Special Commission of Inquiry into Healthcare Funding

Statement of Professor Ian Alexander

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1. This statement made by me accurately sets out the evidence that I would be prepared, if necessary, to give to the Special Commission of Inquiry into Healthcare Funding as a witness. The statement is true to the best of my knowledge and belief.

2. This statement is provided in response to a letter of 24 May 2024 issued to the Crown Solicitor's Office and addresses the topics set out in that letter relevant to my role.

A. INTRODUCTION

3. My name is Professor Ian Alexander. I am the Director of Laboratory Research and a Senior Staff Specialist at The Children's Hospital at Westmead, SCHN, and Head of the Gene Therapy Research Unit at SCHN and CMRI. A copy of my curriculum vitae is at **Exhibit A**.

4. The focus of my research is gene therapy, which has been an area I have been involved in since 1992. This is a field that has been quite protracted in gestation but has developed rapidly in the last five to seven years, and is set to have a significant impact on clinical medicine. In my role, I am focused on the development of novel gene therapy approaches to the treatment of genetic diseases of childhood and on bringing the best paediatric gene therapy trials in the world to Australia at the earliest opportunity. One of the more prominent trials I have brought to SCHN is a gene therapy treatment for Spinal Muscular Atrophy (**SMA**). I am also an expert in the underlying gene transfer technologies, most notably genetically engineered viral vectors, that are required to undertake these unprecedented therapies. I am also co-leading a major initiative through NSW Health to establish a Good Manufacturing Practice (**GMP**) viral vector manufacturing capability to support gene therapy clinical trial activity, the first of its kind

in Australia. I liaise with the Chief Executive of the Agency for Clinical Innovation in relation to this initiative.

B. DEVELOPMENT AND APPROVAL OF CLINICAL TRIALS

5. I play a significant role in identifying world-best clinical trials and managing the initial relationship with the organisations funding those trials so that SCHN is selected and approved as a trial site. If the trials and therapy are successful, the therapy will then go through formal evaluations not only with NSW Health but with the Commonwealth Government. I am not responsible for managing those evaluations.

6. The process for assessment and approval within the scope of my role can be seen using the example of the clinical trial of Zolgensma to treat SMA. Zolgensma is a gene therapy treatment developed to treat SMA, an inherited neuromuscular disorder that was previously a leading genetic cause of infant death in Australia. I advocated and negotiated with a small bio-technology company, AveXis, to establish a key early phase trial site of the gene therapy treatment in NSW. This simultaneously leveraged a pilot study of Newborn Screening for SMA by NSW Health to allow early diagnosis and treatment. Both the trial and treatment were a success, and AveXis was purchased by Novartis, a large bio-technology company who took the treatment to market globally. I was not involved in the process of having the treatment approved by the Therapeutic Goods Administration (**TGA**) nor negotiating with the Commonwealth Government for public funding under the Pharmaceutical Benefits Scheme (**PBS**). Whilst the cost implications for the treatment are relevant to NSW Health, obtaining Commonwealth funding reduces those concerns.

7. I am involved in the approval of clinical trials concerning gene transfer technology. Clinical trials that involve gene transfer technology require consideration of a range of legislative requirements such as the *Gene Technology Act 2000* (Cth) through the Office of the Gene Technology Regulator (**OGTR**) because they involve genetically modified organisms (viral vectors). These activities require an OGTR licence, TGA approval, an Australian Biosecurity Import Conditions (**BICON**) permit from the Commonwealth Department of Fisheries and Forestry (**DAFF**), and ethics approval from the SCHN Human Research Ethics Committee (**HREC**). If approval has been granted from an approved overseas regulator (such as the Food and Drug Administration (**FDA**) or European Medicines Agency (**EMA**)) the TGA only requires notification of the trial and will accept the international evaluation. In respect of ethics approval, SCHN has a paediatric ethics committee which is certified to evaluate early phase trials. Of note, the

SCHN HREC is supported by the SCHN Scientific Advisory Committee (**SAC**). I do not consider the current process is unduly cumbersome. Most of the requirements and approvals do not occur within NSW Health.

