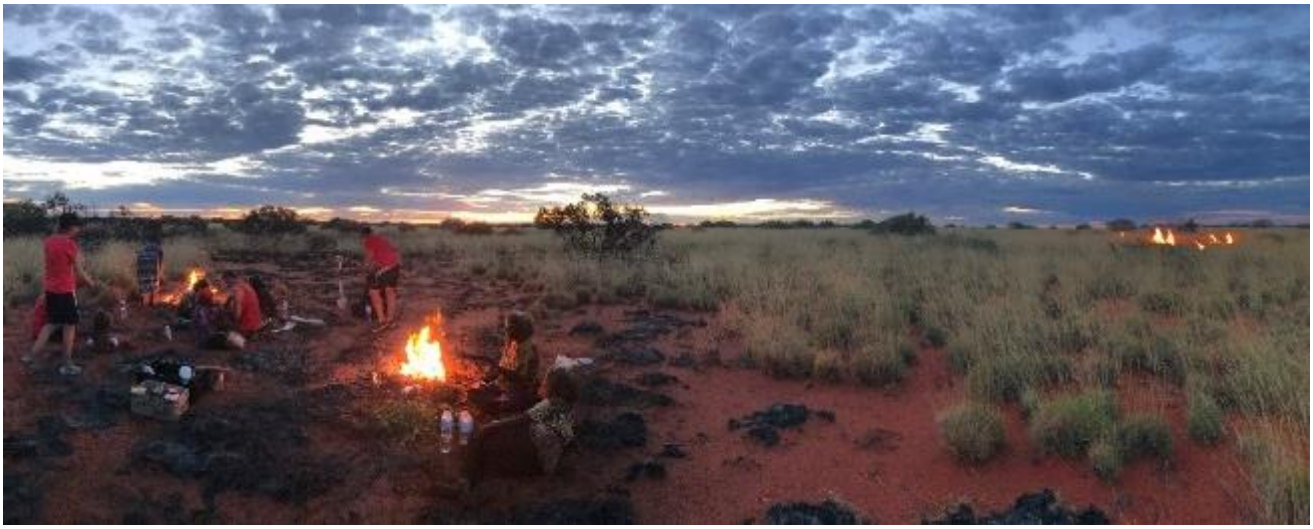

2020-21 Pre-Budget Submission

December 2019

RED DUST

Edwards

FOREWORD

Rheumatic heart disease (RHD) is preventable. As at 31 December 2017, there were 4,255 people living with RHD recorded on state and territory registers, of whom 3,687 were Indigenous Australians and a further 400,000 young Indigenous people are at risk. This represents one of the highest rates of rheumatic heart disease in the world.[1][2]

The disease results from an abnormal autoimmune response to a group A streptococcal infection in a genetically susceptible host. Acute rheumatic fever (ARF) —the precursor to rheumatic heart disease (RHD) —can affect different organs and lead to irreversible valve damage and heart failure. Although penicillin is effective in the prevention of the disease, treatment of advanced stages uses up a vast amount of resources, which makes disease management especially challenging.

Early detection and targeted treatment might be possible if populations at risk for rheumatic heart disease in endemic areas are screened. In this setting, active surveillance with echocardiography-based screening is very important.

Working in partnership with Red Dust, clinicians, hospitals, Aboriginal Controlled Community Health Organisations, government and non-government organisations, we are proposing a ten-year clinical study of 100 RHD patients from our Indigenous communities to benefit from Edwards Lifesciences latest bioprosthesis valve. The improved technology associated with this valve has the potential to vastly improve health outcomes for remote RHD patients and this study will help to assess and quantify those benefits.

In addition to treatment benefits this project will also include training and employment of local remote community residents to support the project outcomes. Local staff will play a key role in ensuring cultural safety of the project and be integral in supporting a community education effort to reduce future RHD incidence. It is the intention of this proposal to "save countless lives"[3] beyond the 100 patients who would receive a RESILIA tissue valve through increased prevention and education that is culturally meaningful.

We believe this study aligns with the Australian Government priority to close the gap in Aboriginal and Torres Strait Islander health by committing to end rheumatic heart disease.

[1] https://endrhd.telethonkids.org.au/SysSiteAssets/media-docs---end-rhd/cost-of-inaction-on-rheumatic-heart-disease_edited.pdf
[2] https://www.aihw.gov.au/reports/indigenous-australians/acute-rheumatic-fever-rheumatic-heart-disease/contents/rheumatic-heart-disease/rhd-among-all-australians
[3] https://www.theaustralian.com.au/nation/health/35-million-in-funding-for-rheumatic-heart-disease-vaccine-will-save-lives/news-story/cdbaafa0d1c6d5ad62ebf2a11e9d81ac

About Red Dust

Red Dust has over 20 years' experience partnering with remote Indigenous communities to deliver health and well-being programs. A unique 'community-as-family' model of programming is helping to close the gap by walking alongside community leaders and elders to create a stronger future for youth and their families. Red Dust draws on the strengths of all the worlds that surround young people in community and utilise positive role models and engaging, high impact programs, to inspire youth to identify and pursue their dreams.

Red Dust's long-term goal is improved health and well-being in remote Indigenous communities. This is to be achieved through better health literacy, realisation of identity (cultural & individual), pursuit of personal aspirations and strengthened cross-cultural competency – the ability to walk strongly in both traditional Aboriginal and western worlds. Red Dust aims to contribute to national efforts to 'close the gap' between Indigenous and non-Indigenous Australians while acknowledging this is not a simple proposition. National efforts to-date have been largely centralised; tending towards homogeneity; biased towards Western medical responses without sufficient regard for strength-based and culturally relevant methodology.

