**Ethics and Politics of Accelerated Access to Medicines: Interview Schedule**

**Introduction**

In this research project, we are interested in exploring the opinions of clinicians such as yourself about access to medicines.

In Australia, there is currently a lot of debate about the processes which govern access to medicines. This has been triggered by concerns that not all patients receive timely access to new therapies.

One way to address this is to speed up the later stages of the medicines life cycle (i.e. regulatory approval by the TGA and reimbursement under the PBS) by changing the way that we assess safety, efficacy and cost-effectiveness. There have been a number of suggestions on how to do this, but one thing that all of these have in common is that medicines will be approved or funded—at least initially—on the basis of less evidence or different kinds of evidence than has been required in the past. This is what I would like to explore with you in this interview.

**Part One: Scenarios**

To begin with, we will explore some scenarios. When we are working through these scenarios, please feel free to also share your own experiences regarding gaining faster access to medicines for your patients.

1. **REGULATORY:**

The first thing I would like us to look at is a scenario about approval of medicines by regulatory bodies such as the Therapeutic Goods Administration (TGA) (show on diagram). Let’s park issues of cost for the moment and focus on issues related to safety and efficacy. We will come to cost issues later in the interview.

1. **Let’s first consider a new medication for a serious, life-limiting disease. It has been shown to be reasonably safe (there are no life-threatening side effects in the trial) and to have a significant effect on a surrogate end-point—say progression-free survival or a radiological finding over a comparator drug —in a large randomised controlled (phase 3) trial involving nearly 1000 patients. However, its effect on survival is unclear. It has been suggested that this drug should be approved for use in Australia on the condition that further data on its efficacy and safety is collected once it reaches the market.**

**[If they baulk even at scenario A—i.e. are very conservative, ask]**

**A2. What would make it OK to put the drug on the market? What would create enough certainty about safety and efficacy in your opinion?**

1. **Let’s now imagine that there has not yet been a large phase 3 trial. All we know is that this drug has been shown to have an effect on a surrogate marker in a phase 2 trial involving approximately 50 patients.**

**[If they say that B is OK, push further with]**

**B1. What if there have been no efficacy trials at all yet, but the drug appears to be safe from a Phase 1 study in patients with the disease?**

**[If they say that B1 is OK, push further with]**

**B2. What if there is no information at all about the use of this drug in patients with the disease, but the drug seems to work well in patients with a disease that has a similar pathophysiology (e.g. both diseases involve idiopathic chronic inflammation)**

**[If they keep saying it’s OK, ask]**

**B3. When would it stop being OK to put the drug on the market? What would be your limit in terms of the amount of uncertainty the regulator should tolerate?**

1. **What if the medicine had been shown in an analysis that was not outlined in the original trial protocol to have an effect on survival in a subset of patients? In other words, there was no effect on average survival for all patients in the trial, but a few—say 10—patients—responded exceptionally well. The issue is that we can’t predict who those people will be, so we would need to register it for everyone with the condition.**

**So it seems you draw the line at [summarise where their limit is]. Now I’d like to know if you feel differently about tolerating uncertainty under different circumstances**

1. **Let’s now imagine that this is a drug used to treat a debilitating but not life-limiting disease.**
2. **Let’s now imagine that this is a drug used to treat a rare disease.**
3. **Let’s now imagine that this is a drug used to treat a condition for which there are currently no other treatment options available.**
4. **Let’s now imagine this is a drug with a brand new mechanism of action i.e. there are no other drugs like it on the market (it is truly innovative)**
5. **Let’s now imagine that this is a drug used to treat children.**

**Prompts:**

* If you were advising the TGA, would you recommend approval of this medication? Why or why not?
	+ For scenario B onwards: Does this change your opinion on whether or not to approve this medicine? Why or why not?
* What are the advantages (if any) of approving this medication? What are the disadvantages? How do you balance potential risks and benefits here?
	+ For scenario B onwards: Are there any additional advantages/disadvantages to approving the medication in these circumstances? If so, what are they? Does this change the risk-benefit balance here?

**Potential advantages for patients**

* **[Efficiency]** The time for regulatory approval to be granted has been mentioned as a barrier to access to new therapies. For example, in Australia, the average TGA approval time is 391 days. Now there are lots of different opinions on this- some say that this is too long for patients to wait while others have said that this may not be enough time to adequately determine the effectiveness and safety of new therapies.
* **[Compassion/hope]** These discussions often occur in the context of debilitating or life-threatening diseases. Another potential advantage is that patients are offered at least the hope of extended life or improved quality of life, even if this is uncertain.
* **[Innovation]** Some have argued that faster approval by regulatory bodies may encourage further drug development. The idea here is that therapies reach the market earlier and drug companies can more quickly recoup their research and development costs (the cost of developing and bringing a new drug to market has been estimated to be as high as $2.6 billion). This is thought to be particularly important for stimulating R&D for disease areas that may otherwise be neglected, such as rare diseases.
* **[Autonomy]** Some people argue that it should be up to doctors and patients to decide how much risk and uncertainty to take on. In other words, they think that medicines should get onto the market quickly and then it is up to those who will actually be affected to decide whether or not it is reasonable to use these.

