THE McKell Institute

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Living with Duchenne & Becker in Australia

SUPPORTING FAMILIES *waiting for* A CURE

SAVE OUR SONS

DUCHENNE FOUNDATION

ANGELA JACKSON / EQUITY ECONOMICS

APRIL 2020

ABOUT THE MCKELL INSTITUTE

The McKell Institute is an independent, not-for-profit, public policy institute dedicated to developing practical policy ideas and contributing to public debate.

For more information phone (02) 9113 0944 or visit
www.mckellinstitute.org.au

ANGELA JACKSON

Angela Jackson is an experienced public sector economist with almost 20 years' experience working as an economist on public policy issues.

Angela was Senior Advisor and Deputy Chief of Staff to the Australian Minister for Finance and Deregulation from November 2007 to September 2010.

Currently completing a PhD in health economics, Angela has specialised knowledge of the health sector alongside an intimate understanding of government.

Angela also serves as a non-Executive Board Member of Melbourne Health, which runs Royal Melbourne Hospital, and is a member of the Victorian Advisory Board for the National Heart Foundation.

Angela was the author of *Disability &Rare Disease: Towards Person Centred Care for Australians with Rare Diseases* published by the McKell Institute in October 2019.

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FOREWORD

In 2019, the McKell Institute released Disability & Rare Diseases: Towards Person Centered Care for Australians with Rare Diseases. That project highlighted the gaps in care for Australians living with rare disease including those with Duchenne muscular dystrophy, and the less common Becker muscular dystrophy, the conditions which are the focus of this report.

Duchenne and Becker are genetic, muscle-wasting conditions that affect around 1000 Australians. While there is hope for a cure, this report highlights the challenges facing many Australians – and their families – living with the condition today.

This report details the issues and challenges facing those living with Duchenne and Becker and their families as they wait for a cure. It explores the gaps in the existing healthcare system and the costs facing families whose family members live with Duchenne and Becker, undertaking a cost of disease analysis, and surveying 150 families and individuals experiencing the impacts of the disease.

The survey results paint a picture of a healthcare system that often fails to meet the needs of those living with Duchenne and Becker. While this report highlights the fact that Australia's system compares well to international benchmarks, it makes clear there is more to be done.

20 per cent of survey respondents had a delay of more than three years between noticing symptoms and receiving a diagnosis, and a clear variation in the quality care was identified across state and territories. Alarmingly, the survey also highlights the shortfalls of the National Disability Insurance Scheme (NDIS) for those with Duchenne and Becker. 16.6 percent of respondents told of worse treatment under the NDIS, while a further 31.1 per cent said the NDIS had neither improved nor worsened their situation.

Of course, Duchenne and Becker is first and foremost a healthcare challenge. But inadequate treatment mechanisms impose a significant economic burden on families and the economy, too. Children born with Duchenne or Becker have a life expectancy of less than 30 years. This report estimates that for families, the costs of lifetime social care and health care can total around $2.25 million, with the reduced workforce participation of families due to caring costing over $600,000.

The NDIS is a landmark, $22 billion per year reform. But it is clear that more needs to be done for Australians with rare diseases such as Duchenne and Becker. To that effect, this report makes 12 actionable recommendations, ranging from ideas aimed at achieving earlier treatment and diagnosis, to improving the delivery of care, funding future therapies, and improving access to clinical trials.

While most Australians enjoy access to world-leading care, our health system always needs improving – especially for those living with rare conditions. This report makes an important contribution towards that aim of achieving a better healthcare system for all Australians.

SAM CROSBY
CEO, MCKELL INSTITUTE

EXECUTIVE SUMMARY

Duchenne muscular dystrophy is a rare disease,[1] but the most common of the muscle-wasting diseases affecting children.[2,3] Children with Duchenne cannot produce a protein needed for muscle strength and function, and over time this leads to muscle damage.[3] Children with the less common Becker muscular dystrophy have an error on the same gene, but experience less severe symptoms as their bodies can still produce some of the protein.[4,5]

Receiving a diagnosis of Duchenne or Becker places a timer on when a child will start to lose physical functioning, and eventually die.[2] Advances in treatment have significantly improved the life expectancy and function of children born with Duchenne,[6,7] but most children with the disease do not live past their 30th birthday.[6,8]

The symptoms of Becker generally don't present until children are older, and often only in adulthood.[4] Damage is slower in Becker because while those with the condition produce some of the muscle protecting protein, this is at insufficient levels to stop damage.[4]

Available therapies have helped slow the progression of Duchenne and Becker, but have not provided a cure.[2,9] There is however hope. Gene therapies in the final stages of development could cure Duchenne and stop the timer for many children – offering the hope of a healthy and long life for children with Duchenne and Becker today and into the future.[10]

For many, when a cure becomes available the disease will have already progressed to the point where they have lost the ability to walk and breathe independently. Even with a cure these children will need ongoing care and support for the rest of their lives.

This paper aims to highlight some of the issues and challenges facing families of children and adults with Duchenne and Becker as they wait for a cure. We aim to better understand how Duchenne and Becker impacts families, how we can ensure that new treatments benefit Australian children sooner and better support those with the condition today.

A cost of disease study undertaken for this report shows that Duchenne is associated with significant lifetime health and social care costs. We estimate that these can total up to $2.25 million for a child living until their mid-thirties. In addition, informal care costs total up to $630,000 in terms of reduced female participation in the workforce. The cost of any gene therapy for Duchenne needs to be seen in the context of these lifetime costs.

Surveying over 150 people and their families with Duchenne and Becker muscular dystrophy we provide a comprehensive picture of the experience of people living with these conditions in Australia today.

The survey highlighted that many Australians are waiting too long for a diagnosis and continue to endure a diagnostic odyssey before being able to access treatment for the condition and receive genetic counselling on their future reproductive choices.[11]

20 per cent of respondents had a delay of more than 3 years between first noticing symptoms and receiving a formal diagnosis.

While Australia compares favourably to international benchmarks,[9,12,13] there are large variations across the state and territories indicating more could be done. Newborn screening for Duchenne and Becker would help end this odyssey and ensure that future genetic treatments are administered before significant loss of function occurs.

The survey also highlighted ongoing issues with the support provided to children with Duchenne and Becker through the National Disability Insurance Scheme (NDIS), that were highlighted in the 2019 McKell Institute report: *Disability and Rare Disease – Towards Person Centred Care for Australians with Rare Diseases*.[14]

The National Disability Insurance Scheme (NDIS) aimed to transform the lives of people with a disability, with an unprecedented boost in funding for services and supports. In this context, a remarkable 16.6 per cent of respondents to the survey said that the $22 billion NDIS had worsened their situation, and a further 31.1 per cent said that the scheme had neither improved nor worsened their situation. Delays in receiving equipment was often raised by those indicating that the NDIS had worsened their situation.

There is an urgent need for the NDIS to ensure that it can quickly meet the changing needs of people with a disability. These issues were reflected in the recent Tune Review of the NDIS, where it was highlighted that the lack of flexibility created issues for participants with changing needs.[15]

The NDIS's ongoing inability to adjust to changes in the needs of clients is significantly impacting children with Duchenne and Becker that have constantly changing needs due to the progressive nature of the disease. We recommend that the Australian Government accept and implement the recommendations of the Tune Review to address these issues, and that the NDIA immediately provide additional support to families of children with Duchenne and Becker to overcome bottle necks.

Meanwhile genomics gets set to revolutionise health care, with over 750 treatments currently under development.[16] From 2025 it is expected that up to 20 new treatments will become available every year[17] – each with the capacity to transform lives but also associated with high additional costs for health systems.

The National Health Genomics Policy Framework provides the roadmap for our health system in dealing with the new treatments in the pipeline, however there is concern that the health system remains unprepared for the tsunami that is about to hit.[16]

This lack of preparedness will undermine the financial sustainability of our health system, but also potentially delay or deny Australians access to life-changing treatments.[16]

We recommend that the Australian Government prioritise the development of clear funding mechanisms for new gene therapies as part of the review of the National Health Genomics Policy Framework in 2020. This will provide industry and those hoping to benefit from the new treatments with greater certainty and understanding of the Government's proposed approach.

There are also ongoing issues with the approval of clinical trials in Australia, that are undermining efforts to ensure Australian children have access to the next phase of clinical trials for the new gene therapies. While national reforms are underway, our review of international practice highlights that they do not go far enough in streamlining and centralising approval processes, nor do they address issues specific to gene therapies. More can be achieved to ensure that Australian children with Duchenne have the opportunity to participate in these clinical trials.

Our review of regulatory regimes in the United Kingdom, Europe and Canada found that **Australia is the only jurisdiction that requires licensing of genetically modified o ganisms for use in clinical trials or approval by a separate gene technology regulator.** This adds to approval times and hinders the ability of Australian children to gain access to important clinical trials.

We make a number of recommendations that will ensure Australia's health system is world leading, and competitive in attracting clinical trials, including a central one-stop platform, a single application form, a national body to oversee clinical trials and national uniform legislation. In addition, we call for the Government to move to streamline applications for undertaking clinical trials with genetically modified organisms, to ensure Australian children do not miss out on participating in these clinical trials.

These are exciting times for Australians with rare genetic conditions, including with Duchenne and Becker. Advances in medical science mean that there is now the real prospect of a cure. As families continue to wait however, the Government can take action today to provide these families with the support they need and ensure the earliest possible access for their children to these life-changing treatments.

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RECOMMENDATIONS

Getting Treatment Earlier

RECOMMENDATION 1
The Departments of Health and Primary Care Networks in New South Wales and Tasmania review the diagnostic processes and pathways for Duchenne diagnosis with the aim of reducing the national variation in time to diagnosis.

RECOMMENDATION 2
The Government fund a trial and evaluate the cost-effectiveness of pre-conception and newborn screening for Duchenne.

Getting the Care that is Needed

RECOMMENDATION 3
Urgent review of delays in access to equipment to ensure that NDIS participants receive approved equipment in a timely manner.

RECOMMENDATION 4
The NDIA establish a specialist team focused on ensuring children with Duchenne and Becker are not facing avoidable delays in receiving equipment.

RECOMMENDATION 5
The Australian Government provide funding to establish up to two Centres of Excellence for Duchenne and Becker in Australia.

RECOMMENDATION 6
The State and Territory Governments to provide funding certainty for neuromuscular nurses to provide care coordination for all patients with Duchenne and Becker.

Funding Future Therapies

RECOMMENDATION 7
The Australian Government include clear funding mechanisms for gene therapies as part of its 2020 review of the National Health Genomics Policy Framework.

Improving Access to Clinical Trials

RECOMMENDATION 8
Australian Government to establish a national ‘one-stop’ clinical trials portal.

RECOMMENDATION 9
Australian Government to develop a single national ethics review and site-specific assessment application form.

RECOMMENDATION 10
Australian Government to establish a national clinical trial coordinating agency.

RECOMMENDATION 11
Introduction of national legislation to harmonise regulatory requirements.

RECOMMENDATION 12
As part of the National Gene Therapy Strategy review the approval process for the use of genetically modified organisms in clinical trials.