C. IDENTIFYING AND PRIORISITING INVESTMENT IN TECHNICAL AND CLINICAL INNOVATIONS

8. New therapies generally emerge organically and governments have to work out how to respond. Close to 97% of global biomedical research and development occurs outside Australia and, as a direct consequence, the vast majority of new therapies will be developed overseas and commonly enter Australia as clinical trials. The funding for these trials comes from overseas, with Australian health authorities exerting little influence over which trials enter the country. NSW Health has recognised the imminent tsunami of advanced therapeutics, including gene therapy and cell therapies, and the related need for health system readiness. They have also invested in capabilities that will fortify the ability of NSW to increase the development and clinical translation of novel therapies locally. These capabilities include the GMP manufacture of viral vectors and Ribonucleic acid (**RNA**) therapeutics for gene therapy and other applications such as vaccine development. Never-the-less, at the clinical level, service planning and related strategic investment will remain heavily influenced by the global environment.

9. An impact of this is that NSW Health is limited in managing the cost structure of technical and clinical innovations. There are several factors which underpin the cost structure of new therapies, one of them is Australia's dependency on international biomanufacturing at the present time. Australia is very good at proximal and distal ends of the translational pathway, that is, laboratory research and clinical trials. However, Australia has limited capability and infrastructure to translate developments from the laboratory into the clinical setting. One of these limitations is Australia's current inability to manufacture genetically engineered viruses required for clinical trials involving new therapies (see above). There are close to 4000 gene, cell and RNA therapies in development globally, with approximately 25% in early phase clinical trials and over 100 already approved in international jurisdictions. In order to advance NSW's investment in technical and clinical innovation, NSW needs to have capability to move pre-clinical research out of laboratories into the clinical trial setting, and it is in this transition that we are more dependent on international partners.

10. NSW Health is motivated to address this deficiency and sees itself as the national leader in the advanced therapeutic space. Vector technology is a big part of the solution. In

time, investment in this area should reduce the cost of treatments, however because Australia contributes minimally to global market forces, it is difficult to predict. A factor to consider is that many Contract Manufacturing Organisations (**CMO**s) involved are interested in the ability to scale therapies to meet market demands rather than delivery of bespoke manufacturing that is required to support early clinical trials for the many disease indications with high unmet clinical need.

D. EVALUATING CLINICAL AND TECHNICAL INNOVATIONS

11. It is very difficult to evaluate the costs and benefits of clinical and technical innovations that are still in development in a prospective manner, and certainly not with the expectation that the outcome of such evaluations will significantly influence eventual clinical uptake. Such studies may, however, improve health system readiness.

12. Research is being conducted into the economic impact and value of advanced therapies with gene therapy for SMA being a good exemplar. Among other factors, consideration is being given to the durability of such therapies and how they will be funded, however this research is not being done prospectively. While the idea of doing prospective assessments on the economic impact and influence of new therapies has theoretical merit it would be difficult to implement in a meaningful way. This is the consequence of multiple factors that include, but are not limited to, the vast number of advanced therapies in development, the number of disease indications involved and difficulty in predicting which therapies will succeed in trials and progress to market authorisation. One possible path is to focus attention on therapies showing promise in late phase clinical trials for diseases with the highest net health and economic impact.

E. FUNDING ARRANGEMENTS AVAILABLE TO SUPPORT CLINICAL TRIALS

13. For clinical trials arising from Australian pre-clinical research, there are funding opportunities available through competitive entities such as the National Health and Medical Research Council (**NHMRC**) and Medical Research Future Fund (**MRFF**). Where funding is granted, the cost structure of advanced therapeutics is such that the funding is generally insufficient to cover the full cost of taking the therapies to clinical trial. Early engagement with the commercial sector is generally required for funding. An alternative is setting up a start-up or spin-out company and bringing in venture capital, however this is challenging, especially in Australia where the venture capital landscape is relatively limited.

14. Conversely there are no fiscal barriers to hosting international clinical trials in Australia for therapies developed overseas as costs are covered by the international sponsors. Australia is also an attractive location for clinical trials to be conducted because it is more cost-efficient to run than in North America, and we have highly regarded health systems. For the SMA trial, SCHN was chosen as an international site because I was aware of the success of the therapy and advocated directly with AveXis, the international biotherapeutics company involved, for it to be run at SCHN.

15. If NSW is proactive, we can bring in trials with the biggest potential health impacts for the state. Many countries look to Australia to conduct clinical trials and the way they currently do that is to look up clinicians on PubMed (and other open sources) who know of the disease. These clinicians may be familiar with the disease but are generally not familiar with the technologies proposed to be used, so commonly do not have the skill set to evaluate whether the trial will be likely to succeed. This is a weakness of the current system. To resolve this issue at SCHN, SCHN has established a Kids Advanced Therapeutics (**KAT**) program which supports clinicians who are approached to not only be more selective about which trials to participate in, but also to implement the trial within SCHN once selected.

