would do is make me more mobile and reduce my pain” (Transcript of Discussion)

Side effects
Jurors considered a number of elements in relation to the side effects of new medicines, including their severity, and whether they were treatable. Jurors were also concerned with how long term and immediate the effects were. For example, short term side effects might only last for a day or two before they pass, long term side effects might increase the risk of developing complications in the future.

Reliability and limitations of the data
Jurors were concerned about the limitations in efficacy and safety data and the impact this might have on decision-making, both for regulators and individual patients. One limitation was missing or 'unknown' data, which was identified as a risk in some of the case studies. For example, when a drug is new to the market there is little known about its long term effects. Unknown risk in this case could be undesirable side effects in the future or a lack of efficacy with long term use. The Jury decided that, even if the mechanism of action were unknown (why the drug is effective), then patients should still be able to take the risks associated with its use. Lastly, the Jury recognised that testing new medicines for rare diseases is inherently problematic owing to the small numbers of participants in clinical trials.

“I think this is what we struggled with on the case studies....the missing data” (Transcript of Discussion)

An additional concern, closely linked to this, is whether a patient can access all of the available information in an appropriate manner. This has been included in the patient checklist (see recommendation four).

Severe mortality
The severity of a condition encompasses many factors such as whether it is life limiting, how it impacts on a patient’s day to day life and the speed of progression. These factors would affect the risk/benefit calculus:

“If you are going to die in three weeks, you might take a very risky treatment” (Transcript of Discussion)

“The balance of risks and benefits is going to be different depending upon the severity of the condition. The more severe the condition, the greater the risk required. It’s also influenced by how individuals perceive their condition....if mobility is limited and you were a climber or very physically active it will have a greater impact” (Reflective Diary)

Excess mortality
The Jury explored several difficulties in evaluating the relative importance of excess mortality as a factor in assessing the impact of a condition and the side effects of a medication. Jurors found it difficult to decide what level of excess mortality they would accept personally. It was highlighted that the acceptable degree of risk would depend on your experience of the condition, and that some patients might even accept a 50% chance of mortality.

“...we are talking about people facing a pretty grim future....that's what makes a big difference here...my choice in that situation...I would take the risk...if the medication causes my death.... I would tell everyone I left behind, I made that choice” (Transcript of Discussion)
Jurors discussed the impact of age, and how this could potentially affect a patient’s perception of risk and benefit, and in particular, mortality. People of different ages may have different perceptions about the risk of sudden death:

“Death for me is not far away...it is not bothering me...but the manner of dying worries me...If I were 25, I'd have a different perception”. (Transcript of Discussion)

Age and experience may also affect one’s view on the issue of quality versus quantity of life:

“It is a feature of age and having experience of someone in the family with...dementia...Personally speaking, I’d rather have a shorter, better life...but if I were younger I might have a different perspective” (Transcript of Discussion)

Jurors considered the way in which excess mortality, and other statistical evidence, is communicated to patients and professionals. How the information is presented can impact on a person’s understanding and interpretation of the facts.
Figure 1: Biomedical and Psychosocial Factors to be considered

Biomedical
- Effectiveness of treatment
- Treatability of side effects
- Duration of side effects
- Severity of side effects
- Credibility of data

Key Biomedical Factors to Consider in Risk/Benefit Calculus

Me
- Anxiety
- Being a patient and taking medication
- Relationship with self and identity
- Autonomy and control

Key Psychosocial Factors to Consider in Risk/Benefit Calculus

My Family
- Relationship with immediate family
- Relationship with friends
- Financial implications

Society and Me
- Financial implications
- Employment status
**Psychosocial Factors | A Patient’s Perspective**

The jurors were asked to create a list of psychological or social impacts that they had experienced or that were important to them in relation to their condition and/or decisions about treatments. The purpose of this discussion was to establish what might be a worthwhile benefit to patients, and what should be given significant weight in regulatory decisions. It should be recognised that it is not just the physiological impacts that are important to patients. There is a whole set of other preferences around the psychosocial\(^8\) that are just as – if not more – important.

"Underlying the whole discussion, there seemed to be an emphasis on 'quality of life', as opposed to 'life expectancy/risk of mortality' which seemed to be the preoccupation of current regulators" (Reflective Diary)

"All of these [psychosocial factors] are about quality of life..." (Transcript of discussion)

25 factors were identified in total. These have been grouped under three headings, ‘Me’, ‘My Family’, and ‘Society and Me’:

**Table 2: Psychosocial Factors**

<table>
<thead>
<tr>
<th>Me</th>
<th>My Family</th>
<th>Society and Me</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (as a result of uncertainty and uncertainty of effectiveness)</td>
<td>Relationship with immediate family (spouse, partner, children, parents, siblings)</td>
<td>Financial implications</td>
</tr>
<tr>
<td>Being a patient and taking medication (time, disruption and anxiety)</td>
<td>Relationship with friends</td>
<td>Employment status</td>
</tr>
<tr>
<td>Relationship with the self and identity</td>
<td>Financial implications</td>
<td>Insurance (all types)</td>
</tr>
<tr>
<td>Autonomy and control</td>
<td>Carers (commitment, resentment, reliability)</td>
<td>Relationships at work (colleagues, employees, peers, managers, clients)</td>
</tr>
<tr>
<td>New opportunities/enlightenment</td>
<td>Relationship with extended family</td>
<td>Driving</td>
</tr>
<tr>
<td>Self efficacy and self esteem</td>
<td></td>
<td>Altruism</td>
</tr>
<tr>
<td>Coping mechanisms</td>
<td></td>
<td>Social pressures (to take or not to take a medicine)</td>
</tr>
<tr>
<td>Short termism</td>
<td></td>
<td>Carers (commitment, resentment, reliability)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress/distress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guilt/regret</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respite/relief</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sense of mourning or loss</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Jurors were asked to select those factors which were most important or most significant to them. These items should therefore be considered and given appropriate weighting in decisions made. These are highlighted in the blue type above, and discussed in more detail below. For more detail on scoring exercises, please refer to Appendix vi. It is important to note that many of the listed factors are closely related and were shown to have significant impact on one another.

Anxiety as a result of uncertainty
Anxiety as a result of uncertainty was viewed as the most significant psychosocial factor by the jurors. Jurors shared their experiences of anxiety. Patients might be anxious in relation to the uncertainty around the future of their condition, and the effects of the treatments they are currently taking. In some cases, this anxiety had a significant impact on the jurors’ quality of life:

“There is one psychological dimension... which must run through all of this... anxiety, worry... [as a result of] uncertainty...will my condition get worse? Will I be able to cope with the level of pain?...will I be able to carry on with my job?...a whole range of things” (Transcript of Discussion)

“My mental health and wellbeing has been affected...I don't know, I don't know what is going to happen with the condition, I don't know what the medication is going to do to me. I know that my wellbeing is not as well as it used to be, I am constantly worried... Is this a symptom of my condition?...you are constantly anxious...your quality of life is not the same” (Transcript of Discussion)

Impact on relationships with immediate family and friends
There were many different types of family relationships that were highlighted by jurors during the sessions. Relationships with immediate family members (such as spouses/partners and children) was highlighted as an important psychosocial factor to consider:

“I don't want my family to say, we can't do that because of [me]” (Transcript of Discussion)

Jurors who were parents shared their experiences of how their condition impacted on their relationships with their children. Because of their conditions, some jurors struggled to maintain stereotypical roles within their families:

“Going out and kicking a football with your kids...it is something that every dad...should do...or you feel you should do...but if you can't do that...it is the pressure on that” (Transcript of Discussion)

“My main priority at this stage in my life is: I don't want to be a burden to my children...I want them to have their lives...not...rattling around looking after an aging parent and looking after young children at the same time. I don't want that for her” (Transcript of Discussion)

Jurors described a feeling of regret or guilt, associated with having a rare condition, which inevitably impacted on their relationships:

“For those of us with rare diseases, we are having to make decisions based on very very limited information...so you are taking huge risks. Those risks are about your...mental health as well as your physical health, and how that will impact on your family... Through that you might have lost relationships and a job, through the treatment as opposed to the
condition itself... it is guilt, regret, frustration about the lack of research... It is a whole burden you carry with you if it goes wrong” (Transcript of Discussion)

Jurors also discussed the impact on their family as primary care givers:

“My husband has to organise everything for me....so actually most of the impact won’t be on me, it will be on my partner...you do worry about that...so if I was thinking about what is important when I make a decision I would think how they would cope with all of this” (Transcript of Discussion)

Similarly, relationships with friends can be placed under considerable strain by the impact of the condition on people’s way of life. Relationships with close family and friends appeared to have a fundamental link to one’s view of oneself and one’s identity (see below).