INTRODUCTION

Background

Around 1000 Australians are currently living with Duchenne and Becker muscular dystrophy in Australia, the most common muscle-wasting disease affecting children.[i]

Duchenne and Becker are rare diseases that present many challenges to families affected by the condition.[18] A lack of understanding or knowledge from medical professionals, and uncertainty around what the condition will mean for individual children makes facing a new diagnosis even more difficult.[19]

Children with Duchenne and Becker are born with a fault, or mutation, in the longest gene in the body.[2,9,20] This fault stops their body producing a protein (Duchenne) or reduces the amount of protein produced (Becker), dystrophin, which is vital for muscle strength and function.[4,20,21] Without the protein all the bodies' muscles, including the heart, progressively weaken over time.[4,21]

Boys are predominately affected by Duchenne and Becker because they only have one of the genes that produce the protein.[2,4,21] Girls have two of the relevant genes and as long as one of them does not have the fault they can still produce the protein and do not develop Duchenne, but can pass the condition on to their children.[4,21]

Duchenne progresses through childhood and into early adulthood.[2] Becker often doesn't start to impact physical functioning until later childhood or early adulthood.[4] While other children gain more physical abilities as they age, children with Duchenne progressively lose function. After taking away their ability to walk at around 13 to 14 years of age, Duchenne robs children and adults of their ability to breathe independently, to talk, and undermines heart function, eventually causing premature death.[2,8]

Because Duchenne impacts so many parts of the body, those affected require large teams of specialists to oversee their medical care.[22] In addition, from early adolescence through to the end of life children with Duchenne require significant social care support, from both formal and informal sources.[23]

The progressive nature of Duchenne means that the needs of those affected are constantly changing, and the treatments they require to maximise their functioning is always shifting. This makes securing the necessary medical and social care supports in a timely manner critically important.

Diagnosis

The first symptoms of Duchene typically emerge after a child's first year of life, but diagnosis does not typically occur until around 5 years of age.[12] Symptoms are varied and can range from frequent falling, difficulty running or climbing stairs and the inability to get up off the floor.[21] Speech delays can also be common, alongside comorbidities including autism, intellectual disability and ADHD.[21]

CASE STUDY

7 year-old Harrison lives in Perth and was diagnosed at the age of 3.

There is no history of Duchenne in our family, but my wife was a carrier of the gene and passed it on to our first son Harrison.

When he was around one, we noticed that he was not developing at the same rate as other children so we started down the process of consulting professionals which ultimately led to diagnosis. This took over two years and by that stage we had had our second son, Jack who was also at risk of having Duchenne. We were lucky that he was not impacted.

Having a son with a rare disease means we often know more about his condition than his Doctors and it's a lot of work to keep up to date with developments in treatments so that he continues to get the best care possible. I think I may have read every single article about Duchenne on the internet!

With treatment including his fantastic physio team Harrison has improved over time, but we have reached the plateau now where the gains are over. Stairs are starting to become harder and we know that without a corrective therapy his physical capabilities will start to deteriorate in the future.

My wife and I try our best to make our family life as normal as possible, so that both our sons experience a childhood just like other kids. It is hard, and behind closed doors the journey we are on can go from being full of hope to full of despair.

We hope that a cure will be found and that our son will live his best possible life. We despair that as much as we will continue to fight for him, accessing a cure may be too late for his journey. So we try and make sure he is happy regardless of what happens to him physically.

We are just trying to keep his body in the best possible shape until help arrives in the form of a corrective therapy.

It is this hope that keeps us going, and why our son taking part in a meaningful clinical trial in Australia would mean the world to our family.

Diagnosis can take years and involve multiple medical professionals, as knowledge of the condition is not high and misdiagnosis common.[13,24]

Earlier diagnosis is important for a number of reasons.[9]

Because the condition is genetic there can be multiple cases within the same family. Delays in diagnosis mean that families have multiple children with the condition before they receive the diagnosis for the eldest child.[12] This compounds the effect on families and could be avoided with earlier screening for the condition.[12]

Importantly the earlier children start treatment the better the long-term prognosis. Treatments currently include physiotherapy and steroid treatments, that can help maximise muscle functioning and reduce the damage to muscles.[9]

i This is based on both population wide estimates and reported number of patients at major clinics around Australia.

COST OF DISEASE ESTIMATES

The medical, formal and informal care costs of a child with Duchenne rise over their life as their physical functioning slowly declines.

In order to better understand these costs we have calculated the cost of Duchenne over a person's life (please see Appendix 1 for full methodology). We have taken the perspective of a child born today to provide a clear picture of future potential costs in the absence of a curative treatment.

Whereas decisions to fund new therapies can often focus solely on the improvements in quality of life and incremental increase in health care costs, in the case of Duchenne a wider perspective provides a more comprehensive picture of the true costs of the disease.

Using previously published research and reported costs from the survey we are able to estimate the cost of a child born with Duchenne today in Australia over their expected life in terms of additional health, formal and informal caring costs.[22]

The analysis shows that the expected lifetime medical costs of Duchenne currently average $300,000, but for a person that survives up to their mid-thirties can reach $590,000. In addition, the expected lifetime social care costs average $700,000, but for a person surviving into to their mid-thirties cost up to $1.67 million.

In addition, we can estimate the impact on maternal labour supply of having a child with Duchenne. It is estimated that lost hours worked can be expected to cost families $339,000 on average with the cost for a child that survives until their mid-thirties rising to $631,488.

The financial cost of Duchenne therefore over the lifetime of a child born today can be expected to be $1.3 million with the cost for a child living to their mid-thirties of $2.88 million.

Treatments for Duchenne

The medical management of all muscular dystrophies has been transformed over the past twenty years, significantly improving life expectancy.[6,8] This has been driven by the widespread use of corticosteroids, alongside the optimisation of physiotherapy and cardiorespiratory care.

Gene therapy treatments are now being developed which promise to stop the progression of Duchenne, however early treatment will be critical as even with these ground-breaking treatments it is not possible to reverse damage already done to muscles.[5,10]

There is also uncertainty over the funding of new gene therapy treatments when they do become available. Australia's current funding of pharmaceuticals is geared towards ongoing treatments rather that one-off curative treatments, and it is not clear how the health system will meet the substantial costs associated with gene therapies.[16]

Clinical Trials in Australia

Any parent of a child with a rare or non-rare disease that is life threatening or life shortening wants their child to be able to access new treatments as soon as possible. The opportunity to participate in clinical trials is critical for Australian children living with Duchenne to enable early access to investigational treatments not otherwise available in Australia that may extend or improve the quality of their lives, as well as the development of urgently-needed new therapies.

While a number of clinical trials have been conducted in Australia for Duchenne and Becker treatments, delays and regulatory complexity in the approval process for gene therapy trials may threaten access for Australian children.

The National Disability Insurance Scheme

Launched in July 2013 the National Disability Insurance Scheme will be fully implemented by mid-2021. The scheme will cover 475,000 Australians when fully implemented and cost over $22 billion a year.[25]

The NDIS has replaced a number of State-based schemes providing support to children and adults with Duchenne and Becker. It provides individualised support which is agreed through face-to-face meetings with an NDIS planner and local area coordinators.[25]

While this greater flexibility is a positive, issues have been identified with the NDIS not being responsive to individuals with changing needs and failing to provide integrated care across the health and disability systems.

In the 2019 McKell Institute report *Disability and Rare Disease – Towards Person Centred Care for Australians with Rare Diseases*, we highlighted that the NDIS is struggling to deal with some clients that have rare diseases, such as Duchenne and Becker.[14] Of particular concern was the fragmentation of care and delays in access to necessary equipment.

For children with Duchenne these issues are particularly relevant due to the underlying medical nature of the condition and the changing needs of the condition.

Current Action

There is significant community and political support for families and those affected by Duchenne and Becker.

Since it was established in 2008, Save Our Sons has raised over $20 million through generous community support. This has allowed the Foundation to fund a number of specialist nurses in clinics for Duchenne across Australia, help Australian children access clinical trials, for important research into the conditions, and to provide quality-of-life enhancing equipment.

However, more is required and with the potential for a cure, there is a need to make sure the system allows Australian children timely access to treatments that offer hope for families impacted by the condition.

LIVING WITH DUCHENNE IN AUSTRALIA

Having a child diagnosed with a rare condition is often a confusing and lonely experience.[18] Unlike other aspects of parenthood those in your social and support networks are unlikely to have ever experienced what you are going through, and this can add to the isolation felt by families.

Medical professionals can lack knowledge of the condition, placing a significant burden on parents to become 'experts' in their child's condition.

The additional needs of children increases the caregiving role and impacts a family's ability to work, and therefore their financial security.[18] Other children in the family may also be affected by the limits that having a sibling with a rare condition places on the activities a family can undertake and the financial resources available.

We undertook a survey of families with children with Duchenne and Becker and those living with Duchenne and Becker in Australia to better understand their experience of living with the condition and how it is affecting their lives. Below we present the findings of the survey before discussing the key issues raised by families and those living with Duchenne and Becker in Australia.

The survey was launched on Survey Monkey on 4 December 2019 and was promoted heavily on social media and through direct communication with families registered with the SOS Duchenne Foundation. Closing on 23 December 2019 there were a total of 173 responses, a sizeable sample of the estimated total population living with Duchenne and Becker in Australia.

CASE STUDY

Sam lives in Queensland and is the father of 13 year-old Lila

Duchenne is a rare disease in boys, but in girls it is even rarer. We noticed Lila was not developing normally at around 2 years of age, and a number of tests were done. If she had been a boy we would have been diagnosed then, but because she was a girl they thought it couldn't be Duchenne and didn't do the final tests.

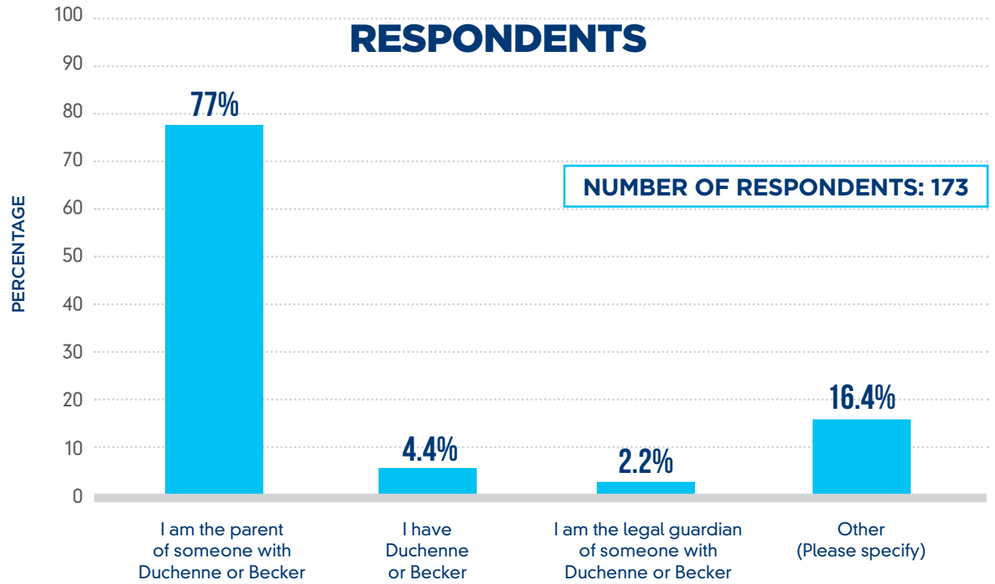
Four years later, and another round of tests and we finally got the diagnosis. This is why if newborn screening is introduced it will be for girls as well as boys, because girls have such a hard time getting a diagnosis. It would also make sure girls know they have the gene, so they don't inadvertently pass it on to their sons.

The doctors looking after Lila have been great, but there is so little research on girls with the condition and so people don't know how it will progress and how will impact Lila. We really hope that more research will be done on girls with the condition so other families have more information and better care for their girls.

We have four other kids, and its hard on them. Lila is very often the focus, because her needs are so great and we try to only do things as a family that she can join in with. This means there is a lot we cannot do.