16. KAT is an entity within SCHN comprised of a multi-disciplinary team which operates to evaluate and implement clinical trials. I played a role in the genesis of the entity and continue to contribute to the initial evaluation and selection of which trials SCHN should participate in, however I am not involved in the day to day running of the entity. In addition to supporting trial selection and all aspects of trials implementation, the KAT program is involved in education and community out-reach though the running of a seminar series, and annual “science meets the clinic” symposium and the development of educational material.

17. SCHN is also discussing the prospect of establishing a consortium of hospitals trialling gene therapies with Children’s Hospitals in Victoria and Queensland. The consortium would facilitate discussions about challenges and shared experiences. Some of the conditions the therapies are intended to treat are relatively rare and it might be prudent if the therapies are trialled in one hospital nationally rather than every major hospital trying to deliver bespoke therapies. There is considerable interstate competitiveness, but there is a clear recognition that a collaborative national approach is the best way forward.

F. FUTURE PLANNING OF TECHNICAL INNOVATIONS

18. An example of future planning in relation to technical innovations can be seen in the SMA trial. When clinical trials are brought into the country, extensive testing needs to be performed on candidates to determine their eligibility. That often includes blood tests to determine their immune system's reaction to the genetically modified virus. Currently, the tests are sent offshore because big pharmaceutical companies that are driving the clinical trials will not allow the tests to go to laboratories without their certification. During the SMA trial and ongoing since TGA approval of Zolgensma in Australia, children receiving therapy continue to be required to have their blood tests sent to Europe or North America for antibody testing, which takes time, increases costs and prevents TGA oversight of the testing. Currently, Novartis is evaluating SCHN's ability to conduct this testing in Australia through the establishment of a national testing laboratory. This is an initiative of NSW Health and if certification is obtained, this will be the first time this type of testing has been undertaken in Australia.

G. EXAMPLES OF TECHNICAL INNOVATIONS

19. Gene therapy can be given through two different methods, ex vivo or in vivo. Ex vivo involves removing the cells from a patient, modifying the cells and replacing them back into the patient. An example of a target of ex vivo gene transfer is bone marrow which can be harvested, repaired and returned to the patient. In vivo therapy involves the direct injection of a gene therapy product into the patient. This product can be in the form of DNA, RNA or synthetic analogues thereof.

20. Another rapidly evolving advanced therapy is being built on stem cell technology where cells can be first converted into stems and then directed to develop into almost any cell type in the body. Such cells and small organ-like structures called organoid have substantial direct and indirect therapeutic promise. There are two different types of cellular therapy, autologous and allogeneic. Autologous cellular therapy involves extracting a patient's stem cells, reprogramming the stem cells and returning them to the same patient. This therapy is bespoke and more challenging because it involves modifying an individual patient's stem cells. Allogeneic cellular therapy involves the use of stem cells that are not derived from the patient being treated but from an unrelated donor whose cells have been expanded and banked for the treatment of multiple recipients. Allogeneic cellular therapy is therefore suited to higher volume use but has the downside of potentially needing associated immunosuppression in recipients.

21. An example of autologous cellular therapy is CAR T-cell therapy. This therapy utilises T-cells (white blood cells) to treat conditions such as leukaemia and lymphoma and is being developed with the hope of being useful for many other forms of cancer.

22. There remains debate among experts about the relative merits of allogeneic and autologous cellular therapies and the implications for biomanufacturing and service delivery are immense. Some experts are pragmatic and consider allogeneic cellular therapy is preferrable because it can be developed on a larger scale, however some experts consider autologous cellular therapy is preferable because it is native to the recipients, more physiological and may be more likely to effectively treat the patient. Because of the differing nature of the therapies, they have different cost structures. Autologous cellular therapy requires the extraction of stem cells from the patient before the cells are transferred to a facility for modification and then sent back to the hospital for re-insertion. If the therapy is allogeneic however, it would just need to be developed and banked and then sent from a storage facility to a hospital for therapy as needed.

Prof Ian Alexander	Witness:
17 June 2024	17 June 2024
Date	Date