Financial implications
There were several different aspects to financial impact including impact on employment status (see below), possible reliance on benefits, reduction in other income, and implications for insurance. It was noted that a condition or treatment option could impact, not only on the patient’s financial circumstances, but also on those of their family or wider society. For example, due to the level and cost of care required:

“If you are going to stop working, what financial assistance will you get” (Transcript of Discussion)

“The people who support me, how will they live financially?” (Reflective Diary)

“Main priority – not to be a burden to the family...don’t want to squander their inheritance” (Reflective Diary)

“Getting travel insurance for me...it becomes prohibitive, trying to find a company that actually understands and will give you travel insurance...so it curtails the whole way you used to live your life” (Transcript of Discussion)

Employment status
Jurors identified the importance of the status which employment (or lack of it) confers on individuals. If their condition – or the treatment – mean they are unable to work, this in turn could have an impact on the way they are viewed within wider society, and the way they view themselves:

“You have lost your employment, and people who have worked all of their life then go onto benefits...to the Daily Mail readers you are a benefit cheat, you are lazy...so you then come down a couple of rungs on the ladder of your own self worth. Lots of people around don’t believe it but when you read it in the media it automatically brings you down” (Transcript of Discussion)

One juror had a negative experience at work, which has led them to ‘cover up’ their illness:

“I am always worried I would be viewed as a sick person...and I would be unemployable...as soon as you are a sick person, that’s it...they see you in a completely different light” (Transcript of Discussion)
Being a patient and taking medication

‘Being a patient’ often entails disruptive and time consuming engagement with the health service, for example, attending medical appointments with GPs and at hospitals or clinics (often some distance from home), organising prescriptions, preparing and taking various forms of medication and/or other treatments. There is a significant journey that a person goes through from when he/she is diagnosed, to becoming a patient. This can change their whole lives. Jurors commented that ‘being a patient’ means they can’t lead a ‘normal’ life:

“Spending your life in a bloody hospital...you have an appointment at 10 and by 12 you might have been seen...being a patient and the amount of time it takes...on average I spend 2 days a week in a hospital....it wrecks your ability to hold down a job” (Transcript of Discussion)

This is closely linked to taking medication:

“One of the big challenges is trying to get my medication regime right...managing your medication becomes really complex and that is a huge stress....the anxiety about getting it wrong...and the way that it changes your life...the logistics are impossible” (Transcript of Discussion)

Relationships with self and identity

The various impacts of the condition can also affect one’s sense of self:

“I often find that as much as family and friends try to understand what it is like to have a chronic illness, they don't, and no amount of explaining will make them understand totally. Being amongst others who I know understood without words, however individual their experiences, was a very positive feeling”

“You can have a concept of yourself, who you are, what you are for and where you are going” (Transcript of Discussion)

“It is how you view yourself and how that affects your relationship with all those people, and how all those people view you....and how it affects their relationship with you” (Transcript of Discussion)

“It’s very interesting...we are consistently being dragged back to the condition and away from the treatment...this is right in a sense...that’s the core that is being operated on by the treatment if you chose to have it....if I took this pill or used this device, what would it do to the self that I have learnt to be with the condition I have got....is it going to change it positively, or make it worse” (Transcript of Discussion)

Sexual function and the ability to have children were also highlighted by the Jury. Such aspects may have different psychological and social effects, which are likely to impact on a person’s sense of self. For example, fertility probably might matter more to younger women and men, than older individuals, but generalisations are difficult, in this as in other areas.

Impact on identity is closely linked to factors described above such as ‘relationship with self’ and ‘being a patient’. Identity relates to the adoption of specific roles within society as well as how one is viewed by others:

“[The] big thing for me is you are suddenly being seen as a patient....you lose your identity. You are seen as disabled, as opposed to a person. That changes your view of yourself” (Transcript of Discussion)
“I do not want to become disabled...and all the negative connotations that go with it...I know there are things I can’t do but actually I want to be positive...and...I do not want to lose my identity as a person. I do not want to be a patient which brings with it a completely different way of life and a different way people look at you...its about the human spirit that shines through...keeping my identity” (Transcript of Discussion)

“For me one of the major worries with my disease is will I cease to be a person?...I will never be who I was” (Reflective Diary)

Jurors recognised that a serious and/or rare condition can also have a positive impact on one’s identity. One juror commented that some patients say the disease has given them more than it has taken away. For example, jurors referred to learning new skills and having new opportunities as a result of their condition. In this light, an identity can be reconstructed, but in a positive way:

“Analogy of the onion....you are adding layers” (Transcript of Discussion)

Autonomy/control
Jurors were concerned with the amount of autonomy and control they maintained in their lives, to live independently, be less of a burden on family members and make their own decisions about their healthcare.

There were many other psychosocial aspects that were identified by the jurors. These are listed and described in Appendix vii.

Further Considerations
This section provides a useful insight into what is important to patients with rare and/or serious conditions. It offers a helpful foundation for the further development of a practical toolkit for regulators and others who influence the development and accessibility of new medicines. In particular, it reminds decision-makers of the multiplicity of factors which should be considered when evaluating the benefits and risk of new medicines.
Recommendation Two | Regulators should be more permissive for people with rare and/or serious conditions

Patients affected by serious and/or rare conditions often have few or no effective treatments available to them. Because of their unique circumstances, such patients may well be willing to take greater risks than the system currently allows, and should be given that choice. Key questions for regulators in their marketing authorisation decisions are ‘do the advantages outweigh the disadvantages of taking the medicine?’ and ‘are the side effects acceptable?’ In the case of serious and/or rare conditions, regulators should lower the threshold of what they consider to be acceptably safe, giving more weight to psychosocial benefits and involving patients in the decision making.

Are Patients with Rare and/or Serious Conditions Willing to take Greater Risks?

Whether patients with rare and/or serious conditions are willing to take greater risks than the current system allows is a complex question. The case study discussions and the voting exercises were a good indicator of the types and levels of risks jurors might ‘trade in’ for a potential benefit:

“The case study methodology is a productive way of identifying and clarifying our views on the risks and benefits involved in using new drugs/treatments for rare conditions, from which we should be able to develop a more general set of recommendations/guidelines reflecting patients perspectives on the balancing of risks and benefits in the regulatory process” (Reflective Diary)

“If you look at all the case studies we have done, I imagine that in most of them it would have been a different decision made [by regulators]” (Transcript of discussion)

However, the jurors recognised the fluidity of their responses in relation to the case studies within the group and over time:

“...the discussion of case studies and debate around decision making....the breadth of opinion and expectations expressed” (November Questionnaire)

“...changing my mind several times in the face of the same scenario” (November Questionnaire)

The six case studies are summarised below. For a more detailed version of the case studies, including information about the discussions they were designed to provoke, please refer to Appendix iv.

Case Study One: A very serious, rare and genetic condition affecting brain development in young children. A lifelong gene therapy has been developed, and although effective in many cases it can cause chronic kidney failure and deafness.

Case Study Two: A common neurological condition causing dementia in older adults. A stem cell treatment has been withdrawn from the market because of its associated risks with brain cancer.

Case Study Three: A relatively unknown condition, which appears to develop in teenagers and young adults causing chronic pain, fatigue and depression. A treatment is available off label, but has shown to cause psychotic disorders.

Case Study Four: A rare breast and ovarian cancer. A new hormone treatment has been developed, which unlike its alternatives does not affect fertility. However, it has been shown to have permanent effects on behaviour.
Case Study Five: An unpredictable autoimmune condition affecting women’s central nervous system. An oral treatment was not licensed due to its links with cancer.

Case Study Six: A very common condition occurring when there is a lack of insulin produced in the body, causing a range of long term medical complications. A treatment has been withdrawn because of concerns it has links to heart disease.