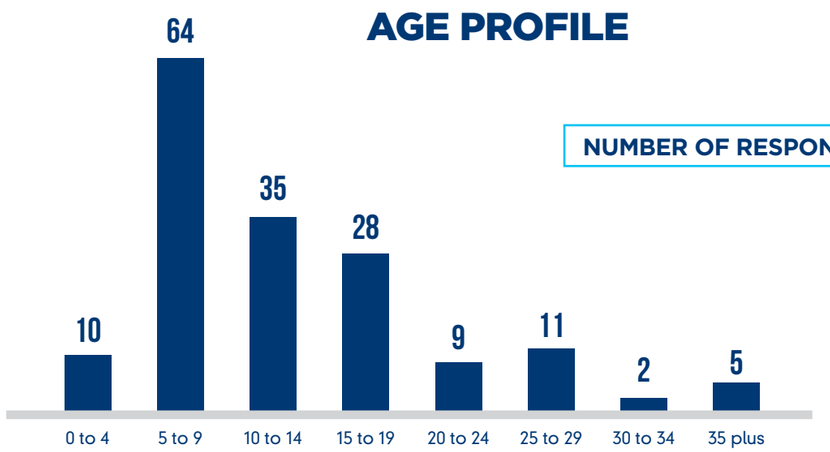
Survey Results

The majority of respondents to the survey were parents of children with Duchenne and Becker, representing 77.05 per cent of the sample. Within the Other Category, the largest groups were Grandparents (23.3 per cent) and Siblings (30 per cent).



Age

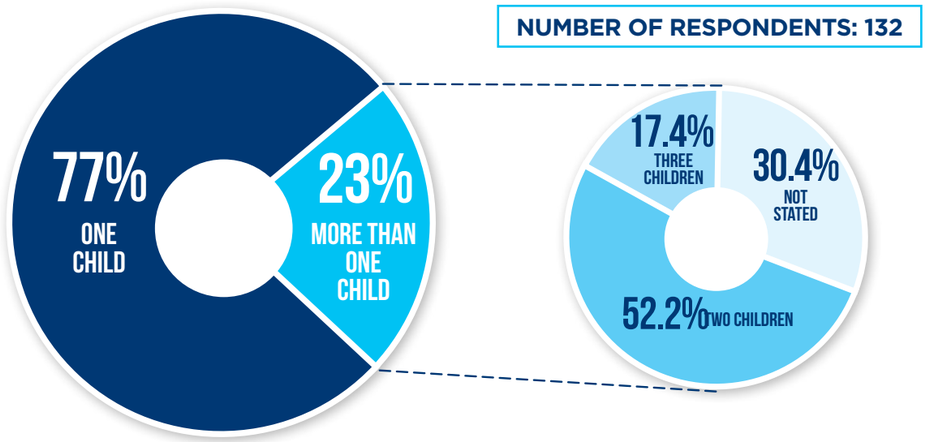
The average age of the person affected by Duchenne and Becker was 13 years, with age ranging from 1 year to 50 years.



Family

We asked whether there were other children in the family with Duchenne or Becker, and if so how many children. **23.5 per cent of parents responded that they had more than one child with the condition.** Of those the majority had two children with Duchenne or Becker.

NUMBER OF CHILDREN WITH DUCHENNE OR BECKER IN FAMILY



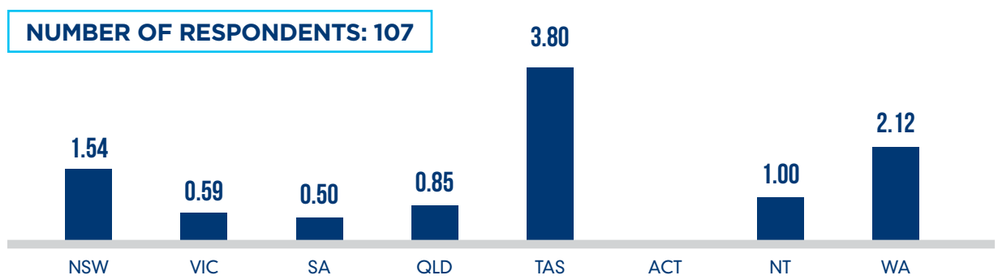
Delays in Diagnosis

Responders were asked at what age first symptoms became apparent and then at what age the child received a formal diagnosis for Duchenne or Becker. The average age of diagnosis was 4.39 years, with a range from 1 to 20.

The average delay in diagnosis was 1.09 years, but we observed variation across state and territories. The longest delay was in Tasmania at 3.8 years. Of interest there was a notable difference between the two largest states, with **the average delay to diagnosis in NSW was 1.54 years versus an average delay in Victoria of 0.59 years.**

The difference between states illustrates that there are gains to be made in reducing the delay between first symptoms and diagnosis, which will become more critical when gene therapy becomes available.

DELAY TO DIAGNOSIS



Getting a Diagnosis

Respondents were asked about the process of diagnosis.

Families saw on average three professionals before they received a diagnosis, with 30.4 per cent seeing four or more health professionals to get a diagnosis. Many respondents indicated that either there was insufficient information or support provided around the diagnosis when asked to comment on what could be improved about the process.

Numerous respondents highlighted the role of the Save Our Sons Duchenne Foundation in providing information when they first received the diagnosis.

"We knew nothing. The process of diagnosis was hard for us because we were not informed at all and we felt so lost and alone. We didn't know what to do." **SURVEY RESPONDENT**

"If GP's knew the signs and listened to my concerns we would of had an earlier diagnosis, earlier intervention and perhaps a better chance of being ambulatory longer."

MOTHER FROM WESTERN AUSTRALIA

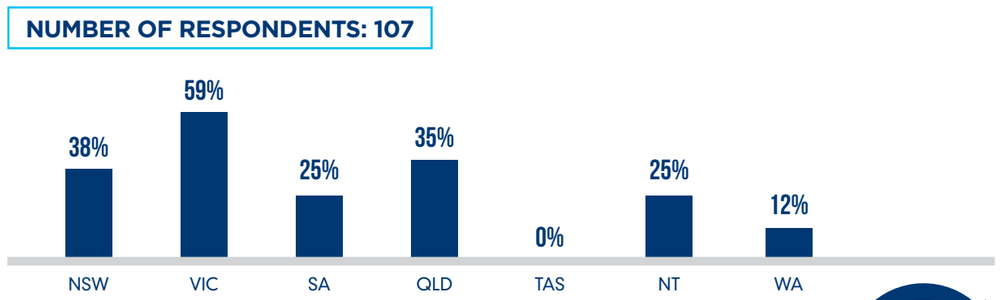
"I THINK ALL CHILDREN SHOULD BE TESTED IF THERE ARE SIGNS OF MUSCLE WEAKNESS, BECAUSE MY DAUGHTER WAS A FEMALE SHE WASN'T TESTED FOR YEARS."

MOTHER FROM QUEENSLAND

Access to Clinical Trials

36 per cent of respondents reported having accessed clinical trials. The majority of these were in Victoria, with almost 60 per cent of respondents from Victoria indicating they had participated in a clinical trial. This compared to 38 per cent of respondents from New South Wales. No respondents indicated that they were involved in a trial for gene therapy.

CLINICAL TRIALS



Treatment

The survey asked respondents a number of questions about their treatment for Duchenne. The gold standard of care includes the use of steroids and regular contact with a Cardiologist, Neurologist and Respiratory Physician.

We found that there were large differences across regional, rural and city areas with the number of respondents accessing gold standard care.

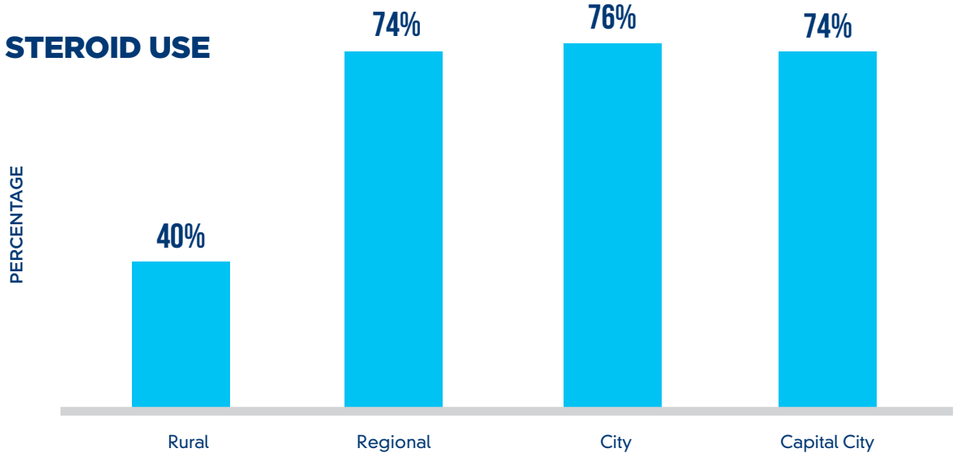
"Overall we are very happy with the care and treatment options of our son since his diagnosis. We feel closely connected to our wonderful team and know we are in the best hands despite the prognosis. We have benefitted from access to local trials and kept informed about ongoing treatments and trials coming up. Information is only a phone call or email away with knowledgeable, kind and caring staff. It helps having a great team involved at times when you feel isolated or unsure." **MOTHER FROM NEW SOUTH WALES**

Steroid Use

While steroid use will not be suitable for every child with Duchenne, it is regarded as the first line treatment to slow the progression of the condition. 72 per cent of respondents reported the use of steroids.

There was a very low level of use in rural areas, with just 40 per cent of respondents reporting the use of steroids. This compared to between 74–76 per cent in regional and city areas.

The main reason given for not being on steroids was a belief that they would not be beneficial and concerns about side effects. A number of children were too young to commence steroid use, and parents reported that they would commence once they were older.

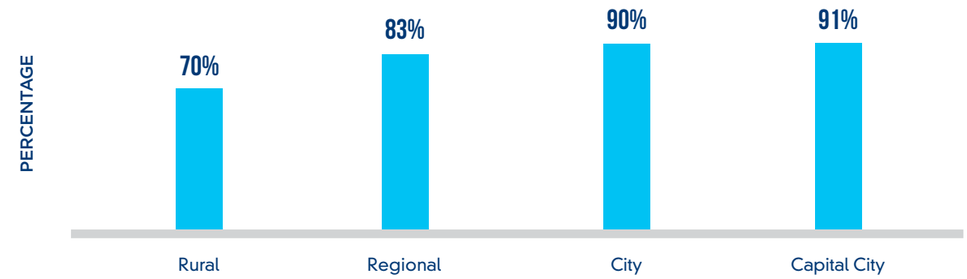


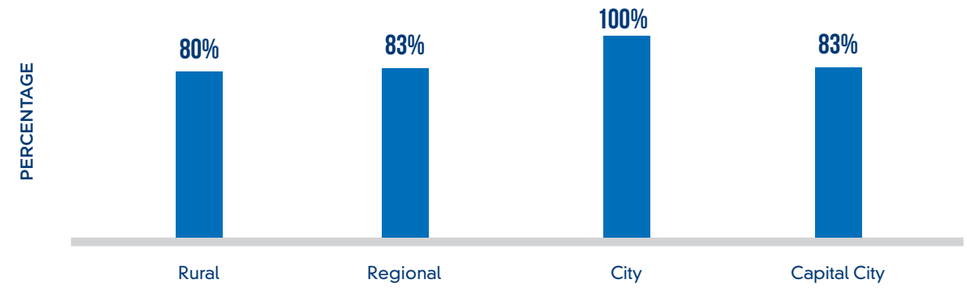
NUMBER OF RESPONDENTS: 109

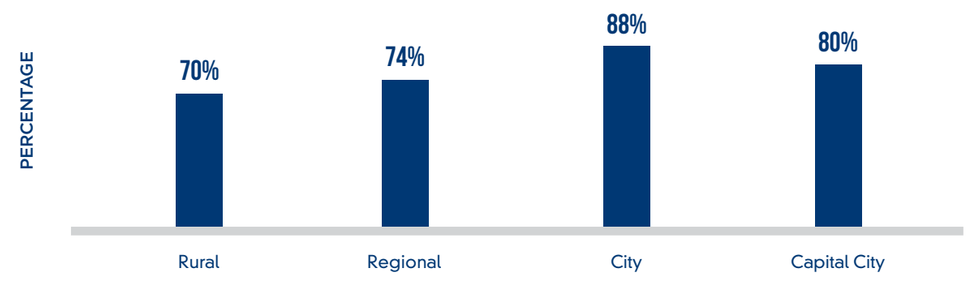
Neurologist, Cardiologist and Respiratory Physician

There are a number of Specialists involved in the care of people with Duchenne, but three specialists – Neurologists, Cardiologists and Respiratory Physicians are considered necessary for gold standard care.