The Red Dust program model addresses these shortcomings by drawing on the strengths of both worlds and placing value on localised cultural frameworks and structures unique to each community. In practice, the program model sees Red Dust teams visiting remote communities armed with various skills, knowledge and enthusiasm and framed by organisational values of being real, ready and respectful. Teams work closely with local leaders and elders to deliver locally relevant program activities that inspire and engage young people and families around priority health and wellbeing themes. They support creation of content such as music videos and artwork that reflect local languages and cultures.

Red Dust incorporates western-evidence-based health concepts alongside ancient local knowledge systems resulting in a two-way exchange that benefits all participants. Ultimately the Red Dust strategy reaches beyond solely improving health outcomes and towards a loftier goal of shared Australian cultural identity. By walking alongside remote communities in a spirit of trust Red Dust builds shared values and goals and aims to deliver lasting change through living and breathing Reconciliation.

About Edwards Lifesciences

Edwards Lifesciences, based in Irvine, Calif., is the global leader in patient-focused medical innovations for structural heart disease, as well as critical care and surgical monitoring. Driven by a passion to help patients, the company collaborates with the world's leading clinicians and researchers to address unmet healthcare needs, working to improve patient outcomes and enhance lives.

Edwards Lifesciences' roots date to 1958, when Miles "Lowell" Edwards set out to build the first artificial heart. Edwards was a 60-year-old, recently retired engineer holding 63 patents in an array of industries, with an entrepreneurial spirit and a dream of helping patients with heart disease. His fascination with healing the heart was sparked in his teens, when he suffered two bouts of rheumatic fever, which can scar heart valves and eventually cause the heart to fail.

Through our actions, we strive to become Trusted Partners with our customers, colleagues, and the patients we serve. We are dedicated to providing innovative solutions for people fighting cardiovascular disease.

RECOMMENDATION: INVEST $7.7 MILLION OVER TEN-YEARS

We are proposing a post-market study of Aboriginal and Torres Strait Islanders in the Northern Territory (NT). The study will include screening prospective patients through existing Red Dust programs in remote NT communities as well as training of a local workforce to support the study and delivery of community education about RHD to reduce future incidence.

Working with existing health networks in NT we will look to screen patients with RHD to receive an innovative tissue valve. The process of screening will be supported by local staff who will be trained to provide on-ground assistance for patient recruitment, advice and care thereby increasing cultural safety for patient participation. Local staff will also support a community engagement and education strategy to raise awareness about RHD risk factors and increase community capacity to reduce future RHD incidence.

The study will include approximately 100 patients and will include yearly follow up for 10 years. In addition to these 100 patients who will receive direct benefit from the project we expect that a significant number of community members will receive long-term benefit through a grassroots community health education approach that will see them avoid RHD in the future.

Standard practice in Australia in young patients is to implant a mechanical prosthesis which comes with a lifelong burden of warfarin therapy. Anticoagulation with warfarin is associated with a cumulative bleeding risk per year. There is also the challenge of regular monitoring and the dangers of drug-drug interactions and drug-food interactions; these challenges and poor compliance bring with it increased mortality. Further to this, there is a 2% per year serious bleeding risk or thrombosis of the mechanical valve. There are also considerations for women and pregnancy, as blood thinners increases complications during pregnancy and delivery.

Most patients with RHD whose suffer from valvular stenosis and have their stenotic valve(s) replaced, are young patients who are best served by a valve that will provide the longest re-intervention period. A bioprosthesis is expected to function for only 5-10 years before undergoing structural valve deterioration (SVD) compared to the general population where a bioprosthesis lasts 15-20 years. Patients who experience SVD will require reoperation which carries significant risks of death, stroke and is a considerable expense to the health system.

New technology developed by Edwards Lifesciences and unique to the market known as RESILIA tissue on the INSPIRIS valve blocks the calcium build-up over traditional valve tissues, which means it could potentially allow the valve to last longer. It has the additional benefit of Vfit technology that means the patient could avoid the need of further open-heart surgery as a transcatheter aortic valve implantation (TAVI) could be placed inside the INSPIRIS RESILIA valve in the future.

The purpose of the study is to help towards closing the gap but in addition provide real-world evidence of durability of RESILIA tissue. The hypothesis is to show RESILIA is superior to other tissue valve and mechanical valves in the treatment of patients suffering from RHD.

The method for patient screening will include a consultation performed by a local health provider partnering with Red Dust during remote community programs to detect any heart murmur, if a murmur

is detected, an echocardiogram will be performed at the closest health facility. Screening is a useful method for detecting RHD in regions of high prevalence.

We are proposing four tertiary level hospitals participate in the study. Flinders Hospital Cardiology Department already provides support to Darwin Private and Public Hospitals. Cardiac Surgery services are based at Flinders Medical Centre (FMC). The other hospitals are Royal Adelaide, Fiona Stanley and Townsville Hospital.