Jurors read each case study, asked questions to clarify understanding, and then discussed the risks and benefits as a group. The Jury is most grateful to Dr Marie-Christine Bielsky for her advice and clarification on clinical symptoms and terminology throughout their discussions. At the end of each discussion, jurors were asked if they thought the treatment should be available to patients. The results of the voting are listed below:

Table 3: Case Study Votes

<table>
<thead>
<tr>
<th>Case Study</th>
<th>Yes</th>
<th>No</th>
<th>Don’t Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>10</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Two</td>
<td>11</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Three</td>
<td>10</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Four</td>
<td>7</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Five</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Six</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

The voting shows that in cases one, two and three, an overwhelming majority of jurors felt the treatment should be available to patients. In cases one and two, there were no jurors who voted against making the treatment available:

“For me the cases felt quite clear cut in the sense that...with autoimmune diseases....a lot of our conditions and drugs increase our cancer rates anyway. I would at least want the opportunity to decide for myself” (Reflective Diary)

“I voted yes to keep the drug because the illness they already had, had an increased risk of heart problems, it wasn’t presenting a new risk, and the overall risk was small. Again, it would be back to patient choice and patient information, which is really feeling like a crucial point” (Reflective Diary)

Towards the end of the process, jurors were asked to state whether they believed that they were willing to take greater risks than the licensing system currently allows. To respond, jurors were encouraged to reflect on what they had learnt during the Citizens’ Jury process. 10 of the jurors felt they were willing to take greater risks.

Table 4: Votes - Are you willing to take greater risks than the system currently allows you to?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Don’t Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients with rare conditions are likely to take medicines off label, if they are faced with no alternative option. Off label medicines have been licensed for a different use in a different patient population. Therefore, the efficacy and safety of a treatment which is being used off label, is largely unknown. Taking off label treatments is an example of how some patients are willing to take greater risks than those considered acceptable by regulatory bodies.
A useful analogy was made in one session, which highlights why some individuals may be willing to take greater risks than others. They were asked an apparently rhetorical question, designed to highlight unacceptable risks: “Would you jump out of a plane if you knew that there was a 1 in 10 chance that your parachute would not open and you would die?” The jurors’ response, however, was quite different to that intended by the questioner:

“Well, if that plane was heading towards a cliff, then yes I would”.

It was suggested that in some cases, if you had nothing to lose, you might be willing to be a ‘guinea pig’ and try risky treatments:

“For anyone with a terminal illness....such as myself, I would even take a 1 in 3 chance, or 1 in 2 chance that a drug could cause harm to [me]...versus it will halt the progression of your disease. If there is a last chance for you to fend off a terminal illness, surely the patients (not regulatory bodies) should decide if they want to take the risks associated with it” (Reflective Diary)

Jurors offered a parental/carer perspective in relation to the issue. One juror stated that although they would be willing to take greater risks, they would find it much harder to accept such levels of risk on behalf of their child. Jurors expressed their concern at the psychological burden associated with making such decisions on behalf of others. This is explored further in relation to recommendation four.

Jurors agreed that in the current system, there was too much focus on risks and side effects, and not enough of a focus on the potential benefits of treatments. For example, in the post-marketing authorisation process, patients are encouraged to report side effects through the yellow card system. Jurors wondered why there wasn’t a similar process to report the benefits of medicines.

“The calculus should still be approved if benefits outweigh the risks. The benefits should be wider than a clinical/medical perspective and also include psychological and social benefits....ability to work (paid or unpaid), ability to socialise, maintain relationships, contribute, quality of life, well being” (Reflective Diary)

A fundamental argument made by one of the advocate witnesses was that clinicians should ‘do no harm’, and that the system is there to protect patients from harm. The jurors, however, found the concept of ‘do no harm’ to be idealistic. In their view, risk is unavoidable and in many cases, choosing to do nothing, or something less risky causes harm:

“Every medication has side effects...whatever you are prescribing...you do harm as a doctor to get a better good...it’s about doing the least possible harm to get the best possible outcome” (Transcript of Discussion)

“The clinicians, using their “Do No Harm” pledge, approach regulation and administration of drugs to prolong life...the patient is more concerned with the quality of life" (Reflective Diary)

This did not necessarily translate in to a recommendation that regulators should be more permissive in their practice. There were some interesting discussions about the individual and the wider community. In the case study discussions jurors considered the implications of licensing a medicine from an individual, family, community and societal focus. For example, the cost implications of taking a treatment or not taking a treatment were often discussed in relation to the family and wider society. One juror noted that they had been challenged in their thinking around informed consent and the “common good”: 
New Medicines for Serious Conditions: Weighing the Risks and Benefits

“What side of paternalism versus anarchy you sit...whether you look at the community/society or the individual...that changes your risk benefit analysis...the minute we started looking at...society, we started becoming a lot more risk averse....as patients we tend to look at the individual” (Transcript of Discussion)

In relation to societal benefits, altruism featured in the discussions. Jurors felt that patients might be willing to take greater risks, for the good of others. If someone has nothing to lose, and in the longer term it can benefit others (by generating data on benefits and risks), they might favour a risky treatment. It was recognised that people don’t normally talk about this. Jurors spoke of the next generation and benefits to them, particularly in relation to genetic conditions.

“One of the benefits is the longer a drug is used...the more we learn about how it operates” (Transcript of Discussion)

Should Regulators be More Permissive?
After considerable discussion amongst themselves, and having considered the evidence of the witnesses, the jurors were asked whether they thought the regulator should be more permissive.

The term permissive is used widely in this report. Permissive means to be more tolerant or lenient. In the context of this report and the jurors’ findings, a permissive regulatory body is not one that should be more lax in their scientific assessment of new medicines. A more permissive regime would give weight to psychosocial considerations and involve patients in their decision making. In doing so, the risk/benefit calculus would permit the licensing of more new medicines for patients with serious and/or rare conditions.

The question was asked of different types of conditions. The results are shown in the table below:

<table>
<thead>
<tr>
<th>Type of Condition</th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious</td>
<td>8</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Rare and serious</td>
<td>10</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Genetic and serious</td>
<td>9</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Immediately life threatening</td>
<td>10</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>All other conditions</td>
<td>1</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

The voting indicates that jurors felt certain conditions (e.g. serious, immediately life threatening and rare) were ‘special cases’. In these circumstances, patients would benefit from a more permissive regime. The majority voted against a more permissive regime for more general conditions, which are less serious. As indicated at the end of the report, it would be worthwhile exploring this recommendation with other patients who experience less serious and more common conditions than those of the jurors.

In summary, jurors argued for regulators to consider a different risk/benefit calculus for new medicines for rare and/or serious conditions. As a result, more new medicines could reach the marketing authorisation stage, be licensed and be made available to patients. The utility of the checklist (at recommendation one), can assist regulators in their decision making, and potentially lead to a more appropriate risk/benefit calculus, which reflects patient preferences.
Recommendation Three | Patients should be more involved from setting the research agenda, to post-marketing authorisation decisions

Patients’ experiences and preferences should be represented in all the processes which lead to the development of new medicines, from the initial determination of research priorities, right through to the regulatory processes which grant and remove marketing authorisation. This would ensure that the benefits which really matter to patients, and the levels of risk they are prepared to tolerate are considered in the decisions. This is particularly important for serious and/or rare conditions, where the stakes are so high. Patient representatives (such as patient group members) should be supported to be joint decision makers, alongside clinical experts, throughout the process.

Current Experiences and Concerns
Jurors argued that the current regulatory process is too clinically driven. Outcomes are measured in clinical terms, by clinical experts. The jurors felt they could add value to the decision making process, by highlighting associated psychosocial factors.

“The decision makers are making ill informed, narrow minded decisions...the decisions that are made have a very cold and clinical view...they don't look at the softer side....all the things we have been discussing” (Transcript of jurors debate session)

“Very very strong feeling...clearly, patients are underrepresented in the process...their views are not sufficiently taken into consideration... the views are...medical... [and] scientific, rather than the patients....attitudes, behaviours, wants, needs” (Transcript of discussion)

Some jurors were concerned about the ways in which patients were currently involved in decision making. Some jurors had personal experience of being ‘involved’. If one patient partakes in a group or committee meeting, their views might be taken as representative of all patients. Consequently, in such cases people trust and rely on the knowledge and judgement of just one patient. This places enormous pressure on that person. As illustrated from the Citizens’ Jury process, patients’ views differ. However, there are not always processes in place to capture the range of views and perspectives from patients.