**Potential patient harms [if they don’t mention these]:**

* **[Harm]** Some people have raised concerns that patients may be more likely to be exposed to ineffective or unsafe therapies if these become available on the basis of less or different types of evidence to what is traditionally used. For example, the drug bevacizumab (marketed as Avastin) was granted accelerated approval by the FDA for the treatment of HER2-negative breast cancer in 2008. But this was revoked in 2011 when further follow-up showed no survival benefits and several side effects (including high blood pressure, bleeding and heart attack or heart failure).
	+ Some people have said that the only thing worse than dying without trying every option is having tried these to no effect and suffering horrible side effects while delaying access to good palliative care.
* **[Harm again]** Any potential risks may be compounded by the time taken to remove medicines from the market once they are made available. For example, there was recently a study of 17 drugs that were approved and subsequently removed from the US market due to safety concerns. It turns out that these drugs had been prescribed more than 100 million times before they were withdrawn.
* **[False hope]** The possibility that patients will be offered “false hope” has also been raised, as the chance of benefitting from an early stage trial is thought to be less than 10%. However, others believe that patients with serious diseases should be offered the chance of improvement or extended life, even if this is small.

**Potential effects on future research and the evidence base for therapies [if they don’t mention this]:**

* As you know, randomised controlled trials are not perfect- they are resource intensive to conduct and conducted in controlled in populations that don’t necessarily represent typical patients using the medicines in routine clinical care, so they do not always provide you as a clinician with the information that you need to treat the patient in front of you. However, they are still currently considered the “gold standard” of evidence for treatment efficacy. There is a concern that companies may be less likely to complete large, randomised phase 3 trials if they are allowed to simply gather “real world” data after the medicine enters the market for regulatory purposes.
* What do you see as the best way to gather adequate data on the safety and efficacy of new therapies?
1. **FUNDING:**

Previously, we were talking about approval for a drug to be marketed in Australia. We will now turn to issues around subsidy of medicines to reduce out of pocket costs for patients [show on diagram]. Here, we want to explore whether we can justify spending money on a medicine in situations where there is uncertainty surrounding its clinical or cost-effectiveness.

1. **Let’s again consider a new medication used to treat a life-limiting disease. It has recently been approved for marketing in Australia by the TGA and the drug company has applied to have it listed on the Pharmaceutical Benefits Scheme at a price of $200 000 per patient per year of treatment. Again, it has been shown to have a significant benefit on a surrogate end-point compared to a comparator drug in a large randomised controlled (phase 3) trial involving nearly 1000 patients. However, its effect on survival is unknown and, as a result, it is unclear what its cost-effectiveness will be. It has been suggested that subsidy be provided on the condition that further data is collected to determine if it should remain on the PBS or if the PBS price should be adjusted.**

**[If they baulk even at scenario A—i.e. are very conservative, ask]**

**A2. What would make it OK to fund this drug? What would create enough certainty about cost-effectiveness in your opinion?**

1. **Let’s now imagine that there has not yet been a large phase 3 trial. All we know is that this drug has been shown to have an effect on a surrogate marker in a phase 2 trial involving approximately 50 patients.**

**[If they say that B is OK, push further with]**

**B1. What if there have been no efficacy trials at all yet, but the drug appears to be safe from a Phase 1 study in patients with the disease?**

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**[If they keep saying it’s OK, ask]**

**B3. When would it stop being OK to fund this medicine? What would be your limit in terms of the amount of uncertainty that payers should tolerate?**

1. **What if the medicine had been shown in an analysis that was not outlined in the original trial protocol to have an effect on survival in a subset of patients? In other words, there was no effect on average survival for all patients in the trial, but a few—say 10—patients—responded exceptionally well. The issue is that we can’t predict who those people will be, so we would need to fund it for everyone with the condition.**

**So it seems you draw the line at [summarise where their limit is]. Now I’d like to know if you feel differently about tolerating uncertainty under different circumstances**

1. **Let’s now imagine that this is a drug used to treat a debilitating but not life-limiting disease.**
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5. **Let’s now imagine that this is a drug used to treat children.**
6. **Let’s now imagine that the PBAC has decided not to list this medication due to an unacceptably high cost-effectiveness ratio. However, it has been suggested that a dedicated fund (similar to the Life-Saving Drugs Program) could be established in order to provide patients with fast access to this medication.**

**Prompts:**

* If you were a member of the PBAC, would you recommend funding of the medication? Why or why not?
	+ For scenario B onwards: Does this change your opinion on whether or not to fund this medicine? Why or why not?
* What are the advantages (if any) of funding the medication in these circumstances? What are the disadvantages? How would you balance these?
	+ For scenario B onwards: Are there any additional advantages/disadvantages to funding the medication in these circumstances? If so, what are they?
* Is there another funding mechanism that may be more appropriate here and, if so, why?