All four hospitals will need to go through ethics committee for approval, given the emphasis is on Aboriginal and Torres Strait Islanders an additional level of scrutiny will be needed given it would be dealing with a vulnerable population. There are some Human Research Ethics Committees (HRECs) with specialist expertise in reviewing ethics proposals for research involving Aboriginal and Torres Strait Islander Peoples. Some institutions require additional ethics review by one of these committees in addition to ethics review from their own institution as a compulsory measure, and some institutions require this additional ethics review on a more ad hoc or as-needed basis. It is a matter for individual institutions to determine if they wish to have all ethics proposals for research involving Aboriginal and Torres Strait Islander Peoples and communities reviewed by HRECs with specialist expertise in this area. However, all institutions must ensure that their HREC has access to the expertise necessary to enable it to address the ethical issues arising from the research it reviews. [4]

The study will provide a primary endpoint at year one, three, five and 10.

Burden

More than 60% of those with ARF go on to develop RHD within 10 years, representing a large burden of morbidity and mortality in this high-risk population.[5] As at 31 December 2017, almost 6400 living persons were recorded in one or more of the four Australian ARF/RHD registers, comprising approximately one third each of ARF alone, RHD alone and both ARF and RHD. Of the people affected, 89% were Indigenous Australians, 61% were female and 41% were aged 5-14 years when registered for the first time.[6]

Based on extrapolation of data from the four ARF/RHD registers, the estimated crude rate of ARF diagnoses in Australia was 4.1 per 100,000 per year in the five-year period from 2013 to 2017. Ninety four percent of ARF diagnoses occurred among Indigenous Australians, for whom the rate of ARF diagnoses was 85.0 per 100,000 per year, compared to 0.3 per 100,000 per year among non-Indigenous Australians. By year, the rate of ARF diagnoses in Australia steadily increased over the five-year study period, from 3.0 per 100,000 in 2013 to 6.0 per 100,000 in 2017. Among Indigenous Australians, the rate increased from 53.0 per 100,000 in 2013 to 111.0 per 100,000 in 2017. The rate of new RHD diagnoses for Indigenous females was around two times that for Indigenous males, which was consistent with the literature.[7]

[4] https://www.nhmrc.gov.au/research-policy/ethics/ethical-guidelines-research-aboriginal-and-torres-strait-islander-peoples
[5] McDonald MI, Towers RJ, Andrews RM, Benger N, Currie BJ, Carapetis JR. Low rates of streptococcal pharyngitis and high rates of pyoderma in Australian aboriginal communities where acute rheumatic fever is hyperendemic. Clin Infect Dis. 2006;43(6):683–9.
[6] https://www.aihw.gov.au/reports/indigenous-australians/acute-rheumatic-fever-rheumatic-heart-disease/contents/summary
[7] Zuhlke LJ, Beaton A, Engel ME, Hugo-Hamman CT, Karthikeyan G, Katzenellenbogen JM, et al. Group A Streptococcus, Acute Rheumatic Fever and Rheumatic Heart Disease: Epidemiology and Clinical Considerations. Curr Treat Options Cardiovasc Med. 2017;19(2):15.

Since the commencement of record keeping by the registers, 1,725 RHD related surgeries have been recorded for 1,277 individuals. More than three-quarters (78%, 1,340) of these surgeries occurred in Indigenous Australians. [8]

In 2013–2017, 322 Indigenous Australians with RHD underwent 350 surgery events. The majority of people had one surgery while 23 people had up to 4 surgeries. Nearly 300 valve replacement procedures occurred, among these, replacement with a mechanical valve (166) was more common than with a bioprosthetic valve (131).[9]

Nearly 50% of the Indigenous RHD cases who died in 2013–2017 were 45–64 years old (108 deaths), and just over one-quarter (61 deaths) were in cases 25–44 years old. Thirteen deaths (5.9%) were in young adults aged 15–24 years. The median age of death was 50 years. In line with overall rates of RHD, around two-thirds of deaths (145 deaths) were in female RHD cases.[10]

The Aboriginal and Torres Strait Islander Australian population made up 2.8% of the total Australian population[11] but, despite its much younger age structure, carried 3.6% of the total population disease burden. The rate of burden increased at much younger ages for Aboriginal and Torres Strait Islander peoples and was also considerably higher for each age group compared with the total Australian population.[12]

In 2005–07, life expectancy for Aboriginal and Torres Strait Islander peoples was estimated to be 11.5 years lower than that of the non-Indigenous population for males (67.2 compared with 78.7 years) and 9.7 years lower for females (72.9 compared with 82.6 years). For the four jurisdictions with Aboriginal and Torres Strait Islander populations of sufficient size to calculate Indigenous life expectancy estimates, the lowest were for those living in the NT and WA and the highest in NSW and Qld.[13] Life expectancy is widely viewed as a key measure of the health of populations. Closing the gap in life expectancy between Aboriginal and Torres Strait Islander peoples and other Australians has been adopted as a high-level target by COAG, which aims to close the life expectancy gap within a generation.