66.4 per cent of survey respondents reported having seen all three of these specialities over the past year. There were some differences across regional and rural areas and access to the specialists, with those living in rural areas less likely to see each of the specialists.







NUMBER OF RESPONDENTS: 109

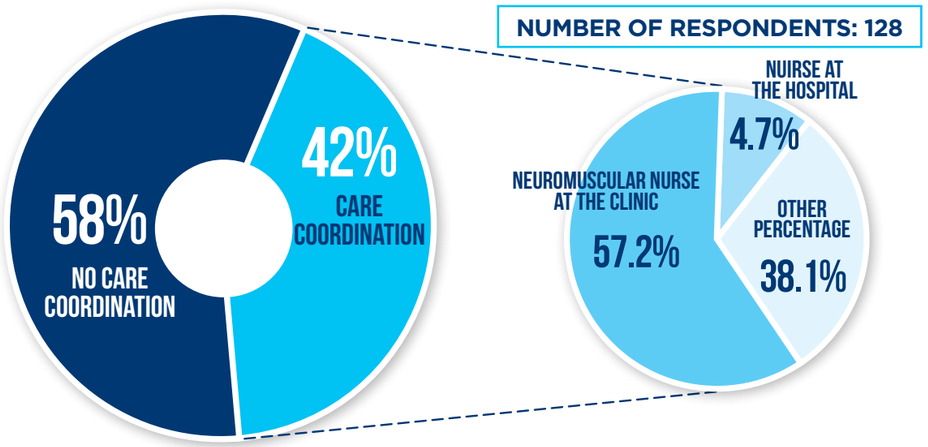
Care Coordination

With respondents reporting seeing an average of 9.65 health professionals over the past year, coordination of care is critical. However only 39.4 per cent of people reported having someone help with their care coordination. Of those the majority were seen by Neuromuscular nurses at clinics which are currently funded by the Save Our Sons Duchenne Foundation, funders of this report.

"I found that once we left the Children's Hospital because he was an adult, we were left on our own. We were linked in with the respiratory team, and a cardiologist. We had and still do have a regular neurologist. Our GP doesn't know anything about Duchenne. So we have nobody overlooking his whole health. We really are out on our own, trying to figure out his health care. It's a disgrace!"
MOTHER FROM REGIONAL SOUTH AUSTRALIA

"We need to have coordinated services in the adult hospitals we end up going multiple times sometimes in a week and have to travel an hour each way to get there. Why is this achievable for children but not adults? What changes the day you turn 18? If anything it gets harder."
MOTHER FROM REGIONAL WESTERN AUSTRALIA

CARE COORDINATION



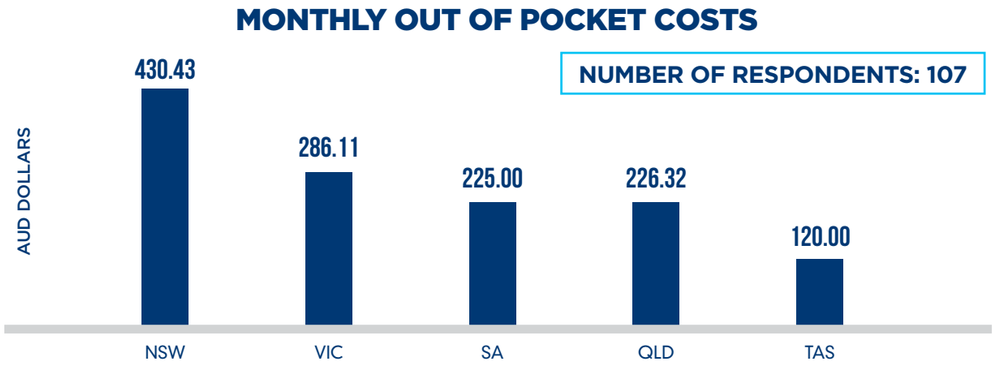
"WE LIVE IN PERTH WA. UNFORTUNATELY CLINICAL TRIALS ARE NOT COMING TO PERTH AT THIS POINT IN TIME. TRAVELLING TO SYDNEY OR MELBOURNE IS NOT FINANCIALLY AN OPTION."

MOTHER FROM WESTERN AUSTRALIA

Cost of Supporting a Child with Duchenne

Families reported high out of pocket medical costs, ranging to $1800 per month. Out of pocket costs were much higher in NSW than in other states and territories.

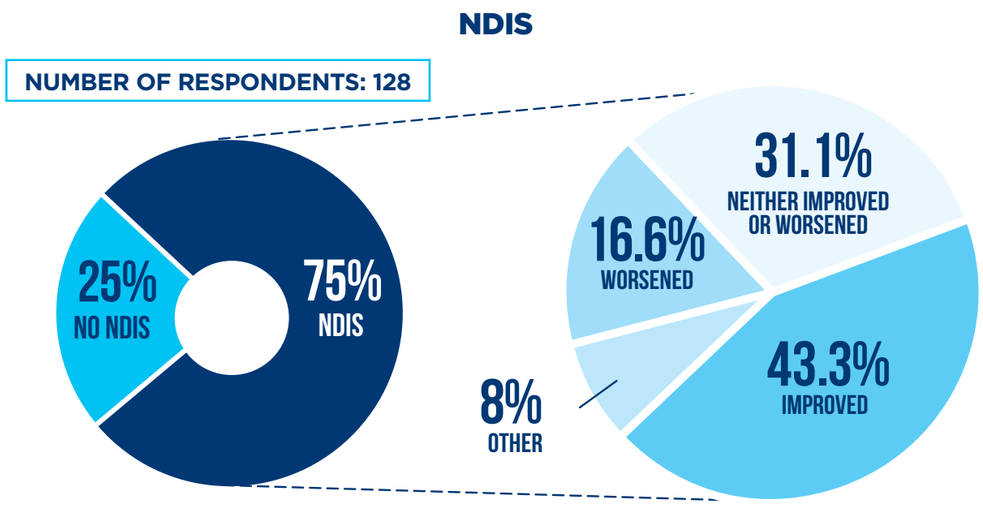
Out of pocket costs in NSW were $430.43 per month on average, compared to $250 per month on average across the other states and territories.



The National Disability Insurance Scheme

Of respondents to the survey 75 per cent receive services and supports under the NDIS.

43 per cent of respondents receiving services and supports from the NDIS indicated that services had improved, and 16 per cent reported that services had worsened.



> "NDIS IS A NIGHTMARE, NO SERVICES IN MY AREA, CAN'T GET RESPITE WORKERS OR PERSONAL CARERS WHEN WE REQUIRE IT, SEVERE SHORTAGE OF OT'S SO CAN'T GET THINGS DONE WITH NDIS"
>
> MOTHER FROM VICTORIA

"Receiving equipment and support is still just as slow under NDIS and amount of paperwork and hoops to jump through is bigger. I'm still waiting for a manual wheelchair after six months even through NDIS only took a few weeks to approve."
MOTHER FROM QUEENSLAND

"We are currently waiting to be enrolled into the NDIS which is a slow frustrating process. Financially looking at renovations for an accessible bathroom & accessible vehicle is both overwhelming & daunting!! We need to find a cure soon as the cost of living with this condition is both financially and emotionally draining for our son and our entire family."
MOTHER FROM WESTERN AUSTRALIA

"NDIS is shocking, cause families unnecessary stress, as they don't understand the condition."
MOTHER FROM VICTORIA

"The constant delays and underfunding had a very detrimental impact on Ali's condition and that these are the things that NDIS don't understand – this condition is degenerative and time is not a luxury for children with Duchenne. "
MOTHER FROM NSW

Key Issues

The survey and stakeholder consultations highlighted a number of key issues facing families living with Duchenne and Becker in Australia.

These include timely diagnosis, the quality and timeliness of care, access to clinical trials and access to new treatments.

Addressing these issues would help support families with a child with Duchenne and ensure that children have the best possible prognosis.

Timely Diagnosis

Timely diagnosis is critical for children with Duchenne and Becker as it ensures that they receive the optimum care and allows genetic counselling to assist in their reproductive planning.[12,13,24]

The average age of diagnosis in the survey was 4.38 years and the average delay between first symptoms and diagnosis was 1.10 years. Both compare favourably to the available international evidence[ii] (see Table below) however variation across state and territories indicates that under current arrangements more could be done in some states and territories.

	AVERAGE AGE OF DIAGNOSIS	AVERAGE DELAY
Previous Papers		
United States[13]	4.9 years	2.4 years
United Kingdom[26]	4.3 years	1.6 years
Europe[26]	4.3 years	1.3 years
SOS Duchenne Survey		
NSW	4.69 years	1.54 years
VIC	3.56 years	0.59 years
SA	2.75 years	0.50 years
QLD	4.50 years	0.85 years
TAS	6.00 years	3.80 years
NT	2.50 years	1.00 years

RECOMMENDATION 1

The Departments of Health and Primary Care Networks in New South Wales and Tasmania review the diagnostic processes and pathways for Duchenne diagnosis with the aim of reducing the national variation in time to diagnosis.

ii Note these figures are for Duchenne only and do not include estimates for Becker.

Many families still experience a 'diagnostic odyssey' with 1 in 3 seeing more than 3 health professionals to receive a diagnosis and 1 in 5 having delays of three years between first seeking medical treatment and receiving a diagnosis.

With the availability of potentially curative gene therapies the importance of earlier diagnosis will become critical. By the stage most children are currently diagnosed, they have already suffered irreversible muscle damage.

Newborn screening would help end this odyssey, and provide much earlier and more accurate diagnosis of the condition.[27] It involves a similar multi-step process to that currently used in the National Screening Programme for cystic fibrosis. First a blood test identifies babies at risk of the condition. Those babies identified then have a diagnosis either confirmed or refuted through a DNA test.

A number of pilot studies internationally have demonstrated the efficacy of newborn screening,[11,28] but no studies have yet been undertaken in Australia.

The current Mackenzie's Mission pilot is undertaking pre-conception screening of 700 autosomal recessive and X-linked conditions, including Duchenne.[29]

However, such a programme if instituted nationally would not necessarily pick up every case of Duchenne, as the error can occur for the first time in a child and not be inherited from a parent. In order to pick up these cases as early as possible newborn screening for Duchenne would still be necessary.

RECOMMENDATION 2

The Government fund a trial and evaluate the cost-effectiveness of pre-conception and newborn screening for Duchenne.

Quality and Timeliness of Care

Duchenne and Becker are progressive diseases, and a child's needs can change quickly. The NDIS is not geared towards participants with changing needs, which means it can often fail to provide children with the equipment and services they need in a timely manner.[15]

When children with Duchenne and Becker do not receive equipment or treatment in a timely manner, it can lead to quicker progressions of the disease. This robs children of more time with the ability to undertake certain activities, before that ability is lost forever.

Analysis of those who responded that the NDIS had made their situation worse in the Save Our Sons Duchenne Foundation Survey showed that it was a lack of responsiveness that drove much of the negative experiences of the NDIS.

> NDIS is a great system but we had waited for 9 months without hearing anything about our minor modification and equipment replacement applications. Took two months of unanswered phone calls and emails to LAC and calls to NDIA to get anything to happen. Claims should be triaged as urgent, non-urgent major, non-urgent minor with rough turnaround times (within life of plan) indicated.
>
> **MOTHER FROM QUEENSLAND**

> There needs to be faster approaches to obtaining equipment needed for a degenerative condition like this. Waiting over 12 months for equipment to help prevent contractures etc, is ridiculous. A treatment has been approved in the USA. We need it here and now. How do we do this?!
>
> **MOTHER FROM WESTERN AUSTRALIA**

These findings are consistent with the findings of the McKell Institute report *Disability and Rare Disease: Towards Person Centred Care for Australians with Rare Diseases* and also the recently released Tune Report into the NDIS.[14,15]

The 2019 Tune report also made a number of recommendations to improve the administration of the NDIS, and notes that the delays in equipment are of particular concern.[15]

Addressing these issues is a priority for children with Duchenne and Becker, and the Government should prioritise these reforms in its forthcoming response to the Tune Report. In the interim we also recommend that the NDIA establish a specialist team focused on ensuring that children with Duchenne and Becker are not facing avoidable delays in equipment.

