Clinician - PACT
New Clinical Trial and Research

Trial title	Genetic research in Idiopathic Pulmonary Fibrosis (GRIPF)
Trial synopsis	Pulmonary Fibrosis (PF) encompasses a group of lung disorders that share the hallmark of fibrosis or scarring of the lung tissue. The single most prevalent and devastating of these is idiopathic PF (IPF), a severe and progressive lung disorder with a median survival rate of only 2-5 years from diagnosis – worse than many cancers. IPF is the primary focus of this study. Although there are a number of established environmental risk factors identified for IPF which include smoking, viral infection and occupational factors, at diagnosis the natural history for an individual IPF patient is still unpredictable. There is an urgent need to better understand how disease progresses and the factors that impact disease outcomes, especially with effective medications now becoming available. While most IPF is sporadic, familial IPF is recognised and appears to have an autosomal dominant pattern of inheritance potentially impacting first and second-degree relatives. The genes involved are likely to be rare in the community but of high impact in those affected. Little is known about this form of IPF and which genes are more likely to be involved pathogenically. Compelling evidence exists supporting a critical role for genetic factors in developing IPF. Indeed, a number of genome wide association studies (GWAS) have been conducted to date with around 26 IPF associated loci. The contribution of these loci to disease varies in different populations. The genetic variants identified to date include both rare and common variants in genes in a variety of pathways. To date the effort has largely focused on using GWAS approach, which has identified common genetic variation underpinning this disease. However, typically GWAS rely on very large numbers of cases, and are designed to detect more common genetic variants of small to moderate effect size. It has been shown that rare variants contributing to complex disease may be missed by GWAS, as has been described for epilepsy. This is because GWAS has a different focus which is a reliance on identifying common genetic variation statistically associated with 'risk'. Therefore, whilst useful, GWAS discovers only explain a portion of IPF risk. Findings from the Fingerlin et al (2013) estimate that the

	known IPF genetic variants described to date explain only about a third of genetic risk for IPF. Further some of the loci identified by GWAS may also harbor rare genetic variation contributing to disease at least in a proportion of affected individuals. There has recently been significant success in the discovery of rare genetic variants contributing to complex disease through next-generation sequencing (NGS) of families, where rare variants are enriched and there is reduced genetic complexity. This approach may be particularly valuable here as evidence from studies to date suggest that familial and sporadic IPF have similar genetic aetiologies. There is strong consensus surrounding the enormous value of careful clinical genotyping for familial-based genetic studies. It is also clear from evidence to date that genetic studies should be undertaken in different populations in order to appropriately capture the spectrum of rare variation underpinning this disease. The approach outlined here combining the familial approach to discover rare variants associated with disease in carefully phenotyped individuals from the Australian IPF Registry represents a valuable opportunity to make significant contribution to our understanding of this disease. We are interested in involving families in this study as this will allow us to look at genetic similarities and differences in family members with and without disease. Ideally these families will have at least one member with IPF and other members impacted by pulmonary fibrosis.
Investigational medicinal product, comparator and randomisation	Nil.
Disease target	IPF
Sponsor	Philanthropic support
Duration	5-years
Trial Status	Recruiting
Trial phase	Not applicable
Key inclusion criteria	Families will have at least one member with IPF and other members impacted by pulmonary fibrosis.
Key exclusion criteria	Not applicable
Primary endpoint	Not applicable

Number of participants sought	20 well described families, family members with and without disease.
Lead site(s) in Australia	Royal Prince Alfred Hospital, Camperdown, NSW
Lead site(s) in New Zealand	Not applicable
Additional sites	Royal Prince Alfred Hospital NSW The Alfred Hospital, VIC The Prince Charles Hospital QLD Fiona Stanley Hospital WA Royal Adelaide Hospital, SA John Hunter Hospital NSW Calvary Surgical Suites TAS Launceston General Hospital TAS Clinical A/Prof Peter Kendal WA (private) Equinox Specialist Centre, ACT Border Physicians Group NSW Sunshine Coast University Hospital & Health Service QLD
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