Based on the Telethon Kids Institute report into the cost of RHD in Australia by 2031 if no further action is taken a further 10,212 Aboriginal and Torres Strait Islander people are projected to develop the disease or its precursor – ARF – by 2031. Of these people: 1,370 will need heart surgery, 563 with RHD will die and $317 million will be spent on medical care.[14]

Treatment and Cost

Management of RHD diagnosis is complex and involves coordination of multiple services such as primary health care (for secondary prophylaxis with penicillin and monitoring of heart medications such as anticoagulation therapy), oral healthcare services, echo, specialist medical care, and other cardiothoracic and interventional cardiology services.[15]

[8] https://www.aihw.gov.au/reports/indigenous-australians/acute-rheumatic-fever-rheumatic-heart-disease/contents/summary
[9] Ibid
[10] Ibid
[11] 2071.0 - Census of Population and Housing: Reflecting Australia - Stories from the Census, 2016
[12] Vos, T, Barker, B, Stanley, L & Lopez, AD 2007, The burden of disease and injury in Aboriginal and Torres Strait Islander peoples 2003, School of Population Health, University of Queensland, Brisbane.
[13] https://www1.health.gov.au/internet/publications/publishing.nsf/Content/oatsih-hpf-2012-toc~tier1~life-exp-wellb~119
[14] https://endrhd.telethonkids.org.au/SysSiteAssets/media-docs---end-rhd/cost-of-inaction-on-rheumatic-heart-disease.pdf
[15] RHD Australia (ARF/RHD writing group), National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand

The main options for surgical management of RHD are:

- Balloon valvotomy, which can be used to treat mitral stenosis. This operation can be performed by threading a deflated balloon on wires up to the heart from a cut in the groin. The narrowed mitral valve is opened by gently inflating a balloon inside the valve. The small incision reduces costs and complications compared with open surgical repair.
- Valve repair involves repairing the heart valve shape and function to allow for normal blood flow. It usually involves open heart surgery. Repair generally offers the best outcomes for children and adults, particularly for mitral valve.[16]
- Valve replacement involves removing the damaged valve and replacing it with a mechanical prosthetic (metal valve) or bioprosthetic valve (tissue valve from animal or human donors). This generally involves open heart surgery.

An individual may have surgical events more than once on damaged valves and may have multiple procedures in one surgical event— that is, multiple valves repaired or replaced in a single surgery.

Compared to a mechanical valve, cost savings arising from implantation of INSPIRIS RESILIA would result from avoidance of warfarinisation and bleeding associated with anticoagulation. Furthermore, cost savings would result from the adverse consequences of inadequate warfarinisation, including thrombosis and need for re-operation.

Compared to 'conventional' aortic bioprosthesis, cost savings arising from implantation of INSPIRIS RESILIA would result from avoidance or delay of re-operation due to structural valve deterioration. A recently-published Australian study by Zhou et al[17] estimated that the cost (in 2018 values) of a surgical aortic valve procedure was $47,384 and the cost of a TAVI procedure was $41,615. These represent cost savings with each type of reoperation avoided.

Furthermore, if re-operation is required and the heart team determines the patient is suitable for TAVI, then a cost saving will result from reduced need for a surgical procedure as opposed to a TAVI, because the VFit expansion frame enables true valve-in-valve. As per the study by Zhou et al 23, the difference in the cost of a TAVI versus a surgical procedure was $5769 ($47,384 minus $41,615). Zhou et al also estimated the cost-benefit of TAVI compared to a surgical valve replacement over a ten-year time horizon in patients with intermediate operative risk. With 5% annual discounting, the total cost savings were $9629.

The primary comparator is another bioprosthetic valve with surgical valve replacement or TAVI at a later time if the valve fails within the patient's remaining lifespan. The 'intervention' is INSPIRIS RESILIA, with a ViV procedure at a later time. The clinical effectiveness of INSPIRIS RESILIA arises from the delay in the need for another valve procedure, and potential avoidance of a surgical re-operation. The second group comprises younger patients for whom lifelong warfarinisation is problematic. For this group, the primary comparator is another bioprosthetic valve if there is an absolute contraindication to warfarin.

2012. The Australian guideline for the prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (2nd edn). Northern Territory: RHD Australia, Menzies School of Health Research.

[16] Wang Z, Zhou C, Gu H, Zheng Z & Hu S 2013. Mitral valve repair versus replacement in patients with rheumatic heart disease. J Heart Valve Dis 22(3):333–9.

[17] https://www.ncbi.nlm.nih.gov/pubmed/31255453

The INSPIRIS RESILIA aortic valve has been extensively tested in animal models, which have demonstrated significantly less calcification compared to valves fixed in glutaraldehyde. To date, available follow-up data (up to four years) for humans have not shown any evidence of calcification. Currently-available data, with follow-up of up to four years to date, has found no structural valve deterioration in INSPIRIS RESILIA valves. By comparison, conventional tissue valves has been observed to have structural valve deterioration in up to 2% at five years.

	Tissue Valve	Mechanical Valve
Long-term blood thinner requirement	**No**	**Yes** Daily blood thinner medication and regular blood tests for rest of life
Valve longevity	**10 to over 20 years. Depending on type of valve, patient characteristics and other factors.** The new INSPIRIS RESILIA aortic valve has the added benefit of RESILIA tissue, (a new tissue that has been shown in animal studies to have less calcium buildup), potentially allowing the valve to last longer.	**Over 20 years in general**
Lifestyle and dietary considerations	**Yes** May need to reduce calcium intake	**Yes** Limits active lifestyle and foods high in vitamin K from diet
Noticeable sounds from valve	**No**	**Yes** Clicking sound as valve opens and closes
Pregnancy consideration	**No** No known pregnancy complication risk	**Yes** High pregnancy complication risk due to use of blood thinners

Trialing RESILIA In a Remote Community Context

This post-market clinical trial provides an opportunity to improve health outcomes for remote Indigenous RHD patients through provision of new heart valve technology that is better suited to population needs. This proposal also provides opportunity for local Indigenous training and employment and the provision of RHD community education to reduce future RHD incidence.