RECOMMENDATION 3
Urgent review of delays in access to equipment to ensure that NDIS participants receive approved equipment in a timely manner.

RECOMMENDATION 4
The NDIA establish a specialist team focused on ensuring children with Duchenne and Becker are not facing avoidable delays in receiving equipment.

CASE STUDY

Chris, 28 year old living with Duchenne in Victoria

My name is Chris and I live in Warrnambool in Victoria. I am 28 years of age.

While Duchenne makes doing a lot of things difficult, I am focused on doing what I can do find a cure. I work hard to raise money and spread awareness through our

Muscular Dystrophy Awareness Warrnambool foundation. Our aim is to help find a cure for future generations.

I am the eldest in my family. Two years after I was born, but before I was diagnosed my mum had my little brother, Aaron. He died of Duchenne two years ago.

While I know it's been tough for my parents, they have always encouraged us to do what we wanted and found a way to make life as normal as possible. Because of this I don't really feel that Duchenne had a big impact on us growing up. Having a positive attitude is really important to me.

I was able to fully participate in school from Prep all the way up to year 12, and completed a three year business traineeship. This is even though physically I declined through this period.

From around 5 to 11 we just needed buggies or a manual wheelchair for long distances, but started using a manual wheelchair from 11 years of age.

My muscle strength has gradually decreased over time, and for the last few years I have not been able to feed myself or go to the toilet without the help of mum and dad.

Some things would have made life easier, including having a standing wheelchair sooner and some respiratory support that could have reduced the impact of cold and flus while I was growing up.

My Mum and Dad have been everything. They have always done everything for my brother and I. They have had a lot of physical injuries from having to help us, but they wouldn't have it any other way.

Specialist Centres

Most children with Duchenne and Becker receive care through major public hospitals around Australia. However, differences in patient's numbers and resourcing constraints lead to difference in the care received.

A number of respondents from outside Victoria and New South Wales commented that there were issues with specialist teams not being up to date with the latest treatments, requiring families to become experts in the disease.

> "WE SPENT 18 MONTHS TRYING TO DETERMINE THE CAUSE OF DEVELOPMENT DELAYS IN WA. ONCE WE MOVED TO SYDNEY WE FOUND MUCH BETTER HEALTH SERVICES AND WERE DIAGNOSED WITHIN 3 MONTHS. INFORMATION AFTER DIAGNOSIS AND GENETIC SCREENING IN NSW WAS GOOD."
>
> MOTHER FROM WESTERN AUSTRALIA

CASE STUDY

Bailey is 13 years old from Western Australia and was diagnosed with Duchenne at the age of 10

Since diagnosis nearly 3 years ago, our family has been turned inside out and upside down, twice (our then 3 year old was also given the same diagnosis). The amount of TIME we lost in those early years of searching for answers we will never get back. I used to say to my son (pre-diagnosis) that "mummy is trying to find a way to help fix your silly muscles" only to discover I was the reason he has the condition, and that I had unknowingly passed it on to two of my sons. It was soul destroying.

We lost our ability to make better, more educated choices for him, he lost years of invaluable support. We have all suffered with our mental health yet getting psychological support in our NDIS plan is like drawing blood from a stone! There is no support for siblings who also lose out big time.

Early screening through the Newborn screening test, early intervention from child health nurses, GP's. If we had of had that kind of information we could have had the ability to make informed decisions about our son's care, his schooling, and get in some good family adventures whilst he was more mobile.

Our deletion is 'friendly', apparently. Just exon 56 is missing. I'm hopeful exon skipping may be an option but here in WA, I'm not holding my breath, and financially relocating to the east coast would be extremely difficult. (This has been hard to write, as for my own sanity I have to actively choose not to look too far back. It's still extremely raw). But Bailey's story deserves to be told as he's an extraordinary kid, despite his DMD.

In Europe and the United Kingdom centres of excellence are a feature of rare disease policy, and sit at the centre of a system that can better respond to the health and disability care needs of people with rare diseases including Duchenne and Becker.

Given the nature of Duchenne and Becker, and rapidly evolving treatments, there is an acute need for the establishment of specialist centres that have the capacity to acquire and maintain knowledge and expertise through both research and patient interaction.

Through providing a central point of contact for people with rare diseases, their families, and health and disability professionals, everyone can have access to the same information on a rare disease.

RECOMMENDATION 5
The Australian Government provide funding to establish up to two Centres of Excellence for Duchenne and Becker in Australia.

Care Coordination

Gold standard care for Duchenne and Becker requires care coordination, due to the number of specialist required to provide patients with health care.

Respondents saw on average 9.65 medical professionals in the past twelve months, however less than half had any help with care coordination. This places significant burden on families and undermines quality clinical care.

Of those that did have care coordination, the majority had a neuromuscular nurse who are largely funded by the Save Our Sons Duchenne Foundation. The reliance on private funding for these roles on an ongoing basis presents some risk to care of children with Duchenne and Becker.

RECOMMENDATION 6
The State and Territory Governments to provide funding certainty for neuromuscular nurses to provide care coordination for all patients with Duchenne and Becker.

Access to New Treatments

A cure for Duchenne is just one of the 750 gene therapies working through the pipeline. By 2025 the US Federal Drug Administration predict that between 10-20 gene therapies will be added to the market each year.[17]

A tsunami is coming and it is uncertain if our health system and funding mechanisms are ready. The current reliance on existing mechanisms and approaches is not taking into account the specific issue raised by gene therapy for our health system, and without a coordinated strategy Australians will not fully benefit from this revolution in health care.

From ensuring that Australians are accessing the early clinical trials for new treatments, to strengthening diagnostic processes, establishing comprehensive patient registries that facilitate treatment and tracking of outcomes and providing certainty in funding mechanisms – there remains significant policy work to be undertaken in Australia. This relates to Duchenne and Becker but also to other diseases that finally have the hope of a cure through new gene therapies.

While the National Health Genomics Framework offers a roadmap to addresses many of these issues, the timeframes on implementation risks creating delays in access to new treatments. The revolution is occurring now, and our health system needs to be reformed to make sure Australians can benefit.

In particular, while the prospect of gene therapies offer new hope to families that a cure may be soon available for Duchenne and Becker, the cost of such therapies will be prohibitive for most families. They will rely on public funding through Australia's Pharmaceutical Benefits Scheme (PBS).

The PBS has demonstrated its flexibility in pursuing novel funding agreements that may be suitable for gene therapies, however it remains unclear what approaches will be used for gene therapies.

Gene therapies are estimated to cost upwards of $2 million per patient, and will place significant upfront cost burdens on health systems. While our analysis has shown there will be significant savings for the health and social care system, who pays for these new treatments will be an important issue.

We recommend that the Australian Government prioritise the development of clear funding mechanisms for new gene therapies as part of the review of the National Health Genomics Policy Framework in 2020. This will provide industry and those hoping to benefit from the new treatments with greater certainty and understanding of the Government's proposed approach.

RECOMMENDATION 7
The Australian Government include clear funding mechanisms for gene therapies as part of its 2020 review of the National Health Genomics Policy Framework.

Access to Clinical Trials

The importance of accessing clinical trials was brought up in a number of free text responses, with many respondents indicating their willingness to participate and previous failed attempts to be enrolled in clinical trials.

There are currently no trials of the new generation of gene therapies being undertaken in Australia, and there are concerns that Australian children will miss out on the next phase of trials due to be undertaken in 2020.

Pharmaceutical companies claim that it is due to the regulatory burden. Government claims that these problems have been addressed and that Australia is a competitive place to undertake clinical trials.

These are not easy issues to navigate, and in the next section we undertake a review of the approval process for clinical trials in Australia, finding that despite reform efforts there remains a number of areas of concern.

CLINICAL TRIALS

Access to clinical trials is of critical importance to families of children with Duchenne, as they represent the chance to gain early access to new treatments. With the development of potential cures for Duchenne through gene therapy this urgency will become greater.

Clinical trials are also important to the Australian economy, contributing more than $1 billion annually in direct expenditure and investment, as well as broader flow-on benefits.[30]

There are concerns that Australia is not as competitive at attracting clinical trials as it could be, and that its regulatory processes are too cumbersome. In particular there are additional layers of regulatory approval for gene therapies that further slow down processes and undermine the ability of Australians to be included on clinical trials.

There have been recent efforts to streamline processes and provide a more consistent approach across the state and territories, however we recommend that Australia should go further in streamlining and centralising processes. We find this is consistent with international best practice.

Below we outline current approval processes in Australia and compare these to overseas jurisdictions. From this analysis it is possible to make a number of recommendations on possible reforms to the Australian process for clinical trial approval.

Clinical Trials in Australia

Australia has strengths as a clinical trial destination, many of which have been achieved through significant reform efforts over the past decade. These include:[30,31,32]

- efficient regulatory timeframes under the Therapeutic Goods Administration's Clinical Trials Notification Scheme;
- reduced duplication in ethics reviews through the National Mutual Acceptance scheme;
- high quality research and data outputs;
- good reputations of research teams and key opinion leaders;
- established referral networks and national patient databases;
- standardised costing to assist with budget negotiations;
- research and development tax incentives; and
- an ethnically diverse English-speaking population.

However, barriers that contribute to delays in trial start-up times and may work against selection of Australia as a clinical trial site include:[30,33]

- lengthy and variable timeframes for local site governance approvals;
- the lack of a truly nationalised system for ethics approval, resulting in the need for multiple ethics submissions;
- long and separate process for genetically modified organisms; and
- difficulties meeting patient recruitment targets.

Although Australia is a relatively expensive clinical trial location (particularly compared with South-East Asian and Latin American countries), pharmaceutical companies report that they balance cost considerations against data quality, trial start up times and patient recruitment capacity (though companies note that data quality is increasingly seen as a minimum requirement rather than an advantage).

CASE STUDY

Michele's Son David has Becker Muscular Dystrophy and lives in Western Australia

I carried the gene that gave our son David Becker muscular dystrophy without ever being aware. And our daughter carries the gene as well. But only David is affected.

From around three months of age we noticed that he was not developing as expected. David also has an intellectual disability.

There is a massive impact on the whole family unit from what activities we can do as a family. My daughter had to have tutoring in early school years due to most of my time taken up caring for my son who was experiencing delayed development and needed constant watching for his safety. She missed out on a lot of attention as a result.

David has become progressively more and more dependent on support as time progresses rather than becoming more independent with age like a typical kid. These constant caring needs places a massive stress emotional and financially on the whole family unit.

There was no referral or information provided to us about who we could contact for support when David was diagnosed. I luckily found Muscular Dystrophy WA online who then put me in touch with the Save Our Sons Duchenne Foundation. These ladies were amazing once I was connected with them, providing information and about standards of care and lived experiences.

It often feels like we have to fight every step of the way to get David the care he needs, which is exhausting. Here in Western Australia we often find the Neuromuscular clinic is not up to date with current trends and standards of care that are advocated for in other states of Australia and Worldwide.

A cure for Duchenne and Becker Muscular Dystrophy is now a goal within sight, and this is what we should all be aiming for – while it would be great if David could be on a clinical trial, the most important thing is that we get the cure sooner rather than later. Then all kids would benefit.

Australia's cost disadvantage will only negatively influence trial site decision-making if Australia is not seen as offering an advantage in these other areas, underscoring the importance of reform efforts to address identified barriers[30, 33].