Others in the group felt that some involvement by patients was just tokenistic or ‘ticking a box’. Their views and commitment to the process are not valued. For example, patient representatives are usually unpaid, and they may not be voting members in the decision making:

“The patient role currently is a tokenism, and not clearly defined...are they representing all patients on the group?” (Reflective Diary)

Lastly, it was felt that patients often do not have enough support to become involved. There are many patients and patient groups who want greater involved, but don’t know how to or don’t have the support they need to do so. For example, many jurors had not heard of the MHRA or the Yellow Card
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reporting programme before becoming jurors. They felt this was indicative of the lack of commitment from regulators to involve patients in a meaningful way:

“Nobody goes back to the GP...to tell them it didn't work...there must be a huge amount of drugs out there that end up in the bin... why isn't there a public campaign... to feedback...surely things would be picked up a lot earlier” (Transcript of Discussion)

“It’s such a complicated process it automatically alienates patients who want to be involved. Also, there is a lack of knowledge out there” (Reflective Diary)

One juror argued the need for an evaluation of current patient involvement in the regulatory system:

“I'd like to see a recommendation that there should be a systematic and rigorous evaluation of the current system of patient participation...in the regulatory process and especially in the balancing of risks and benefits in relation to new medicines. How effective is the current system? Does it adequately and accurately represent patients' views? How might the system be improved?” (Reflective Diary)

Why Should Patients be Involved?

Jurors argued that any decisions affecting them should involve them:

“unless you know what you are going through, you cannot be paternalistic and make a decision for that person if they have the ability, no matter what age they are, to make decisions for themselves. You can support them, enable them...empower them with the information available, make sure they understand the risks and the benefits, but ultimately it has to be their decision” (Transcript of Discussion)

“Why do we [society] find it hard to accept that people can make their own decisions when in ill health?” (Reflective Diary)

An analogy was made by one of the jurors: tobacco and alcohol is available to society even though they cause significant harm. Regulators are happy for individuals to make some choices for themselves.

Jurors noted that patients with rare diseases are more likely to be informed, expert patients, who would devote time and effort to be involved in research and decisions making. Since current regulations were established, the age of the internet has revolutionised patients' access to medical information and allowed them to become experts in their own conditions in a way that was not possible even a few years ago.

As mentioned earlier in the report, many patients with serious and/or rare conditions take off label medication. Currently, there is no formal mechanism for the collation of data on the effectiveness of the medication use in these groups. Patients could play a valuable role in contributing to the knowledge of the risks and benefits of off label medicines.

As people with experience of the condition and the way it affects people in everyday life, patients can bring a new perspective to the decision making process:

“I have an example...we have worked with professionals...to understand what patients’ priorities were....and [they] were quite shocked about their views about what should be researched and what patients think should be researched” (Transcript of Discussion)
“Greater and more effective patient representation would strengthen and enrich the data on which risk/benefit judgements are made....such voices...in the process would reduce the essentially conservative and risk averse bias of current regulators...it is particularly true in the case of rare inherited conditions” (Reflective Diary)

Jurors argued that at present, the balance between patient experts and clinical experts in regulatory processes was unacceptable and that regulatory decisions should be aligned with patient and societal preferences (see recommendation one for more detail).

How Should Patients be Involved?

“How reasonable people these days... think that consulting patients about their views about drugs is a good thing... the real interest...is not whether or not we should involve patients...that’s probably a no brainer...but rather how you actually do that...how you involve patients in practical ways” (Transcript of Discussion)

Jurors identified different levels of involvement, ranging from consultation after the decision has already been made, to the patients making the decision themselves. These levels were based upon their own experiences of patient involvement. Some of the jurors’ had prior knowledge of Arnstein’s Ladder of Participation, which also inspired the levels in the table below. Jurors discussed patient involvement across all stages of the research and regulatory process, from setting the research agenda to post-marketing authorisation decision making and voted on what they felt would be the most appropriate level of patient involvement at each stage:

Table 6: Votes: Levels of Involvement Across Stages of Research and Regulation

<table>
<thead>
<tr>
<th>Level of involvement</th>
<th>Setting the Research Agenda (pharma and commercial research)</th>
<th>Setting the Research Agenda (public research)</th>
<th>Clinical Trial Research Design</th>
<th>Marketing Authorisation Decisions</th>
<th>Post-Marketing Authorisation Decisions (withdrawal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Decides and takes responsibility for decision</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Joint Decision Making (e.g. a significant number of patients around the table voting in a collective decision)</td>
<td>6</td>
<td>11</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Involvement (e.g. Patients are actively involved in the discussion)</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Consult Before deciding (e.g. patients are not in the room or they have a tokenistic presence, but a serious process of consultation has taken place)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Consult After deciding</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
In the main, jurors would argue that patients should be involved in joint decision making. In practice, this means that patients should be voting members on decision making groups and panels within the research and regulatory system. This would ensure that their opinion is valued and not just tokenistic:

“I would certainly go for the second level down, the joint representation...which would mean... that there is equal representation between patients bringing their experience, and the scientific committee bringing their knowledge” (Transcript of Discussion)

“We are passive recipients of what the pharmaceuticals think is right for them to develop...it is not about patient preferences...it is so important to start right at that end, with patients being involved in deciding what is important to them, in terms of research for the future” (Transcript of Discussion)

Practical support should be provided, to encourage and establish ways for people to get involved in this manner. The detail outlined in recommendation one helps illustrate where patients’ input can add value to the current decision making processes. The final recommendation offers support to patients making decisions about new medicines, in partnership with their doctors.
Recommendation Four | Patients should be supported in their decision making

Patients wish to decide which medicines they take, reflecting their individual circumstances, beliefs and preferences. The result of Recommendations 1-3 above will be that patients with serious and/or rare conditions will in future be faced with more choices, as more medicines are made available to them. Such decision-making is challenging, but possible for most patients. But people need help, from their clinical team, and from a variety of other sources, including relevant, credible and understandable information about the potential risks and benefits of the new medicines. Jurors welcomed work to improve the way in which such risks and benefits are communicated, and also generated a list of questions to help guide patients when deciding on their own treatment options. Tools such as these should be used by clinicians and patients to aid a shared decision making or a partnership approach to prescribing practices.

Jurors recognised that there is variation in patients’ desire to make decisions about medical treatment. While many people with serious and/or rare conditions actively research new medicines and seek involvement in decision making activities, at the other end of the spectrum, some patients prefer to leave the decision making to the doctors. In any case, it was recognised that doctors faced very difficult decisions:

“I wouldn’t like to be the doctor or physician who makes the decision. [We are] asking them to take massive risks on their behalf”. (Transcript of Discussion)

“The choices I have made now, my consultant feels really guilty... about the medication regime I’m on...I say don’t be so paternalistic, I made the decision...I know the risks I am facing....that is my choice” (Transcript of Discussion)

There is often not enough information or evidence to help support the decision making process at a prescribing level. This is particularly true for unlicensed or off label medicines. In such cases, patients (and clinicians) are required to make informed decisions based on very limited evidence. In addition, patients might want to be as informed and involved as possible in the decisions, but won’t know the right questions to ask.

Bearing these differences and difficulties in mind, jurors were keen to highlight the importance of informed consent. This was a re-occurring theme across the weekend events. Informed consent was discussed in terms of vulnerable people (e.g. people with dementia) and children. The law states that children under the age of 16 cannot consent to or refuse medical treatment. However, for those aged 16-18, the law is less clear. The group discussed in some detail what level of control and responsibility a parent should have over their child’s decision making:

“Children and probably teenagers don’t have the long term foresight to decide whether to take a potentially dangerous drug... because they don’t have the perspective...” (Transcript of Discussion)

“I feel very strongly about this....it kind of frightens me...there are children as young as three who are carers and children of six who run households...the whole idea that children are not...able to make their own decisions...I disagree...you have to have an outlook that starts with the view that they are [capable]” (Transcript of Discussion)

“Not always the case that parents know best...it’s their body and their life” (Transcript of Discussion)
A Checklist for Patients

Jurors recognised that patients need support to make an informed decision or give consent. The jurors developed a list of questions, or a toolkit, to assist patients making decisions.

There were a number of other important factors considered by the jurors that were neither biomedical nor psychosocial. These have been discussed below, and incorporated into the patient checklist.

Information to make an informed decision

As discussed above, patients should be sure that they have all of the information available to them before they make a decision. They should ensure that this information is credible and trustworthy. Not all data will be communicated in an effective way, and clinicians and patients should work together to understand the information.