The burden of RHD in Australia is far greater in the Aboriginal and Torres Strait Islander population, and in particular the remote population of the Northern Territory, and current 'standard' clinical procedures are not optimal. Mechanical valve replacement requires the use of Warfarin which has a significant compliance requirement including monitoring of diet and regular blood tests. This can be very challenging for remote community residents. Replacement with a tissue valve provides a solution for

this however known issue with calcification mean that further open-heart surgery is often required within a sub-optimal timeframe adding cost and significant impact on quality of life. It is anticipated that the technological benefits of RESILIA would lead to significantly improved quality of life through reduced need for medication compliance, a longer period between valve replacement and a reduced health burden when replacement is required due to the ability to replace via catheter rather than further open-heart surgery.

In addition to the direct health benefits to patients this trial offers additional benefit through the involvement of an experienced and trusted Northern Territory not-for-profit Red Dust, who will support the project through community engagement, the employment of remote community staff to support the trial and the development and delivery of localised RHD education to help reduce future incidence.

A Community-as-Family Approach

Red Dust's Healthy Living Program is a powerful vehicle for health and well-being promotion in vastly underserved remote Australian Indigenous communities. Community consultation and engagement regarding this project has commenced using the unique strengths of Red Dust programs in partnership with Edwards Lifesciences. Following this consultation it has been possible to plan for a rheumatic heart disease awareness and screening pilot in one remote community in 2020.

Red Dust's community-as-family model of programming engages Aboriginal youth and families and is developed and delivered in partnership with local elders and community organisations, ensuring cultural authenticity, complementarity with existing services and opportunities for local training and employment. It is proposed that local remote community staff will be employed to support the implementation of this clinical trial. Local staff will support the process of informing and educating the community, liaising with the local clinic, identifying prospective patients, assisting with genuine informed consent processes and supporting the patient journey through the trial including potentially travelling with patients as a carer support person during surgery visits interstate. The involvement of local staff will increase the cultural safety for patients involved in the trial.

Furthermore, local staff will support the development and delivery of customised community education initiatives. Red Dust knows from experience that the most effective health promotion efforts are those that speak to local language, culture and custom. A one-size fits all approach does not work in a remote context and the best results come when community is engaged in an intergenerational storytelling process. Red Dust has pioneered the use of various engagement techniques such as music, video and animation to create engaging health promotion assets that stand the test of time. Through this project there is an ability to work closely with community to raise awareness about RHD, about risk factors and to develop localised strategies to reduce incidence in the long term.

Stakeholder Engagement

Stakeholder engagement is critical to the success of this study. Two key stakeholder groups have been identified for consultation - (i) remote community Leaders and Elders and (ii) organisations providing research/health promotion/services for the remote communities.

Initial stakeholder consultation pre-submission

A small selection of community and organisational stakeholders were consulted in the development of this submission. Positive feedback received from this small selection of stakeholders established our confidence in outcomes from a formal stakeholder consultation process.

The formal stakeholder consultation with community and organisational stakeholders will begin once the Minister has provided feedback on this submission and/or part of implementation plans.

Remote community leaders and elders

Informal consultation has been undertaken with a select group of community leaders to obtain initial feedback and consent for further exploration of this proposal. Feedback was very positive with strong interest to understand more about the potential treatment and the opportunities for local involvement in both the screening/treatment and the community education elements.

Health promotion/service provider engagement

The following organisations have been identified and recommended to include for the initial stage of formal stakeholder consultation. Some informal consultation has taken place in the preparation of this submission.

- National Heart Foundation of Australia
- Aboriginal Health Council of Western Australia (AHCWA)
- National Aboriginal Community Controlled Health Organisation (NACCHO)
- RHDAustralia,
- Aboriginal Medical Services Alliance Northern Territory (AMSANT)
- Telethon Kids Institute (home of the END RHD Centre for Research Excellence)
- NT Centre for Disease Control
- NT Department of Health, Primary Health Networks,
- Aboriginal Medical Services Alliance Northern Territory
- State and Federal Health Departments
- Royal Adelaide Hospital
- Fiona Stanley Hospital
- Townsville Hospital
- Darwin Private and Public Hospitals
- Flinders Medical Centre
- Australian & New Zealand Society of Cardiac & Thoracic Surgeons
- Professor Alex Brown (South Australian Health and Medical Research)
- Dr Misty Jenkins (Walter and Eliza Hall Institute of Medical Research)

SUMMARY

We commissioned Monash University Professor Danny Liew[18] to calculate the cost effectiveness of converting RDH patients away from conventional tissue valves and or mechanical towards this new INSPIRIS value.

[18] Deputy Head of School (Education and Enterprise), Chair of Clinical Outcomes Research, and Co-Director of the Centre of Cardiovascular Research and Education (CCRE) at the School of Public Health and Preventive Medicine.

Based on data from 2013-2017, 95 Indigenous Australians per year undergo repair or replacement of heart valves due to rheumatic heart disease. Of the 95, 24 per year undergo repair or replacement of the aortic valve. Of the 24, 10 receive a replacement mechanical valve and 10 receive a replacement 'conventional' bioprosthetic valve.

Over a 20-year time horizon from the time of surgery, the total costs of aortic valve replacement in the 20 people would amount to $1.70 million (with 5% annual discounting).

The costs take into account the costs of anticoagulation and associated bleeding among those who receive a mechanical valve, and the need for another replacement valve among those who receive a 'conventional' bioprosthetic valve.