Pharmaceutical companies have reported that difficulty meeting patient recruitment targets in Australian clinical trials has a significant impact on future decisions about whether to include Australia as a trial site.

Factors contributing to poor patient recruitment include Australia's small patient pool sizes and inaccurate estimates of potential patient populations; whereas establishment of national patient databases is highlighted as a significant enabling factor for patient trial participation[30, 33].

The establishment of the Australian Duchenne Registry, a collaboration between Save Our Sons Duchenne Foundation, the Office of Population Health and Genomics in Western Australia, and the Murdoch Children's Research Institute in Melbourne, is an important initiative that will facilitate Duchenne patient recruitment and improve the attractiveness of Australia as a location for Duchenne clinical trials.

The Registry will enable accurate estimates of patient pools, facilitate speedy recruitment of Duchenne patients and carriers, and assist pharmaceutical companies with clinical trial planning.

However, delays and variability in timeframes for ethics and research governance approvals may shorten the time available for patient recruitment and are likely to impede the selection of Australia as a site for Duchenne trials. For clinical trials of novel gene therapies for Duchenne and other diseases, time to trial start up is particularly likely to be a barrier due to extremely lengthy timeframes for the issue of genetically modified organism (GMO) licences by the Office of the Gene Technology Regulator.

Concerted action is needed to address these timeframes in order to prevent Australian children with Duchenne from missing out on accessing potentially life-saving new treatments through clinical trials, and to avoid delaying the development of novel gene therapies and other treatments that will save lives.

Current Reform Efforts in Australia

Substantial work is underway to streamline clinical trial processes, with the aim of reducing time to trial start up and ensuring Australia remains a preferred clinical trial destination.

The Australian Government's Encouraging More Clinical Trials in Australia initiative has provided $7 million nationally to support state and territory governments to redesign clinical trial systems in accordance with the revitalised Council of Australian Governments Health Council clinical trials agenda.

Through the Clinical Trials Project Reference Group, Australian jurisdictions have agreed to collaborate on measures to address priority action areas. These include:[32]

- establishing central points of contact in each jurisdiction to coordinate clinical trial management and improve system navigation for trial sponsors and participants;
- developing and capitalising on networks, partnerships and infrastructure to drive coordinated change across the clinical trials sector;
- data collection to inform systems improvement and enhance sector knowledge and performance;
- embedding clinical trials into core hospital governance arrangements; and
- creating a clinical trials governance framework.

Work has commenced across these action areas.

The Framework is due for imminent release and will be piloted in health services in 2020 ahead of full implementation in 2021.[34] This is a first step towards national accreditation of health services undertaking clinical trials, and a nationally consistent approach to clinical trial governance.[35]

While these are important steps forward, issues of fragmentation and inefficiency in Australia's clinical trial processes remain. Urgent work and investment by Australian Governments is needed to ensure Australia is a preferred destination for Duchenne clinical trials, and Australian children have timely and equitable access to Duchenne treatments.

International Comparisons

There is global competition to attract clinical trials given the benefits for healthcare systems and economies. Factors influencing a country's competitiveness as a clinical trial destination include its reputation for quality and reliability of research and data, trial start-up times and regulatory burden, cost, and patient pools and patient recruitment.[30]

We investigate the clinical trial approval processes and timeframes in New Zealand, the United Kingdom (England and Wales), the United States and Canada to enable comparison with Australia.

SUMMARY OF CLINICAL TRIAL APPLICATION AND APPROVAL REQUIREMENTS AND PROCESSES BY COUNTRY

COUNTRY	SINGLE OR MULTIPLE ETHICS APPLICATIONS IN MULTI-SITE TRIALS?	SINGLE OR MULTIPLE RESEARCH GOVERNANCE APPLICATIONS IN MULTI-SITE TRIALS?	SEPARATE OR COMBINED ETHICS AND RESEARCH GOVERNANCE PROCESSES?	CENTRALISED OR DECENTRALISED ETHICS REVIEW?	CENTRALISED OR DECENTRALISED GOVERNANCE REVIEW PROCESS?	SEPARATE GENE THERAPY APPROVAL PROCESS?
AUSTRALIA	There is a single national Human Research Ethics Application Form. A single HREC application may be possible in NMA jurisdictions, but trials with sites in different jurisdictions may require multiple HREC applications.	Multiple. A site-specific authorisation is required for each trial site.	Separate.	Partially centralised. HREC reviews are state-based but a single HREC approval may be accepted across NMA jurisdictions.	Decentralised. Site-specific authorisation is required for each trial site.	Yes. A GMO licence must be issued by the OGTR to use GMOs in clinical trials.
NZ	A single HDEC application covers all trial locations.	Multiple. Each locality requires a separate locality authorisation.	Separate.	Centralised. Only one HDEC review is required nationally.	Decentralised. Each locality is responsible for providing local authorisation.	No. Regulatory applications are reviewed by GTAC as part of the clinical trial regulatory process.
USA	Multiple. Ethics applications to each trial site IRB are required.	Multiple. Research governance is addressed in ethics applications to each trial site IRB.	Combined.	Decentralised. Each site IRB is individually responsible for ethics review.	Decentralised. Each site IRB is individually responsible for research governance review.	No. However, sponsors must submit a more in-depth IND to the FDA (including a Chemistry, Manufacturing and Control component), and Institutional Biosafety Committee approval is required at each trial site.
UK	A single ethics and governance application to the HRA covers all trial sites.	A single ethics and governance application to the HRA covers all trial sites.	Combined.	Centralised ethics reviews are conducted under the HRA.	Centralised research governance reviews are conducted under the HRA.	No. Ethics reviews of trials involving gene therapy are by GTAC as part of the HRA ethics review process.
CANADA	Multiple. Ethics applications to each trial site are required.	Multiple. Research governance is addressed in ethics applications to each trial site.	Combined.	Decentralised. Ethics reviews are conducted at individual trial sites.	Decentralised. Governance reviews are conducted at individual trial sites.	No. Sponsors are required to submit the same CTA with additional content relating to manufacturing and controls. This is reviewed by the Biologics and Genetic Therapies Directorate within Health Canada.

In all the jurisdictions, as in Australia, approval of a clinical trial involves approval by a health products regulatory authority, as well as ethics and research governance approval, and specific approval of the use of GMOs or gene therapies.

New Zealand

REGULATORY APPROVAL (INCLUDING GMO APPROVAL)

To undertake a clinical trial in New Zealand of a new or unregistered medicine or technology, the trial sponsor must submit an application to Medsafe (the New Zealand Medicines and Medical Devices Regulatory Authority) for approval by the Director-General of Health.

Medsafe then forwards the application to the relevant Health Research Council. This is either the Standing Committee on Therapeutic Trials, or if the trial involves a new or genetically modified organism, the Gene Technology Advisory Committee (GTAC). These committees provide recommendations to the Director-General of Health, who approves, provisionally approves or rejects the application based on the proposed trial's compliance with the Good Clinical Practice requirements, as well as scientific validity. The sponsor will receive notification of the outcome within 45 days of confirmation of the application.[36]

ETHICS REVIEW

In addition, all clinical trials require ethics review by a Health and Disability Ethics Committee (HDEC). Higher-risk trials will undergo a full review pathway and be reviewed at an HDEC meeting, while lower risk trials can be reviewed between meetings. Final decisions from the HDEC are received within 35 days for higher-risk trials, and 15 days for lower-risk trials. Only one HDEC review is required for any number of trial sites across New Zealand, and trials can commence as soon as confirmation of approval is received.

RESEARCH GOVERNANCE

Locality authorisation is the New Zealand equivalent of Australia's research governance and site assessment authorisation. Sponsors apply for locality authorisation through the Online Forms website.[37] However, each locality may have different requirements for sponsors.

The Medsafe, HDEC and locality authorisation processes can all occur in parallel. The processes can take as little as 40 days from application to full approval if sponsors are organised with documentation.[38]

United Kingdom (England and Wales)

REGULATORY APPROVAL

In the United Kingdom (England and Wales), clinical trials involving unapproved medical products are required to obtain a Clinical Trial Authorisation from the Medicines and Healthcare Products Regulatory Authority (MHRA). This application is submitted through the Common European Submission Portal, which allows a single application to be within reach of all relevant agencies. In regular cases, the MHRA's assessment is completed within 30 days of the application. However, for lower risk trials, the trial can go ahead 14 days after the MHRA acknowledges receiving the application, providing no objections are raised.[39]

ETHICS AND RESEARCH GOVERNANCE APPROVALS, INCLUDING GENE THERAPY APPROVALS

Since 2016, United Kingdom ethics reviews and local research governance reviews have been combined into one process under the Health Research Authority (HRA).[40] Clinical trial sponsors are required to submit only one application for HRA approval, which involves an assessment of governance and legal compliance, as well as a Research Ethics Committee review.

Review of trials involving gene therapy is part of the HRA approval process. Applications to the HRA are considered by the Gene Therapy Advisory Committee (GTAC), the UK national Research Ethics Committee for gene therapy research.

The benchmark for HRA approval is 60 days.[41] However, according to 2016 data, the mean time for HRA approval was approximately 90 days.[40] For gene therapy trials, the benchmark for GTAC approval is 90 days.[42]

United States

REGULATORY APPROVAL

For a clinical trial to be conducted in the United States, sponsors must submit an Investigational New Drug (IND) Application to the Food and Drug Administration (FDA). A sponsor must then wait 30 calendar days before commencing any trial, during which the FDA assesses the IND to ensure scientific validity and safety, and may discuss objections with the sponsor or issue a clinical hold if the trial poses unreasonable risk.[43] For clinical trials involving gene or cell therapy, the IND must include specific information about manufacturing specifications, testing and collection procedures.[43,44]

ETHICS AND RESEARCH GOVERNANCE APPROVAL

All clinical trials regulated by the FDA require institutional ethics committee approval by an Institutional Review Board (IRB) before a trial may commence. This may occur in parallel with FDA approval. As it is institutionally based, an IRB also assesses site-specific aspects of the trial. It is possible for a trial to be approved by a central IRB, and the judgment accepted by other trial sites. However, individual ethics applications may still need to be submitted to each trial site.[45]

Different IRBs also have different average timeframes for reviews, which depend on whether the trial requires a full board review. However, there is a 30-day national benchmark for processing of IRB applications.[45].

If the FDA has no objections to the IND within 30 days, and IRB approval is obtained, the trial may commence. This means that clinical trials in the United States may be approved in only 30 calendar days if the 30-day benchmark for IRB review is met.

GENE THERAPY/GMO APPROVAL

In addition to review by the FDA and IRB, clinical trials involving gene therapy or GMOs must be reviewed by an Institutional Biosafety Committees (IBC) at each trial site, as well as comply with FDA regulations applying to gene therapy in clinical trials. Each institution must establish an IBC to review proposed clinical trials and sponsors must apply directly to the IBC for each trial site.[46] In the IND submitted to the FDA, there is an additional Chemistry, Manufacturing, and Control (CMC) section of the application for clinical trials involving gene or cell therapy.[44]

Canada

REGULATORY APPROVAL (INCLUDING GENE THERAPY APPROVAL)

To undertake a clinical trial involving an unapproved medicine or pharmaceutical in Canada, a Clinical Trial Application (CTA) must be submitted to Health Canada.[39] CTAs involving un-marketed pharmaceuticals must only include summarised information about the drug and are sent to the Therapeutic Products Directorate, while CTAs involving biologicals, radiopharmaceuticals or gene therapy must include additional information with respect to manufacturing and release controls and are sent to the Biologics and Genetic Therapies Directorate.[47,48] All CTAs are subject to a 30-day default review period following receipt of the application by Health Canada.[48,49]

ETHICS AND RESEARCH GOVERNANCE APPROVAL

Canada has a decentralised process for ethics review of clinical trials. Trial sponsors are required to apply to the Institutional Ethics Committee of each participating clinical trial site for ethics and research governance approval, and this may occur in parallel with the CTA submission. Requirements may differ across provinces, so different sites may have different application processes and components.[45] Each institution individually reviews legal and contract issues and other research governance matters, including insurance and indemnity arrangements. The time taken for each Institutional Ethics Committee to reach its conclusion varies according to the institution and the frequency of meetings. However, Canada has a 30-day benchmark for processing of ethics review applications.[50]

If a CTA and ethics review application are submitted in parallel and the ethics review benchmark of 30 days is met, clinical trials in Canada may be approved in as little as 30 days.