“The information needs to answer all of the questions we are asking” (Transcript of Discussion)

“Although I believe everyone has the right to make their own decisions about treatments, we can only do that if we are presented the facts properly without the figures being spun” (Reflective Diary)

“It’s so hard to know who to trust (which bodies, which articles)” (Reflective Diary)

High quality coordinated care

Patients may want to consider the type of care they will receive in the future as a result of the medication. This may be care and support from the NHS or other organizations such as social services and charities.

Alternative treatments

Jurors placed great importance on the availability of possible (or comparable) alternative treatments, now and in the future. The jurors learnt that if an alternative treatment is licensed already, this is taken into account in regulatory decisions. However, medicines under development are not taken in to account. A further consideration of jurors is the availability of clinical trials, and the potential to be involved in researching new and developing alternatives. Patients may also want to consider whether there are any unlicensed or off label treatments available to them.

In case study discussions, jurors felt that their decisions would be affected by the availability of alternative treatments. They may ‘grab’ a risky treatment, if there were no alternatives in the pipeline at all. Or, if there was a possibility something more effective, or less risky were available in the near future they might chose to wait. For example, patients might chose to wait 6 months (if something better could be in the pipeline), but not 5 years!

“As a parent of a child with this disease, I would want to know what sort of research was ongoing so that I could weigh up the benefits of this verses possible further research which provides better medication, less toxic medication, that doesn’t destroy your kidneys or hearing. Or, I’d want to know what research was going on to ensure that the hearing [loss] wasn’t permanent”. (Transcript of Discussion)
“One of the challenges for anyone with a rare disease... is that so little research is directed towards it...so that would also affect any decision you make...if it’s the only research going on you are going to grab what comes out of this research” (Transcript of Discussion)

“That is a really important question...if there is nothing else in the pipeline then that may be my only choice. [But] if something is going through a trial...I might wait six months.” (Transcript of Discussion)
Figure 2: A Checklist for Patients

Understanding the Science
- What impact will it have on the following: Mobility, Cognitive, Pain, Sensory, Psychological, Fertility?
- How effective is the treatment?
- Are the side effects treatable?
- How long will the side effects last?
- How severe are the side effects?
- How credible is the data?

Impact on you
- How will it affect my anxiety levels?
- How will it impact on ‘being a patient’?
- How will it impact on my relationship with my self and my identity?
- How will it affect the autonomy and control I have?

Impact on you and your family
- How will it impact my relationship with my immediate family?
- How will it impact on my relationship with my friends?
- How will it impact my family financially?

Impact on you and Society
- What would the wider financial implications be?
- How might it affect my employment status?

Other things you might want to consider:
- What role do I want to play and what support do I need to make a decision?
- Do I have all of the information available to me to make an informed decision?
- Will I get the high quality coordinated care I need?
- How person centred will my care be?
- Are there alternative options available? (What are they, and when are they available?)
Conclusion and opportunities for further research

In conclusion, the Citizens’ Jury offered a valuable insight into how patients (and family members) affected by serious and/or rare diseases perceive risks and benefits of new medicines. Findings demonstrated that jurors are willing to take great risks for the potential cure or improvement of their condition, and recommend that regulators involve them in their decisions, allowing for the more appropriate development and licensing of medicines for patients with rare and/or serious conditions. Lastly, jurors used their findings to produce a ‘patient checklist’, to support individuals in their own assessment of risks and benefits.

“It was an enjoyable and enlightening experience, which I’m very glad to have been part of...[I] hope that it turns out to be as influential as it deserves to be”

During the course of their deliberations, the jurors identified several areas where they felt strongly that further work was still needed. They hoped that in the future there will be opportunities in research to explore the following:

- A review of patient involvement within the current research and regulatory system – The jurors recommended that patients are involved as joint decision makers. There is an opportunity to explore and develop this concept further. There was some uncertainty about the current level of involvement and associated value of it. Jurors suggested a full review should be undertaken into how patients are currently involved, and what impact this has on decisions made.

- The further development of a toolkit – Recommendation one includes a checklist for regulators, which is based on the preferences of 12 jurors with rare and/or serious conditions. It provides a useful foundation of new knowledge, but has the potential to be developed much further. For example: How do these preferences compare with other patients with rare and/or serious conditions? How can regulators, and others use the tool effectively?

- Other patients – The findings in this report were based on a jury of 12 individuals affected by rare and/or serious conditions. It would be interesting to explore the findings on a bigger scale: Would other patients with rare and/or serious illnesses agree with the jurors verdict? How do these recommendations fit with all patients, or patients with less serious and/or common conditions?

- A European perspective – Increasingly, regulatory decisions are being made on a European wide basis. For this reason it would be interesting to explore how the findings compare with the views of non-UK patients.

- Cost of medicines – The cost effectiveness of medicines did not feature on the agenda, as the focus was on risks and benefits. Regulators do not include cost in their assessment. However, this was an issue for jurors. Some jurors had experience of being denied a potentially effective medicine on the grounds of cost.
Appendix I

Steering Group members

Representatives of Regulatory Bodies
Dr Gopalan Narayanan; Medical Assessor, Biologics and Biotechnology Unit, Medicines and Healthcare products Regulatory Agency (MHRA)
Professor Peter Littlejohns; Clinical and Public Health Director, National Institute for Health and Clinical Excellence
Colin Pavelin; Head of Genetics and Advanced Therapies, Health Science and Bioethics Division, Department of Health

Patient Representatives
Dr Caitlin Palframan; Policy Manager/Laura Shalev Greene, Involvement and CAN Manager, Breakthrough Breast Cancer
Chris Friend; Chair of Trustees, Genetic Alliance UK
Roger Wilson; Founder, Sarcoma UK
Rod Mitchell; Vice Chairman, Crohn's in Childhood Research Association

Clinicians
Professor John Dodge; Consultant Paediatrician and Professor of Child Health, Singleton Hospital, Swansea
Professor Ros Eeles; Professor of Oncogenetics, The Institute of Cancer Research and Honorary Consultant in Clinical Oncology & Cancer Genetics Royal Marsden NHS Foundation Trust

Pharmaceutical Industry representatives
A “roving” membership, with two representatives attending each meeting:
Ken O’Reilly; Director of Patient Advocacy, Shire
Liz Swain; Director, Pharmacovigilance Advocacy and Policy, GlaxoSmithKline
Silvia Matile-Steiner; Head of Government Affairs, Roche (Until August 2011. Nathalie Steiger since August 2011)
Warren Cowell; HTA Policy Analysis and Strategy, Pfizer

Public Engagement Specialists
Dr Tom Ziessen; Public Engagement Adviser, The Wellcome Trust / Amy Sanders, Special Projects, Public Engagement, The Wellcome Trust
Dr Shirley McIver; Senior Fellow, Health Services Management Centre, University of Birmingham
Appendix II

A profile of all survey respondents

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| Do you have a close family member or do you care for someone who is affected by a chronic or long-term medical condition? | Yes: 40 | No: 32 |
| Do you regard this condition as severe? | Yes: 35 | No: 2 | Don't Know: 3 |
| Do you regard this condition as rare? | Yes: 31 | No: 8 | Don't Know: 1 |
| Do you regard this condition as genetic? | Yes: 29 | No: 6 | Don't Know: 5 |
Appendix III

Citizens’ Jury Programme

Friday 4th November

15:00 Welcome Session for Jurors
16:00 Introduction to Case Study One and Discussion
17:00 Break
17:15 Two Advocate Presentations
18:30 Finish
18:45 Jurors to re-group in bar (optional)
19:30 Dinner and Discussion (optional)

Saturday 5th November

9:00 Juror Reflections
9:15 Introduction to Case Studies 2-5 and Discussion
11:15 Break and Lunch
12:45 Witness Presentation | Drug Development and Nature of Scientific Evidence
14:15 Break
14:30 Witness Presentation | The Role of the Regulator
15:30 Finish
18:45 Jurors to re-group in bar (optional)
19:30 Dinner and Discussion (optional)

Sunday 6th November

9:00 Juror Reflections
9:30 Re-visiting the Case Studies
10:30 Discussion Space
10:45 Break
11:30 Witness Presentation | The Role of the Patient
12:30 Discussion Space
13:00 Finish and Lunch
Friday 2nd December

15:00  Welcome Back Session for Jurors
15:30  Witness Presentation | The Role of the Prescriber and Prescribing Difficulties
16:45  Break
17:00  Case Studies Discussion | Cases Four and Five
17:45  Focusing on Conclusions and Recommendations | A First Cut
18:30  Finish
19:30  Dinner and Discussion

Saturday 3rd December

09:00  Re-focusing on Conclusions and Recommendations | Jurors' Reflections and Revisions
10:45  Break
11:15  Advocate Presentation | Making A Case for Change
11:25  Advocate Presentation | Defending the Status Quo
11:35  Preparing for the Jurors' Debate | Coached Group Work
12:00  Lunch
12:45  Group Presentations and Jurors' Debate
14:15  Break
14:30  Making Sense of the Discussion
15:30  Finish
19:30  Dinner and Discussion

Sunday 4th December

09:00  Finalising Conclusions and Recommendations | How do patients perceive the risks and benefits of new medicines?
10:45  Break
11:15  Finalising Conclusions and Recommendations | How should these decisions be made, and who should make them?
13:00  Conclude and Lunch
Appendix IV

The Case Studies considered by the Jury

Case Study One
A very serious, rare and genetic condition affecting brain development in young children. A lifelong gene therapy has been developed, and although effective in many cases it can cause chronic kidney failure and deafness.