**Potential advantages**

* **[Compassion]** Many people emphasise the need to be more flexible in regards to cost-effectiveness in order to **ease the financial burden for patients**. For example, new cancer drugs can cost upwards of $100 000 per year of treatment and without some form of subsidy, most patients cannot afford this. Patients may be able to receive assistance through other sources (such as a hospital drug and therapeutics committee, company compassionate access program or private health insurance); however, this is not guaranteed. Patients who cannot access these programs may have to mortgage their home or rely on personal fundraising to fund their treatment.
* **[Innovation]** Companies can really only recoup their R&D costs when someone is paying for their medicines. So there is an argument that governments should not be so strict about cost-effectiveness and also think about encouraging future innovation. This is thought to be particularly important for patients with rare diseases, where small patient populations mean that companies may need to charge more for treatments in order to recoup their research and development costs.

**Potential problems**

* **[Sustainability]** However, others have raised concerns about the **financial impact** of medicines entering the market on the basis of higher or more uncertain cost-effectiveness thresholds. This can have serious implications for the sustainability of healthcare systems. For example, in Australia, concerns about sustainability were evident in the Abbott government’s proposed changes to PBS co-payments and safety net entitlements and a decision to review the Life-Saving Drugs Program on the basis of sustainability.
* **[Opportunity costs]** There are also concerns about the opportunity costs of funding new medicines where there is uncertainty surrounding their cost-effectiveness. Although the PBS budget is not capped, we are in a resource-limited environment with a number of competing priorities and we may gain better value for money by using the money that is spent on this drug for a different purpose.
* **[Disinvestment realities]** Concerns have also been raised about the difficulty of removing a medicine from the PBS if it is found to be less clinically or cost-effective than initially thought once it is on the market and patients and physicians become familiar with it. For example, a recent review found that very few drugs have been delisted from the PBS; those that have were drugs that had been voluntarily withdrawn from the market by the manufacturer for reasons other than safety or had their marketing approval revoked by the Therapeutic Goods Administration, primarily due to safety concerns.
* **[PBS as gatekeeper]** Some people have said that the PBS plays an important gatekeeping role- i.e. we have doctors to advocate for individual patients but a body like the PBS is needed to advocate for the interests of society as a whole.

There is also some debate about who benefits from these more lenient reimbursement schemes. Some argue that it is primarily pharmaceutical companies that benefit, as their product enters the market and they can start earning money while further data is gathered. In other words, it is the government, rather than industry, that is subsidising later-stage clinical trials. However, others have noted that pharmaceutical companies may have to accept a lower price than they think that their drug is worth in order to receive subsidy (at least initially). What are your thoughts on this? In your view, are funding initiatives such as the ones discussed here primarily in the public interest, the business interest or a combination of the two?

1. **PRACTICAL ISSUES:**

We have explored a number of advantages and disadvantages to patients of “accelerated access” mechanisms. Let’s now imagine that we decide to introduce mechanisms that allow medicines to be approved or funded on the basis of less evidence or different types of evidence to what is traditionally used (usually on the condition that further data will be gathered once the medicine reaches the market). How do you think this would work in practice? Can you see any potential issues?

Factors that may affect the **timely collection of data** include:

* Collecting, analysing, de-identifying, linking and sharing real world data is a **time- and resource intensive exercise** for everyone involved (including clinicians and manufacturers). Who would fund this? Is it appropriate for industry to do this or should this be kept at arm’s length to industry?
* Companies may be less concerned about collecting further data on the medicine once it has been listed on the PBS and is widely available. This could, in turn, result in **required studies not being completed**.
* **Cooperation between a number of parties** (including payers, sponsors, physicians and administrators) is needed for efficient data collection but this may not occur.

In order to provide useful information, **observational studies need to be carefully designed** to avoid bias and confounding.

There has been some talk about the **extra regulator and payer resources** needed to implement a system such as this one. Additional staff may be needed to ensure that data is collected and evaluated in the required timeframe. For example, a recent report in the US found that ***less than half*** of the potential safety issues that were known about during accelerated reviews were being monitored in the general population.

**Part Two: Imagining the Future**

Throughout this interview we’ve been talking about balancing issues such as patient safety, access and affordability for both individuals and healthcare systems . Now I would like you to think about **what sort of system you would like to see** for the regulation and funding of medicines that provides the best balance of these issues.

First, let’s imagine a “blue sky” scenario—what would you like to see happen in an **ideal world**?

* Why are these changes necessary?
* What would you like from regulators and funders to allow this to happen?
* What advantages does this system have over the current one?
* Can you identify any problems with this system?

Given that we live in a world with many constraints, what **realistic changes** to the current system would you prioritise?

**Part Three: Sources of Information**

In this last part of the interview, I would like to explore why you feel that you expressed the **opinions** you did earlier and how you **access information** about new medicines.

* Where did your ideas about access to medicines come from?
* Who have you talked to about this issue, if anyone?
* You have said that you access information from X, Y and Z. How accurate do you think this information is? Do you think it is applicable to you as [a clinician]? What level of trust do you place in this?