How Does Australia Compare with Other Jurisdictions?

Australia's CTN Scheme is the most efficient regulatory process of the jurisdictions studied and a key strength of Australia's clinical trial system. The CTN Scheme is unique among the jurisdictions in requiring regulatory notification rather than approval and allowing trials to commence as soon as the CTN is submitted, provided ethics and site authorisations have been obtained. This means that the CTN process need not add any time to the total clinical trial approval timeframe.

TABLE 2 SUMMARY OF CLINICAL TRIAL APPROVAL TIMEFRAMES BY COUNTRY

COUNTRY	REGULATORY APPROVAL TIMEFRAMES	GMO/GENE THERAPY APPROVAL TIMEFRAMES	ETHICS AND RESEARCH GOVERNANCE APPROVAL AVERAGE TIMEFRAMES AND BENCHMARKS
AUSTRALIA	› Trial can commence immediately upon CTN notification. › 30-50 working days for CTX approvals.	› 90 working days for DNIR licence. › 150 working days for DIR licence.	› 60-day benchmark for HREC review. › No benchmark for SSA timeframe. Timeframes vary between trial sites. › Average total timeframe for HREC review and SSA of 150 to 160 days (2014-17 data). › Average timeframe for HREC review of 25-26 days when time spent waiting for information from applicants is discounted (2014-17 data). › Average timeframe for HREC review of 78-87 days when time spent waiting for information from applicants is included (2014-2017 data). › Average timeframe for SSA authorisation following HREC approval of 147 days (2016-17 data).
NZ	› 45 days.	› 45 days (as part of regulatory approval timeframe).	› An HDEC decision must be made within 35 days for high-risk trials and 15 days for low-risk trials. › No benchmark for locality authorisation. Timeframes vary between trial sites. › Average timeframes not available.
USA	› 30 days.	› Decentralised institutional approvals differ in timeframe.	› 30-day national benchmark. › Average timeframe not available.
UK (ENGLAND AND WALES)	› 30 days for regular trials. › 14 days for lower risk trials.	› 90-day national benchmark (as part of ethics approval).	› 60-day national benchmark. › Average timeframe of approximately 90 days (2016 data).
CANADA	› 30 days.	› 30 days (as part of CTA review).	› 30-day national benchmark. › Average timeframe not available.

Any time gain from the CTN Scheme in Australia may be eroded, however, by variable and lengthy HREC review and SSA timeframes, and by extended GMO licence approval timeframes for clinical trials involving gene therapies.

Australia's ethics approval timeframes are faster than international benchmarks (30 days in Canada and the United States, 15-35 days in New Zealand and 60 days in the United Kingdom) when time spent waiting for information from applicants is discounted. From 2014 to 2017, the mean timeframe for ethics review ranged from approximately 25 to 26 days. However, when this waiting time is included, the mean timeframe increases to between approximately 78 and 87 days and falls behind international benchmarks.

This suggests a need for improvement in the planning and performance of trial applicants, and for provision of more comprehensive information at the time of the initial application.

Australia's mean ethics review timeframes are substantially slower than the required timeframes for ethics review in New Zealand, the only other jurisdiction studied with a separate ethics review process.

In New Zealand, a single ethics review is accepted for any number of sites across the country, and reviews occur within only 35 days for high-risk trials and 15 days for lower-risk trials. The speed of ethics reviews in New Zealand suggests that further efficiencies could be gained in Australia if a truly national system for ethics review were introduced. As discussed, for multi-site trials across more than one jurisdiction in Australia, multiple applications are likely to be required which may have different information requirements for different trial sites, leading to duplication and inefficiency.

Australia's research governance processes contribute significantly to clinical trial approval timeframes. Australia is not unique in having decentralised and fragmented research governance processes.

Of the jurisdictions studied, only the United Kingdom has a centralised national process of research governance review. However, a key difference between Australia and Canada, the United States and the United Kingdom is that ethics review and research governance/SSA are separate processes in Australia, whereas in the other jurisdictions ethics and governance review functions are combined.

This appears to at least partly explain slower timeframes in Australia, where the average time for completion of the two processes ranges from 150 to 160 days (2014-17).

Only a very small proportion of trials (8-17 per cent in 2014-17) complete ethics and SSA processes within 60 days, most take 60-120 days (approximately 30-50 per cent in 2014-17), and the remainder take 120-180 days or longer.[50]

In comparison, the mean time for ethics and research governance approval in the United Kingdom is approximately 90 days according to 2016 data. Comparative data from United States and Canada is not available, but the 30-day benchmarks in these jurisdictions for ethics and research governance indicates that Australia is well behind.

Although separation of the processes in Australia has enabled streamlining of ethics reviews under the NMA, an unintended consequence has been that HREC review and SSA most often happen in sequence rather than in parallel. This appears to be one of the main contributors to delays in clinical trial approval timeframes in Australia.

In contrast, in the United Kingdom, the introduction of a single application and centralised process for ethics and governance review under the HRA has significantly reduced approval timeframes. Previously, there was a dual-application system and review of legal compliance was undertaken locally at each NHS organisation.

According to 2016 data, the mean time from HRA submission until HRA approval was approximately 90 days, with 53 days between HRA approval and recruiting the first patient. Within the HRA assessment, there was a mean of only 20 days between the ethics approval and the HRA approval. In the previous system which relied on sequential ethics then research governance/site specific approvals, there was a mean of 176 days between ethics approval and the first patient being recruited.[40]

For clinical trials of gene therapy for Duchenne, Australia's GMO licence approval process is far lengthier than any of the jurisdictions studied and is likely to be a major impediment to selection of Australia as a site for gene therapy trials. Australia is the only jurisdiction that requires licensing of GMOs for use in clinical trials or approval by a separate gene technology regulator.

In Canada and New Zealand, use of gene therapies in clinical trials is reviewed by a directorate or committee within the relevant regulatory authority as part of the central approval process for clinical trials. This means that gene therapy clinical trials are approved within the same regulatory approval timeframes of 30 days in Canada and 45 days in New Zealand.

KEY ISSUES & RECOMMENDATIONS

Despite significant efforts to improve the clinical trials environment in Australia, the selection of Australia as a site for Duchenne trials is likely to be impeded by lengthy and variable ethics and research governance timeframes; the lack of a truly national and harmonised ethics review system; and extended timeframes for licensing of the use of GMOs in clinical trials of gene therapies.

Implementation of the new National Research Governance Framework and national clinical trial accreditation of health services will go some way to improving research governance processes and reducing timeframes. It is hoped that this will lead to greater clarity and understanding of relevant roles and functions, adoption of a single national SSA form and increased use of standard contracts, as well as improving institutions' strategic planning and increasing their focus on meeting national approval timeframe benchmarks.

However, further action is needed to streamline and harmonise ethics and research governance approval processes and requirements, and to reform the process for approving the use of GMOs in clinical trials.

The following recommendations are made to ensure that Australians are able to access clinical trials:

RECOMMENDATION 8
Australian Government to establish a national 'one-stop' clinical trials portal.

Australian governments should collaborate to develop a national 'one-stop' clinical trials portal similar to the Common European Submission Portal. This should be supported by a single IT platform, provide a central gateway for submission of all clinical trial application documents, and allow a single application to be within reach of all relevant agencies. This would eliminate the need for multiple applications, help to promote transparency and increase inter-institutional trust and acceptance of HREC reviews, and promote standardisation of requirements.

RECOMMENDATION 9
Australian Government to develop a single national ethics review and site-specific assessment application form.

A single national online application form for ethics and research governance/SSA should also be developed. The form should consolidate information requirements for HREC review and SSAs and should be divided into modules for different areas. A single national form would ensure parallel approval processes, encourage pre-submission planning, and drive applicants to provide comprehensive information and documentation at the application stage. It would also reduce duplication in information requirements and eliminate the need for multiple different applications.

RECOMMENDATION 10
Australian Government to establish a national clinical trial coordinating agency.

The Australian government should establish a national clinical trial coordinating agency to support a centralised and nationally consistent approach. The agency would be responsible for upfront assessment and triaging of applications to relevant bodies, and act as a central point of contact for trial sponsors and applicants. This would help applicants navigate approval processes and reduce inefficiencies such as delays in providing requisite information.

RECOMMENDATION 11
Introduction of national legislation to harmonise regulatory requirements.

Australian governments should collaborate to introduce uniform legislation setting consistent national requirements for clinical trials, including in relation to privacy of personal and health information, data protection, and capacity to consent to trial participation, as well as a uniform national policy framework. The uniform legislation would supersede state/territory legislation to the extent that it applies to clinical trials. This would support centralisation and streamlining of ethics review processes by encouraging mutual recognition of HREC reviews due to standardisation of requirements, and removing the need for multiple applications with different information requirements in different states and territories. It would also help to improve clarity and understanding of regulatory obligations and compliance.

RECOMMENDATION 12
As part of the National Gene Therapy Strategy review the approval process for the use of genetically modified organisms in clinical trials.

The Australian Government should undertake an urgent review of the process for approving the use of GMOs in clinical trials. The review should consider options for introducing a specific clinical trial approval process in recognition of the need for timely approvals and that use of GMOs in clinical trials is likely to be more contained and lower risk than more widespread use of GMOs. Options should include:

- review by a gene therapy directorate or committee within the TGA as part of the central regulatory approval process for clinical trials, following the approach in Canada and New Zealand;
- review by a specific clinical trials division of the OGTR; or
- review by a separate, specially constituted agency or committee for approving the use of GMOs in clinical trials.

The review should also consider the use of risk assessment to fast-track approvals of lower risk use of GMOs or previously approved use of GMOS in clinical trials. Additionally, it should set benchmarks for approval timeframes that are competitive with international timeframes.

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CONCLUSION

There is hope. Before long there will treatments that effectively cure Duchenne, but as families wait there is work to be done to ensure they receive the care and support they need and provide the earliest possible access to new treatments.

Feedback from families highlights the importance of early diagnosis with twenty per cent of families waiting over three years. Delays impact long term outcomes and lead to families making reproductive choices without full information. A pilot study on the use of newborn screening will provide evidence of its efficacy and in the future ensure any genetic treatments can be delivered before long-term muscle damage occurs.

The NDIS continues to not provide adequate flexibility for participants with changing needs, leading to delays in equipment and supports. For children with Duchenne months do matter, and the system needs to be reformed to ensure every Australian with a disability benefits from the scheme.

As the prospect of gene therapy gets closer, Australian children risk missing out on pivotal clinical trials due to ongoing perceptions of a cumbersome regulatory system. Reforms to clinical trial approval processes should be expedited and expanded to include the approval of genetically modified organisms.

As part of a broader gene therapy strategy, Australia needs to prepare for the tsunami of new therapies that will test our health systems capacity. This will ensure that the hope which is filling families and children with Duchenne and Becker turns into reality. A future where Duchenne or Becker no longer means a shortened life.

APPENDIX A

COST OF DISEASE ESTIMATES

Health Care Costs

Health care costs associated with Duchenne are well established. A 2016 Study by Teoh et al outline the health and social care costs by age of a child with Duchenne.

We include the health care costs from this study, updating the figures to account for health inflation.

As Duchenne progresses the need for medical intervention grows, and the costs increase. In the later stages of the disease medical costs tend to fall.

AGE	AVERAGE HEALTH CARE COSTS (2014 AUSTRALIAN DOLLARS)
0-4 years	$5,672
5-14 years	$7,587
15-24 years	$15,808
25-34 years	$3,861

Total direct health care costs over the lifetime of an individual with Duchenne are estimated at between $0.3 to $0.6 million.