Condition
An uncommon (1 in 20,000 children), serious disorder which begins in childhood (usually between the ages of 2 and 5).

It affects the development of the brain and central nervous system, severely damaging the child’s mental functioning and muscle control/movement. Once the child develops the condition, they would be expected to deteriorate quite rapidly over a period of 2-4 years. If a child develops the condition, they will live with severe cognitive and motor impairment. With severe motor impairment, increased mortality rates are expected.

The condition is genetic, but because it is inherited as an autosomal recessive trait, the disease may not be present in the parents (but they may be carriers of the gene). This means that many healthy individuals in the population will be unaffected carriers, with a single altered copy of the gene as well as an intact copy. Someone becomes affected if both parents are carriers of the abnormal gene and if both parents transmit the altered copy to the same child. When both parents are carriers, there is a 25% chance of this happening (of a child inheriting both abnormal genes and therefore developing the disease). However, there is also a 25% chance that the child would inherit both normal genes and a 50% chance of a child inheriting only one abnormal gene, in which case the child would become a carrier, like the parents.

Treatment
A treatment for the disorder has been developed and has been shown in clinical trials to have a helpful effect, if started before there are any signs of the disease. If licensed, the treatment is to be used on younger affected siblings of definitely affected children.

The treatment may work in close to half of cases, depending on the particular type of gene mutation. There are different types of gene mutations, one of which is called a ‘nonsense’ mutation. The treatment works by giving a drug which suppresses the ‘nonsense’ mutation. So, in order for patients to benefit from the treatment, we would need to identify the mutation in affected children. Half of the affected children would not be suitable for the treatment trial because they would have the wrong type of mutation.
For those families in which the mutation was appropriate, there would be the choice to be made of whether or not to treat any subsequent child born with the same gene mutation. The treatment would be given intravenously, every three weeks. It would be a life-long treatment.

**Side Effects**
The efficacy and safety of the treatment is not guaranteed, despite the encouraging results in the animal research and the clinical trials. The research so far shows that high doses of the drug are very effective. Of those given high doses, 75% did not go on to develop the condition. However, in approximately 50% of these successful cases, the treatment has shown to cause chronic kidney failure and/or lead to irreversible deafness. Lower doses, which do not cause these side effects, have been effective in 30% of cases.

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**Questions:**
What do you consider the benefits to be in this case?
What would you consider to be the risks in this case?
Should this treatment be available to patients?
What new information might influence or change your decision?

What difference does the age of the patient make to your perceptions of risks and benefits? (i.e. what if the patient was an adult, and the onset of the disease could be prevented at a later age?)
What difference does the way the medicine is administered make to your perceptions of risks and benefits? (i.e. what if the drug was to be given to the child every three weeks for a year only?)
Which dose should be available to patients?
Case Study Two
A common neurological condition causing dementia in older adults. A stem cell treatment has been withdrawn from the market because of its associated risks with brain cancer.

Condition
A relatively common disease (affecting 1 in 500 individuals), which causes gradual deterioration of the central nervous system. The condition usually presents at about 45-50 years of age and causes dementia. The disease occurs when cells die in an area of the brain called the ‘basal ganglia’. This part of the brain affects a variety of functions, including motor control, reward/motivation learning and procedural/habit learning.

The death of these cells is caused when clumps of toxic protein build up. Many areas of the brain are affected, including a person’s memory, attention, perceptual awareness, thought, language and consciousness.

Treatment
A stem cell treatment has been developed, licensed and has been available to treat the condition for the past 3 years. Stem cell treatment works by introducing new cells into damaged tissue in order to treat disease or injury. Adult stem cells are manipulated to become neural cells and are then implanted into the brain by a surgical injection. A neural cell can process and transmit information by electrical and chemical signalling.

Over the past 3 years, since license, the treatment has been given to approximately 5,000 individuals. The precise efficacy of the treatment is difficult to ascertain, as the course of the debilitating disease varies between individuals. However, follow up clinical examination, psychiatric assessment, and neuropsychological assessment presents positive results. In 60% of cases after the treatment the disease has not continued to progress at the expected rate and in 20% of cases there has been no deterioration at all.

Side Effects
Although the efficacy was not certain from the clinical trial data, there was little evidence of any negative side effects. In the past few months however, new evidence has come to light, suggesting that the manipulation of the stem cells may pose a risk of tumour development once the cells are implanted in the patient’s brain. So far, of those 300 individuals treated in clinical trials (treated 3-7 years ago), there has been a 5% excess mortality rate. A high proportion of those individuals died due to cancerous tumours in the brain. Currently, all individuals who have had the treatment are being assessed for tumour development. The treatment’s licence has been withdrawn and can no longer be prescribed.
Case Study Three
A relatively unknown condition, which appears to develop in teenagers and young adults causing chronic pain, fatigue and depression. A treatment is available off label, but has shown to cause psychotic disorders.

Condition
This is a condition which predominantly develops in teenagers and young adults. It is very difficult to diagnose the condition, and although initially thought to be rare, the actual occurrence of the condition may be significantly greater.

Those who have the illness suffer from chronic pain, fatigue and depression. Little is known about the cause. Currently, generic pain medication and antidepressants are prescribed to affected individuals, although these are only symptomatic treatments. Those who develop the condition are set to rely on the medication for their whole lives. Many never find the right combinations of medicines and feel unable to cope with their symptoms and day to day life. Suicide rates are particularly high for those diagnosed with the condition.

Treatment
There is a medicine that had been available off label to patients for the past 5 years. The treatment is licensed. Usually, the drug is taken for two years. After taking the drug for a couple of years, some patients have come off the drug and are still living completely symptom free. In this period, suicide rates have also decreased.

Side Effects
However, some patients have become addicted and have not been able to stop taking the drug after the recommended time. The longer term effects and impact are unknown at this point, although there is a suggestion that the drug is linked to psychotic disorders such as schizophrenia. Due to the nature of the condition, and the difficulties with its diagnosis, there is not yet any reliable data about these side effects.
Case Study Four

A rare breast and ovarian cancer. A new hormone treatment has been developed, which unlike its alternatives does not affect fertility. However, it has been shown have permanent effects on behaviour.

Condition

A rare form of cancer, simultaneously affecting the breast and the ovaries. The cancer typically affects women under the age of 30. Surgery and chemotherapy has shown to be highly effective in treating many different types of ovarian and breast cancer. However, this decreases the woman’s fertility significantly, and can have a huge psychological impact. This form of cancer is hereditary, and those with the gene mutation are highly likely to develop the two forms of cancer.

Treatment

A new hormone treatment has been developed, and has shown to be an equally effective alternative to the more common treatment of surgery and chemotherapy. Unlike others, the new treatment would does not affect fertility. The patient would be required to take high doses of the treatment orally twice a day, over a period of 6 months. It works to reduce or eliminate the cancerous cells. Following this, patients would be required to have lifelong prophylactic treatment (lower doses of the treatment) to prevent cancer from coming back. The treatment has just finished in the third phase of clinical trials and is due to apply for a license.