The average 20-year cost would be $83,971 per person.

If INSPIRIS RESILIA is used instead of a mechanical or 'conventional' bioprosthetic valve, the 20-year total costs of aortic valve replacement in the 20 people would amount to $1.62 million (with 5% annual discounting).

The average 20-year cost would be $80,272 per person.

The net savings in healthcare costs amount to $74,715 for the 20 people, and $3698 per person.

This analysis does not take into consideration improved quality of life arising from avoidance of anticoagulation and bleeding, as well as of another replacement valve.

CONCLUSION

This submission recommends investment in an innovative partnership approach to tackle an insidious health issue that should not exist in Australia in 2020.

Through the combined efforts of a leading multi-national health company and a grass-roots Indigenous health not-for-profit there is an opportunity to provide an improved treatment option to around 100 remote community RHD patients which will likely result in a much better quality of life. In doing so the project will simultaneously deliver local training and employment to ensure a culturally safe screening and treatment environment as well as localised community education to improve community capacity to reduce long-term RHD incidence.

Red Dust and Edwards have recently committed to partnering on a pilot community RHD education program in 2020, critical work that will inform this proposed larger scale screening/treatment and education project. Initial consultation with community has been very positive and the trust that Red Dust has built from over twenty years of remote community work will ensure that the project can commence in an efficient manner.

We would welcome an opportunity to discuss this submission in detail and can facilitate the involvement of community representatives in this process.

APPENDIX A: THE EPIDEMIOLOGY OF ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN AUSTRALIA

Prof Danny Liew, November 2019

Introduction

Rheumatic heart disease (RHD) is characterised by long-term cardiac valve damage resulting from a single episode or multiple episodes of acute rheumatic fever (ARF) (1). ARF results from a systemic autoimmune response occurring 2-4 weeks after respiratory infection with group A streptococcus, and manifestations include carditis/valvulitis, arthritis, erythema marginatum, subcutaneous nodules and Sydenhams' chorea (2). Diagnosis is based on the modified Jones' criteria (3). Penicillin is used both for primary prevention of ARF (treatment of group A streptococcus infection) and secondary prevention (prevention of recurrent attacks). The long-term management of RHD comprises prevention of ARF recurrence and monitoring (via echocardiography) and treatment of left ventricular function. The management of arrhythmias (notably atrial fibrillation) and valvular disease may also be required (1).

RHD is typically a disease affecting people of low socioeconomic state, associated with overcrowding, poor sanitation and lack of access to adequate healthcare services (4). The following brief report outlines the current understanding of the epidemiology of ARF and RHD in Australia.

Methods

A literature search was undertaken on 27 November 2019 of the PubMed database using the search terms "rheumatic heart disease" and "prevalence" and "Australia". Titles and abstracts were reviewed for relevant publications, which were retrieved in full text form. A 2019 report by the Australian Institute of Health and Welfare (AIHW) entitled 'Acute rheumatic fever and rheumatic heart disease in Australia' (5) was also reviewed. The report was based on analysis of data from four ARF/RHD registers (registries) in Queensland, Western Australia, South Australia and the Northern Territory. These registers are supported by the Australian Government's Rheumatic Fever Strategy, which also seeks to promote the primary and secondary prevention of ARF and increase awareness and understanding of ARF and RHD among health professionals and vulnerable communities.

Results

There was significant variation in the published estimates of incidence and prevalence of ARF and RHD in Australia. This reflected heterogeneity in terms of study populations, methods used for disease ascertainment and diagnostic criteria applied. Given this, the present report focused on results presented in the 2019 AIHW report (5), given that they were based on state/territory-based disease registers and were the most recently available.

As at 31 December 2017, almost 6400 living persons were recorded in one or more of the four Australian ARF/RHD registers, comprising approximately one third each of ARF alone, RHD alone and both ARF and RHD. Of the people affected, 89% were Indigenous Australians, 61% were female and 41% were aged 5-14 years when registered for the first time.

Based on extrapolation of data from the four ARF/RHD registers, the estimated crude rate of ARF diagnoses in Australia was 4.1 per 100,000 per year in the five-year period from 2013 to 2017. Ninety four percent of ARF diagnoses occurred among Indigenous Australians, for whom the rate of ARF diagnoses was 85.0 per 100,000 per year, compared to 0.3 per 100,000 per year among non-Indigenous Australians. By year, the rate of ARF diagnoses in Australia steadily increased over the five-year study

period, from 3.0 per 100,000 in 2013 to 6.0 per 100,000 in 2017. Among Indigenous Australians, the rate increased from 53.0 per 100,000 in 2013 to 111.0 per 100,000 in 2017.

Based on extrapolation of data from the four ARF/RHD registers, the estimated crude rate of new RHD diagnoses in Australia was 3.0 per 100,000 per year in the five-year period from 2013 to 2017. Eighty three percent of new RHD diagnoses occurred among Indigenous Australians, for whom the rate of new RHD diagnoses was 49.9 per 100,000 per year, compared to 0.4 per 100,000 per year among non-Indigenous Australians. By year, the rate of new RHD diagnoses in Australia remained constant over the five-year study period. The rate of new RHD diagnoses for Indigenous females was around two times that for Indigenous males, which was consistent with the literature (2)

As at 31 December 2017, there were 4255 (44.0 per 100,000) living persons with RHD recorded in the four registers, with more females (58.0 per 100,000) than males (31.0 per 100,000) (5). Eighty seven percent of affected people were Indigenous Australians, among whom the prevalence was 845.2 per 100,000, compared to 5.4 per 100,000 among non-Indigenous Australians.