Social Care Costs

As Duchenne progresses the need for social care increases substantially, due to the loss of physical function. While families often provide much of this support through informal care, formal care supports are heavily relied upon alongside aids and equipment.

From the Save Our Sons Duchenne survey we know that the majority of children with Duchenne rely on supports from the NDIS, and that these costs increase as the children age.

Unlike the direct health care costs, these were found to be highest amongst the young adults aged 25-34, and indicate that this stage of the disease the costs become more care rather than medical related.

AGE	AVERAGE HEALTH CARE COSTS (2014 AUSTRALIAN DOLLARS)
0-4 years	$16,703
5-14 years	$20,812
15-24 years	$68,888
25-34 years	$72,290

Informal Caring Costs

A number of studies have highlighted the impact of having a child with a disability on maternal labour supply.[51,52,53,54,55] In the case of Duchenne, because the disability is progressive the impacts increase with age especially when compared to mothers of children without a disability.

We asked survey respondents about their hours worked, both before and after having children and found that mothers in the survey worked 10 hours less per week than similar mothers in the 2016 census.

The loss of productivity was then calculated using average hourly female wages in current dollars of $36.80 per hour from 6302.0 Average Weekly Earnings Australian, May 2019.

Expected Costs

In order to calculate expected costs we used estimates of the life expectancy of children born with Duchenne. In the absence of a long-term registry in Australia, these have been taken from recent international studies that are likely to underestimate current life expectancy.[6,8]

PROBABILITY OF SURVIVAL AT DIFFERENT AGES

AGE	PROBABILITY OF SURVIVAL
0-4 years	1.0
5-14 years	0.9
15-24 years	0.5
25-34 years	0.25

APPENDIX B

CLINICAL TRIAL APPROVAL IN AUSTRALIA

Clinical Trial Approval Processes in Australia

Approval of a clinical trial in Australia involves the following processes:

- Notification to or approval by the Therapeutic Goods Administration (TGA) under the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) Scheme if the trial uses an unapproved therapeutic good.
- Ethics and scientific review by a Human Research Ethics Committee (HREC) to ensure the trial is in accordance with the National Statement on Ethical Conduct in Human Research (2007) (the National Statement).[56]
- Research governance review by each institution at which a trial will take place, including a site-specific assessment (SSA) of the institution's capacity to undertake the trial and ensuring necessary contractual and insurance arrangements are in place.

In addition, clinical trials involving a genetically modified organism must generally obtain a licence from the Office of the Gene Technology Regulator (OGTR). This is a requirement for clinical trials of gene therapies for Duchenne.

TGA Notification or Approval under the CTN or CTX Scheme

Australian clinical trials involving unapproved therapeutic goods must either be notified to the TGA under the CTN Scheme or approved by the TGA under the CTX Scheme[iii].

The CTN Scheme is generally used for later phase (III and IV) and bioavailability/ bioequivalence trials of medicines but may also be used for earlier phase (I and II) trials if there is adequate preclinical trial information available, especially regarding safety.[57] Most clinical trials in Australia are notified to the TGA under the CTN Scheme.

Under the CTN Scheme, a clinical trial applicant is only required to notify the TGA of the trial and the TGA does not review or evaluate data. The target timeframe for processing of online CTNs is 5–7 working days. However, as soon as the CTN has been submitted, the TGA is deemed to have been notified and the clinical trial may commence, so long as necessary ethics approvals and site authorisations have been provided. The CTN Scheme is recognised as a major enabler of clinical trials in Australia and one of the most efficient regulatory processes for clinical trials internationally.[30]

The CTX scheme is generally used for high-risk or novel treatments where there is no or limited knowledge about safety.[33] The CTX Scheme involves evaluation by the TGA of information about the clinical trial, including scientific data.

There is a 30-50 working day period for the evaluation of a CTX application, meaning that the wait for approval for a clinical trial under the CTX Scheme can be up to three months.[iv] CTX review can occur in parallel with HREC approval and site authorisation, but a trial may only proceed once these approvals are obtained. At the time of writing, the CTX Scheme is under review and may be subject to change.

iii CTN notification or CTX exemption is required for any product not on the Australian Register of Therapeutic Goods (including any new formulation or route of administration of a product) and use of a product beyond the conditions of its marketing approval. Clinical trials of products on the Australian Register of Therapeutic Goods and used within the conditions of their marketing approval are not subject to CTN or CTX requirements but must still be approved by a HREC.

iv The applicant may be the trial sponsor, lead investigator, trial coordinator or a Contract Research Organisation engaged by the trial sponsor.

Ethics and Scientific Review by a Human Research Ethics Committee

All clinical trials in Australia must be reviewed by an HREC according to the National Statement.[v] [56,58] The HREC reviews the scientific validity, ethical acceptability, and the risk versus potential harm of the trial proposal.[58]

Each Australian State and Territory has separate ethics and scientific review requirements and processes. To help streamline these processes, the Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria and Western Australia have agreed to National Mutual Acceptance (NMA), under which each jurisdiction mutually accepts single scientific and ethical reviews of multi-site clinical trials across jurisdictions. This may avoid the need for the trial sponsor to apply to multiple HRECs and allow a project with ethical approval obtained in any of the NMA jurisdictions to be expanded to sites in other jurisdictions.[59]

This has made considerable progress towards streamlining HREC reviews. However, a single national ethics approval process has not yet been established and there continues to be fragmentation between states and territories. Northern Territory and Tasmania have not yet signed up to the NMA, there are some exceptions to the NMA in participating jurisdictions,[vi] and the NMA applies to public health organisations only and not private organisations.

There is also variability in application requirements across the NMA jurisdictions. Although a national Human Research Ethics Application form has been developed for NMA jurisdictions, there are four different IT platforms and application portals across the jurisdictions, requiring applications to be submitted differently depending upon the jurisdiction in which they are lodged.[vii] In addition, trials involving one or more sites in Victoria and Western Australia require a specific module or forms with additional information requirements due to differing legislative requirements in relation to matters such as privacy of personal and health information, data protection and capacity to consent.[59,60]

This means that multi-site trials, or recruitment of participants from multiple jurisdictions, may still require multiple HREC applications and reviews. This leads to duplications and inefficiencies, which may impact approval timeframes and costs.

Despite this, the NMA scheme has contributed to shorter ethics approval timelines, which have been noted by pharmaceutical companies as one of Australia's competitive advantages.[30,33]

From 2014-2017, when days spent waiting for applicants' responses to requests for further information were discounted, between 89 and 94 per cent of HREC approvals met a benchmark timeline of 60 days, with the mean timeframe ranging from approximately 25 to 26 days. This is highly competitive with international benchmarks for time to process ethics applications, which include 145 days in China, 60 days in England and Wales, 35 days in New Zealand and 30 days in the United States and Canada. However, when total time was measured and wait times were not discounted, only 45 to 49 per cent of HREC approvals from 2014-2017 met the 60-day benchmark, and the mean time for approval increased to between approximately 78 and 87 days.[50]

This indicates delays may largely result from deficiencies in initial information provided by applicants, as well as inefficiencies in communications between applicants and ethics committee investigators.[50] It has been reported anecdotally that in most cases approval is not granted on first review, indicating that improving the quality of information the applicant provides to the HREC in the first instance may help to further reduce timeframes.[61]

v Therapeutic Goods Regulations 1990, r 12AD.

vi Phase 0 (first time in human or patient) and Phase I trials are excluded from single ethics review under NMA in South Australia and the Australian Capital Territory.

vii Applications in New South Wales and the Australian Capital Territory use the REGIS website (https://regis.health.nsw.gov.au/), applications in South Australia use the online forms website (https://au.ethicsform.org/SignIn.aspx), applications in Queensland and Victoria use the ERM website (https://au.forms.ethicalreviewmanager.com/Account/Login), while in Western Australia, applications need to be submitted either to the Research Governance Service for Western Australian Health HRECs, or via Online Forms (https://au.ethicsform.org/SignIn.aspx) for non-WA Health HRECs participating in the NMA.

Research Governance Approval, including Site-specific Assessment

Research governance refers to the processes by which each institution undertaking a clinical trial ensures it is accountable for the research. Research governance addresses the safety and quality of research, as well as financial management, risk management, and legal and regulatory compliance.

As part of research governance, institutions undertaking a clinical trial complete a site-specific assessment (SSA) to assess the suitability of the trial for the site. This involves considering trial budgets, physical resources, staff, insurance and indemnity requirements, and contractual arrangements. Both ethics approval and SSA are required before a trial can commence at a site.[62]

It has been reported that the SSA process can be lengthy and may vary widely from site to site and study to study.[30] Standard contract templates for clinical trial agreements and indemnities have been developed. However, it has been suggested that some sites nevertheless apply inconsistent requirements due to inadequate understanding of essential and non-essential steps, leading to lengthy contract discussions.[63]

The major cause of delays and variability in ethics and SSA approval times, however, appears to be that the two processes are often conducted sequentially. Most jurisdictions have a policy of encouraging submission of site assessment documents before or at the same time as submission of ethics applications so that the SSA and HREC approval processes can run in parallel. This supports speedy approvals in some cases, with examples of site authorisation granted in less than two weeks after ethics approval,[33] and even in as little as two days.[61] However, it has been reported that parallel submission rarely happens in practice, contributing to delays in SSAs of 3-6 months after ethics approval.[33,50] From 2014-2017, only around 30 per cent of SSAs occurred within 60 days of HREC approval. In 2016-17, the average time for SSA following ethics approval was 147 days.[50]

When considering the entire timeframe for the ethics and SSA processes, only between 8 and 17 per cent of trials from 2014-2017 completed the processes within 60 days. The proportion of trials completing the processes within 120 days ranged from 31.5 per cent (2014-2015) to 42 per cent (2015-2016) and 51 per cent (2016-2017), with the remainder of trials taking between 120 and 180 days to receive necessary approvals. The average time for completion of the two processes ranged from 150 to 160 days.[50]

Reasons suggested for the delay in submission of SSA/site assessment applications until after ethics approval include:

- a lack of understanding by research governance officers of the roles of SSA and ethics reviews, leading to the view that they ask for similar things and reluctance to devote resources to SSAs until ethics approval is finalised;[33]
- industry delays in providing key documents;
- protracted negotiations on trial budget; and
- clinical loads, lack of resources and/or lack of funding leading to delays in submitting applications.[50]

GMO licence approval

For clinical trials of gene therapies for Duchenne, a licence to use GMOs must also be obtained from the Office of the Gene Technology Regulator (OGTR) before the trial can proceed. If the GMO is expected to be shed or excreted from trial participants and consequently released into the environment, a Dealing involving Intentional Release (DIR) licence is required. If the GMO is expected to be contained in the bodies of trial participants and not shed or excreted, a Dealing Not involving Intentional Release (DNIR) licence is required.

To apply for a GMO licence, an institution must be accredited under the *Gene Technology Act 2000 (Cth)*. GMO licence applications must be endorsed by an institution's Institutional Biosafety Committee before being submitted to the OGTR.[64]

A GMO licence application can be submitted concurrently with HREC and TGA applications. However, the licence approval timelines are extremely lengthy. The OGTR has 90 working days (about 4.5 months) to decide DNIR licence applications and generally 150 working days (about 8 months) to decide DIR licence applications, though if the OGTR seeks information from the applicant, any days it waits for the information do not count towards these timeframes. A longer timeframe may apply for DIR licence applications if the OGTR finds that the GMO may pose a significant risk to people or the environment or the applicant has not proposed appropriate limits and controls.[64]

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CONTACT THE MCKELL INSTITUTE

T. (02) 9113 0944 **F.** (02) 9113 0949 **E.** mckell@mckellinstitute.org.au
PO Box 21552, World Square NSW 2002
@McKellInstitute www.facebook.com/mckellinstitute
www.mckellinstitute.org.au