Side Effects

However, side effects of the new hormone treatment have become apparent during trials. Of the patients trialling the new treatment, 30% (250 participants) experienced behaviour change of varying degrees. Behaviour change reported ranged from mild anxiety and panic attacks (in 180 participants), through to severe violent and psychotic symptoms (in 70 participants). Although in half of these cases the behaviour change was relatively temporary (only during high dose 6 month period), the other half have reported more permanent effects, even once they have stopped taking the medication.

Dimensions Covered:

- Benefits and Success
  - Cures Condition
  - Incidence of Success – High

- Side Effects and Risks
  - Disabling Side Effect
    - Nature of Disabling Side Effect – Psychological
    - Extent of Side Effect - Uncertainty about reversibility and duration
    - Incidence of Side Effect - Medium

- Other
  - Alternatives Available
  - When? Life Long
  - How? Orally
  - Marketing Authorisation Stage

Questions:

- What do you consider the benefits to be in this case?
- What would you consider to be the risks in this case?
- Should this treatment be available to patients?
- What new information might influence or change your decision?

How does the way you receive the treatment influence your perception of the risks and benefits? (i.e Surgery/Lifelong/Oral Medication)

How does the alternative option compare to the new treatment?

How might your perception of the risks and benefits be influenced by personal or social factors?
Case Study Five
An unpredictable autoimmune condition affecting women’s central nervous system. An oral treatment was not licensed due to its links with cancer.

Condition
An unpredictable autoimmune condition which is not known to be genetic. The condition affects the central nervous system, as well as causing severe arthritis. Affecting over 100,000 people in the UK, is most commonly diagnosed in women between the ages of 20 and 40. There is currently no cure for the condition.

Treatment
An oral drug that has recently completed phase 3 of clinical trials, with individuals affected by the relapsing, remitting version of the condition. Traditionally a cancer drug, it works by killing immune cells (which are involved in the damage caused by the condition).

Commonly, those with the condition suffer periods of time (days, weeks or months) when the severity of their symptoms increase drastically. Those taking the drug (1000 patients to date) experienced almost 60% reduction in relapse rates per year compared with people taking the placebo treatment. Those taking the drug were also 50% less likely to experience a relapse during the course of the trial. There was also a 30% reduction in disability progression (measured over the course of 12 months). For many participants, this meant that their condition was not deteriorating at the same rate as it had previously.

Side Effects
Last year regulators did not license the drug, as the benefits were not considered to outweigh the risks. Severe lymphopenia (a reduction in the number of circulating immune cells) is the only serious side effect reported to date, which can leave patients vulnerable to infections; there were slightly more serious infections in the patients taking the drug in the clinical trials. There were also 34 cases of breast cancer in those taking the drug. Approximate cases per 1000 of the general female population in the UK are 6.

Questions:
What do you consider the benefits to be in this case?
What would you consider to be the risks in this case?
Should this treatment be available to patients?
What new information might influence or change your decision?

This condition eventually causes premature mortality, after a long and unpredictable course. The treatment has only shown to slow down the rate of progression. How does this influence your perception of the risks and benefits?

How would your perception of the risks and benefits be influenced if the treatment offered a cure?

What difference does the incidence of side effects in this case influence your perceptions? (i.e. If there were 200/1000 cases of breast cancer)
Case Study Six
A very common condition occurring when there is a lack of insulin produced in the body, causing a range of long term medical complications. A treatment has been withdrawn because of concerns it has links to heart disease.

Condition
A chronic metabolic condition, affecting over 2.8 million people in the UK. The condition typically affects people later in life (maturity-onset), and occurs when not enough insulin is produced by the body for it to function properly, or when the body’s cells do not react to insulin.

Long-term complications related to the condition can include increased risk of heart attacks, strokes, amputation, and kidney failure. For extreme cases, circulation of limbs is affected, potentially requiring amputation. Loss of hearing, eyesight, and cognitive ability has also been linked to this condition.

Although in its early stages, the condition can be managed by diet and a healthy lifestyle, it is a progressive disease, and patients eventually require insulin medication.

Treatment
A drug, which is very popular for the treatment of the condition, has recently been withdrawn from the market, due to growing concerns of links to a higher risk of heart attack. It was previously taken by over 2 million people worldwide. The drug works by controlling blood sugar levels through making patients more sensitive to their own insulin.

Side Effects
Analysis of short-term clinical studies comparing the treatment to others showed that the drug increases heart attack risk by 43% and increases risk of death from heart disease by 64%. However, the overall risk was small. Among the 15,560 patients who were taking the drug there were 86 heart attacks and 39 deaths, compared with 72 heart attacks and 22 deaths among the 12,283 patients not taking the said drug.

Regulators took action to suspend the drug as individuals with the condition already have an increased risk of having a heart attack or stroke.

Dimensions Covered:
- Benefits and Success
  - Stops Disease Progression
- Risks and Side Effects
  - Mortality
  - Prevalence of Side Effect - Low

Questions:
What do you consider the benefits to be in this case?
What would you consider to be the risks in this case?
Should this treatment be available to patients?
What new information might influence or change your decision?

There are a number of possible long term complications associated with the condition – can these be placed in a hierarchical way? (i.e. if a patient would definitely need an amputation, how would that influence your perception of the risks and benefits? Or, if the patient would definitely lose their sight as a result of the condition, how would that influence your perception of the risks and benefits?)
The condition is very common – does this influence your views about the availability of the treatment?
Appendix V

Expert Witness Biographies

Marie-Christine Bielsky, M.D.
Senior Medical Assessor | Medicines and Healthcare products Regulatory Agency (MHRA)

After studying medicine in Strasbourg (France), she made a career in the pharmaceutical industry, where she participated in the clinical development of a number of medicines to treat various diseases. In particular, for 10 years, she developed orphan drugs for the treatment of several very rare inherited metabolic disorders, which were granted marketing approval. In 2006, she joined the Biologics and Biotechnology Unit of the Licensing Division at the UK Regulatory Agency. As a medical assessor, she is conducting the clinical evaluation (efficacy and safety) of a range of biological medicines (blood products, vaccines, therapeutic proteins).

Dr. Jayne Spink
Director of Policy and Research | Multiple Sclerosis Society UK

Penny Copley
Patient and Ambassador | Multiple Sclerosis Society

Jayne Spink is Director of Policy & Research with the Multiple Sclerosis Society UK, leading on policy, public affairs, campaigns, research, international and strategy development. Jayne is a former post-doctoral biomedical researcher and has a PhD in Genetics. From 1998-2005 she worked for the Department of Health where she led the Genetic Science Safety and Regulation team, a role which included supporting the Gene Therapy Advisory Committee (the national ethics committee and ministerial advisory group for gene therapy and stem cell therapy clinical trials). Immediately before joining the MS Society Jayne worked for the National Institute of Health & Clinical Excellence as Associate Director of the Centre for Clinical Practice.

Dr Emma Mason
Consultant Physician | Princess of Wales Hospital

Emma completed her medical undergraduate training at University of Liverpool in 1994. Her interest in pharmacology started whilst as an undergraduate and this continued throughout her post-graduate career. After completing her training in clinical pharmacology and general internal medicine based in Cardiff she then spent further years in training to develop a sub-specialty interest in palliative medicine. She is currently a consultant physician in acute medicine based at the Princess of Wales Hospital in Bridgend. She is also the course tutor for the MSc in Palliative Medicine and a Honorary Senior Lecturer in Pharmacology and Palliative Medicine based at Cardiff University.

Dr Robert Bracchi
Associate Medical Director | Welsh Medicines Partnership

Dr Robert Bracchi is a general practitioner with an interest in Pharmacology. He is the Associate Medical Director of the Welsh Medicines Partnership and Chairman of the New Medicines Group which reports to the All Wales Medicines Strategy Group (AWMSG). He sits on the Pharmacovigilance Expert Advisory Group and Herbal Medicines Advisory Committee at the Medicines and Healthcare Products Regulatory Committee (MHRA).