Comparisons of these prevalence figures can be made to those estimated in a global study (4), which found the age-standardised prevalence of RHD in 2015 to be 444 per 100,000 for countries with an endemic pattern, and 3.4 cases per 100,000 for countries with a non-endemic pattern.

Limitations of the four state/territory ARF/RHD registers should be acknowledged, the primary of which were data misclassification (inaccuracy), information bias (for example, differential reporting between Indigenous and non-Indigenous Australians) and selection bias (for example, differential recruitment of Indigenous and non-Indigenous Australians). The AIHW report did not discuss these limitations, and hence the extent to which they were issues was not clear. Furthermore, the directions of any biases, if present, were not known. Other major limitations of the AIHW analyses were that only crude (that is, not age-adjusted) estimates of incidence and prevalence were presented, and it was not stated how incidences and prevalences were calculated.

References

1. Carapetis JR, Beaton A, Cunningham MW, Guilherme L, Karthikeyan G, Mayosi BM, et al. Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers. 2016;2:15084.
2. Zuhlke LJ, Beaton A, Engel ME, Hugo-Hamman CT, Karthikeyan G, Katzenellenbogen JM, et al. Group A Streptococcus, Acute Rheumatic Fever and Rheumatic Heart Disease: Epidemiology and Clinical Considerations. Curr Treat Options Cardiovasc Med. 2017;19(2):15.
3. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Carapetis J, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation. 2015;131(20):1806-18.
4. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990-2015. N Engl J Med. 2017;377(8):713-22.
5. Australian Institute of Health and Welfare 2019. Acute rheumatic fever and rheumatic heart disease in Australia. Cat. no. CVD 86. Canberra: AIHW. Viewed 29 November 2019, https://www.aihw.gov.au/reports/indigenous-australians/acute-rheumatic-feverrheumatic-heart-disease

APPENDIX B – **INSPIRIS RESILIA COST SAVINGS**

Aortic Valve Replacement for Rheumatic Heart Disease Among Indigenous Australians
Prof Danny Liew, December 2019

Based on data from 2013-2017 [1], an average of 95 Indigenous Australians per year undergo repair or replacement of heart valves due to rheumatic heart disease. Of the 95, 24 undergo repair or replacement of the aortic valve. Of the 24, 10 receive a mechanical valve and 10 receive a 'conventional' bioprosthetic valve.

Over a 20-year time horizon from the time of surgery, the total healthcare costs incurred by the 20 people who receive a replacement aortic valve would amount to $1.75M.

These costs take into account the costs of anticoagulation and associated bleeding among those who receive a mechanical valve, and the need for another replacement valve among those who receive a 'conventional' bioprosthetic valve [2-8].

The 20-year cost would be $86,738 per person on average.

If INSPIRIS RESILIA is used instead of a mechanical or 'conventional' bioprosthetic valve (and it assumed that this reduces the probability of need for another replacement valve by half among those who receive a 'conventional' bioprosthetic valve), the 20-year total costs of aortic valve replacement in the 20 people would amount to $1.62M.

The 20-year cost would be $80,272 per person on average.

The net savings in healthcare costs amount to $130,635 ($74,715 if discounted at a 5% annual rate) for the 20 people, and **$6466 ($3698 discounted) per person**.

This analysis does not take into consideration improved quality of life arising from avoidance of anticoagulation and bleeding, as well as of another replacement valve.

References

1. Australian Institute of Health and Welfare 2019. Acute rheumatic fever and rheumatic heart disease in Australia. Cat. no. CVD 86. Canberra: AIHW. Available at: https://www.aihw.gov.au/reports/indigenous-australians/acute-rheumatic-fever-rheumatic-heart-disease/data
2. Swinkels BM, et al. Long-term bleeding events after mechanical aortic valve replacement in patients under the age of 60. *Neth Heart J.* 2015 Feb;23(2):111-5.
3. Bourguignon T, et al. Very Long-Term Outcomes of the Carpentier-Edwards Perimount Valve in Aortic Position. *Ann Thorac Surg* 2015; 99: 831-7.
4. Eikelboom J, Merli G. Bleeding with direct oral anticoagulants vs warfarin: clinical experience. *Am J Emerg Med*. 2016 Nov; 34(11S): 3-8.
5. Independent Hospital Pricing Authority. National Hospital Cost Data Collection, COST WEIGHTS FOR AR-DRG VERSION 8.0, Round 21 (2016-17), Public. Available at: https://www.ihpa.gov.au/publications/national-hospital-cost-data-collection-report-public-sector-round-21-financial-year

6. Australian Government Department of Health. Pharmaceutical Benefits Scheme. Available at: http://www.pbs.gov.au/pbs/home;jsessionid=rraud5vnqp751mapat66uc9bw
7. Australian Government Department of Health. Medical Benefits Schedule. Available at: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home
8. Australian Government Department of Health. The Prostheses List. Available at: https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-privatehealth-prostheseslist.htm

APPENDIX C – STUDY SYNOPSIS

Protocol Synopsis

Title:	Prospective, non-randomized, multicenter clinical evaluation of the Edwards Inspiris Resilia Valve
Trial Device:	Edwards Pericardial Aortic Bioprosthesis, Model 11000A
Indication for Use:	The Edwards Pericardial Aortic Bioprosthesis, Model 11000A, is indicated for patients who require replacement of their native or prosthetic aortic valve.
Trial Objective:	The objective of this trial is to confirm the safety and effectiveness of the Edwards Inspiris Resilia Bioprosthesis (Model 11000A) in Aboriginal and Torres Straight patients who require replacement of their native or prosthetic aortic valve.
Trial Design:	Multicenter, prospective, single arm trial – Up to x 100 aortic valve replacement (AVR) subjects at four (4) clinical sites will be enrolled.
Trial Sites:	Participating sites are chosen based on their experience in conducting clinical trials, their surgical experience implanting bioprosthetic valves, as well as their ability to maintain robust subject enrollment and follow-up.
Trial Duration:	Total enrollment period for this trial is estimated to be 10 years. Interim Analysis of the study data will be conducted at 1, 3, 5 and 10 years.

Trial Follow-Up Visits:	**Visit**	**Visit Window (Days)**
	Screening/Baseline	
	Discharge[1]	
	30 Days	-5/+10
	3 months	- 15/+30
	1-10 years	-25/+45
	[1] Subjects who are not discharged within 10 days post procedure must have an echocardiogram to assess performance of the trial valve. Those subjects will not require an additional echocardiogram at discharge.	
Trial Endpoints:	***Primary Safety Endpoint (up to 390 days post-implant):*** The primary safety endpoint for the trial is the rate of implanted subjects that experience structural deterioration of the trial valve by the time of the one year follow-up visit. The null hypothesis is that the rate of structural valve deterioration at one year is greater than 1%. The alternative hypothesis is that this rate is less than 1%. ***Secondary Safety Endpoints***:	

Safety is established by comparing the occurrence of specific safety endpoints to the objective performance criteria (OPC) reported in Table R.1 in ISO 5840:2005, Annex R.1 as recommended by the FDA in the Draft Guidance involving Heart Valves – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications (2010).

- Thromboembolism
- Valve thrombosis
- All bleeding/hemorrhage
- Major bleeding/hemorrhage
- All paravalvular leak
- Major paravalvular leak
- Non-structural valve deterioration
- Endocarditis
- All cause mortality
- Trial valve-related mortality
- Trial valve-related reoperation
- Explant
- Hemolysis

***Effectiveness Endpoints*:**

- Clinically acceptable hemodynamic performance confirmed by core lab evaluation of echocardiography
- New York Heart Association (NYHA) functional class compared to baseline
- Change in Quality of Life questionnaire Short Form 12 version 2 (SF-12v2) from baseline/screening to one year visit

Subject Enrollment:

Inclusion Criteria:

Each subject is required to meet all of the following inclusion criteria:

1. Is 18 years or older
2. Is of Aboriginal or Torres Straight heritage or descent
3. Provides written informed consent prior to trial procedures
4. Agrees to attend all follow-up assessments for up to 10 years and is willing to comply with specified follow-up evaluations at clinical investigational sites that are participating in the trial and/or obtain the protocol-specified diagnostic tests at centers that are under the same IRB or the same healthcare system
5. Diagnosed with aortic or mitral valve disease requiring valve replacement based on pre- operative evaluation
6. Scheduled to undergo planned aortic or mitral valve replacement with or without concomitant bypass surgery
7. Scheduled to undergo planned aortic valve replacement with or without resection and replacement of the ascending aorta from the sinotubular junction and without the need for circulatory arrest for hemi arch or arch replacement

Exclusion criteria:

A subject meeting any of the following criteria shall be excluded:

1. Requires emergency surgery
2. Requires multiple valve replacement/ repair (with the exception of mitral valve replacement with tricuspid valve repair)

3. Has prior valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*
4. Requires a surgical procedure outside of the cardiac area (e.g. vascular bypass)
5. Requires surgical replacement of the aortic root
6. Has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months to the scheduled aortic or mitral valve replacement surgery
7. Has renal insufficiency as determined by creatinine (S-Cr) level ≥ 2.5 mg/dL or end-stage renal disease requiring chronic dialysis at screening visit
8. Has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to planned valve surgery
9. Has acute myocardial infarction (MI) within 30 days prior to planned valve surgery
10. Has presence of non-cardiac disease limiting life expectancy to less than 12 months
11. Diagnosed with hypertrophic obstructive cardiomyopathy (HOCM)
12. Diagnosed with abnormal calcium metabolism and hyperparathyroidism
13. Exhibits left ventricular ejection fraction ≤ 20% as validated by diagnostic procedure prior to planned valve surgery
14. Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
15. Hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to planned valve surgery
16. Documented leukopenia (WBC < 3.5x 10^3/µL), acute anemia (Hgb < 10.0 gm/dL or 6 mmol/L), or thrombocytopenia (platelet count < 50x10^3/µL) accompanied by history of bleeding diathesis or coagulopathy
17. Has prior organ transplant or is currently an organ transplant candidate
18. Current or recent participation (within 6 weeks prior to surgery) in another drug or device trial
19. Was previously implanted with trial device (Model 11000A or Model 11000M)[19]
20. Pregnant (female subject of childbearing potential only), lactating or planning to become pregnant during the duration of participation in trial
21. Currently incarcerated or unable to give voluntary informed consent
22. Requires concomitant left ventricular assist device (LVAD) placement

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[19] Note: Previously implanted means that the index valve replacement procedure was completed. The procedure is complete when the surgeon takes the subject off cardiopulmonary bypass and restarts the heart.