Jamie Hayes BPharm(Hons), ClinDipPharm, PCME, MBA(Dist), MRPharms
Director | Welsh Medicines Resource Centre

Jamie has been Director of the Welsh Medicines Resource Centre and one of the Directors of the Welsh Medicines Partnership since 2003. His interests include medical education, influences on prescribing behaviour, evidence based therapeutics and Lean Thinking in healthcare. He runs regular courses, masterclasses, workshops and lectures to doctors, dentists, nurses, pharmacists, pharmacy and medical students. Previously: Head of Prescribing Advice, Conwy Local Health Board; Training advisor for the National Prescribing Centre, Liverpool and Clinical pharmacist, primary and secondary care, UK and New Zealand.
Appendix VI

Psychosocial factors scoring exercise

Jurors were asked to select up to 10 factors, which they considered to be the most important to them. The results are shown in the table below:

<table>
<thead>
<tr>
<th>Psychosocial factors</th>
<th>No. Of votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (as a result of uncertainty and uncertainty of effectiveness)</td>
<td>6</td>
</tr>
<tr>
<td>Being a patient and taking medication (time, disruption and anxiety)</td>
<td>6</td>
</tr>
<tr>
<td>Relationship with the self and identity</td>
<td>7</td>
</tr>
<tr>
<td>Coping mechanisms</td>
<td>3</td>
</tr>
<tr>
<td>New opportunities/enlightenment</td>
<td>3</td>
</tr>
<tr>
<td>Self efficacy and self esteem</td>
<td>3</td>
</tr>
<tr>
<td>Autonomy and control</td>
<td>6</td>
</tr>
<tr>
<td>Short termism</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
</tr>
<tr>
<td>Stress/distress</td>
<td>4</td>
</tr>
<tr>
<td>Depression</td>
<td>3</td>
</tr>
<tr>
<td>Guilt/regret</td>
<td>1</td>
</tr>
<tr>
<td>Respite/relief</td>
<td>2</td>
</tr>
<tr>
<td>Sense of mourning or loss</td>
<td>4</td>
</tr>
<tr>
<td>Relationship with immediate family (spouse/partner/children/parents/siblings)</td>
<td>10</td>
</tr>
<tr>
<td>Relationship with extended family</td>
<td>0</td>
</tr>
<tr>
<td>Relationship with friends</td>
<td>6</td>
</tr>
<tr>
<td>Carers (commitment/resentment/reliability)</td>
<td>3</td>
</tr>
<tr>
<td>Relationships at work (colleagues/employees/peers/managers/clients)</td>
<td>5</td>
</tr>
<tr>
<td>Financial implications</td>
<td>8</td>
</tr>
<tr>
<td>Insurance (all types)</td>
<td>1</td>
</tr>
<tr>
<td>Employment status</td>
<td>7</td>
</tr>
<tr>
<td>Driving</td>
<td>3</td>
</tr>
<tr>
<td>Altruism</td>
<td>3</td>
</tr>
<tr>
<td>Social pressures (to take or not to take a medicine)</td>
<td>1</td>
</tr>
</tbody>
</table>
Appendix VII

All Psychosocial Factors

Coping Mechanisms
Jurors recognised that patients (and their families) can adopt both negative and positive coping mechanisms in relation to their condition and their symptoms. Examples of negative coping mechanisms might be substance misuse or eating disorders. A positive coping mechanism might be to find new skills or new opportunities, such as getting involved in illness-based charities.

“because my daughter misses a lot of school, she has become extremely determined...and so she works probably harder than all of her peers and has become a little bit of a star...she has taken on her adversity and tried to make the best of it”

Enlightenment
This related closely to positive coping mechanisms. Some jurors have experienced what might be called a sense of enlightenment, in response to living with an illness or their child’s illness.

“It opens up...you feel so grateful...even the bad things you actually feel a little bit grateful for...you look back and think if that hadn't of happened then this wouldn't have happened”

Self esteem and self efficacy
Self efficacy and self esteem are implicitly linked. Jurors noted that a condition/treatment impacts upon the way they evaluate or appraise themselves. In turn, this can determine their beliefs about whether they can achieve specific goals or outcomes in their lives. Self esteem and self efficacy can therefore affect healthcare decisions, coping mechanisms and the self management of a condition.

Short termism
Short termism is a term that can be used to describe a distressed state associated with the symptoms of a condition or a treatment. For example, the distress caused by severe pain can affect a person’s normal thinking processes, making them irrational and impatient.

“I think pain is a very difficult issue, and how people manage pain. When people have a lot of pain, it is very difficult to make rational decisions. What you want is for the pain to go away...it is all consuming and is such a major feature of your life.”

Fatigue
As well as a physical symptom, fatigue was used to describe how patients can feel in relation to their chronic condition. They may be tired of their symptoms, the management of their symptoms, and the impact of those symptoms on their daily lives.

Stress/distress
Many of the psychological impacts on a patient are interlinked. Stress/distress was linked closely to short termism.

“I don’t suffer physical pain, but I do have distress or discomfort because of the additional effort it takes me to do the run of the mill things I used to do without thinking about it”

Depression
Depression can encompass many of the psychological affects listed in this report.
Guilt/regret
Guilt and regret were discussed in terms of risk taking and decision making. Patients acknowledged that the decisions they make about their own healthcare can have an impact on their own wellbeing, and their families too.

“For those of us with rare diseases, we are having to make decisions based on very very limited information...so you are taking huge risks. Those risks are about your...mental health as well as your physical health, and how that will impact on your family... it is guilt, regret, frustration... It is a whole burden you carry with you if it goes wrong”

Respite/relief
Patients must live with their conditions, and their symptoms, day in day out for the rest of their lives. Jurors felt it was important to experience a sense of relief sometimes. For example, pain relief. This was seen as important to their psychological wellbeing.

Sense of mourning or loss
Some jurors expressed a sense of mourning since their diagnosis. They feel like they have lost who they used to be and the future they imagined for themselves – their identity or sense of self has changed in some way.

Relationship with extended family
Relationships with extended family members could also be affected, although it was not viewed as important as relationships at work, with friends, or immediate family members.

Carers (commitment/resentment/reliability)
Jurors discussed ‘carers’ in a number of ways. This element was especially important for those patients who had family members caring for them. They felt that if one person has to adopt a carer role, this can have a significant impact on the relationship between those two people. For example, there may be feelings of resentment on the carers’ behalf. The competence or commitment of carers was also discussed amongst the jurors.

Relationships at work (colleagues/employees/peers/managers/clients)
Jurors noted that relationships at work can be affected. A number of different relationships were identified in the workplace, each of which has the potential to be affected by a patients’ condition or treatment. Relationships at work were closely linked to employment status, financial implications and identity.

Insurance (all types)
Jurors spoke of the complex nature of the insurance systems, including getting appropriate insurance related advice and insurance cover. In many cases, negotiating insurance cover has had a significant impact on the jurors’ lives.

“Life insurance, travel insurance, car insurance – ‘as soon as you get the prognosis everything kicks in!’”

“Getting travel insurance for me...it becomes prohibiting, trying to find a company that actually understands and will give you travel insurance...so it curtails the whole way you used to live your life”

Driving
Jurors talked about the impact their conditions have had on the ability to live independently. One element of this was the ability to drive.

“If you take the car from me, that’s it, you may as well lock me in the house”
Altruism
The jurors discussed altruism. In some cases, jurors felt patients might be willing to take a risky medicine, for the greater good. They acknowledged that if they had 'nothing to lose' they might be willing to take part in a clinical trial to increase knowledge in that area, so that others can benefit in the future.

Social pressures (to take or not to take a medicine)
A patient may be under pressure to either take a medication or not take a medication by family members and wider society. For example, family members may be more concerned about side effects than the patient themselves. The high cost of a medicine may also be an indirect social pressure for a patient.
Notes

1. Regulatory bodies, such as the Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) operate a system where by a medicine must be licensed before it can be marketed. Medicines which meet the standards of safety, quality and efficacy are granted a marketing authorisation (previously a product license), which is normally necessary before they can be prescribed or sold. ([www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/index.htm, accessed on 26.1.12]).

2. Individuals under the age of 18 were not allowed to participate in the study. However, parents formed part of the jury offering an insight into the issues faced by children with rare and/or serious conditions, and by them as parents of those children.

3. The focus of the jury was defined by the project team with the support of various key stakeholders including Genetic Alliance UK and a Steering Committee.

4. About Rare Diseases, [www.raredisease.org.uk, accessed on 16.1.12]


6. This final report also benefits from a wealth of material which jurors included in their individual ‘reflective diaries’, which Simpson and Longley analysed after the event, together with their responses to self-completion questionnaires administered at three points during the jury process.

7. Biomedical refers to the application of biological or physiological principles to understand health and illness.

8. A psychosocial model encompasses psychological and social principles in the understanding of health and illness.

New Medicines for Serious Conditions: Weighing the Risks and Benefits

The Verdict of a Jury of Patients

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