WHITE PAPER

OUTCOMES AND METHODOLOGY FOR TREATABLE
TRAITS BASED RESEARCH

Chronic lung diseases vary in clinical presentation and treatment response. A proposed solution to address the excessive disease burden faced by people with asthma and COPD is a personalised medicine based strategy called "Treatable Traits". Furthering the research and implementation of "Treatable Traits" will depend on answering a two fundamental questions in regard to study design and outcome measures

Centre of Excellence in Treatable Traits
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Outcomes and Methodology for Treatable Traits Based Research

Chronic lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD) adversely impact the lives of millions of people globally. Asthma is common and affects over 330 million people worldwide, including one in nine Australian adults. Asthma imposes a major burden on the healthcare system, on people who live with the disease, their loved ones and on society. Chronic obstructive pulmonary disease is one of leading causes of death globally and is associated with multiple comorbidities or coexisting medical problems. The significant burden caused by these common conditions is increasing and action is required to improve the lives of people affected by these conditions.

How can we improve the outcomes for chronic lung disease?

A feature of asthma and COPD is the heterogeneity of presentation. Heterogeneity assumes that within and between individuals, the clinical, biological and functional presentation of diseases vary. While current management approaches have led to significant improvements in outcomes, they are unable to sufficiently address this heterogeneity. Personalised medicine is a new approach to disease management that is delivering considerable improvements in disease related outcomes and health related quality of life in many areas of medicine, including cancer and other respiratory diseases. Personalised medicine accounts for heterogeneity by targeting to the needs of individuals on the basis of distinguishing genetic, biological, phenotypic or psychological characteristics.

The variability of clinical presentation and treatment response is recognised among clinicians who manage chronic lung diseases, however this variability is not routinely addressed. A proposed solution to address the excessive disease burden faced by people with asthma and COPD is a personalised medicine based strategy called "Treatable Traits".

Treatable Traits- The Concept

The distinguishing feature of the Treatable Traits approach is the recognition that not all people with chronic lung disease are the same, and therefore recognising the individual variation is critical. In addition, these conditions are complex, meaning that not all problems (or traits) are present in all people at the same time. Treatable Traits characterises this individuality and allows for the

implementation of targeted treatments to address it. The Treatable Traits approach involves a multidimensional assessment and characterisation of 'traits' which guides the application of evidence based personalised-medicine according to the identified traits.

The traits that form the Treatable Traits approach are phenotypic or endotypic characteristics, which can include characteristics of the lung (such as the presence of airway inflammation), comorbidities (for example anxiety, vocal cord dysfunction and gastroesophageal reflux), risk factors (including obesity, smoking and bone density) and self-management skills (adherence and inhaler technique to name a few).

To meet the criteria of a 'trait' each characteristic must be 1) clinically relevant, 2) identifiable and measurable, and, 3) of course, be treatable. Representing Treatable Traits are three specific domains in which traits fall: the pulmonary, extrapulmonary and behavioural/risk-factors domains.

Complex problems require a complex solution

Recently the National Health and Medical Research Council (NHMRC) invested in the current crisis faced by people with chronic lung diseases by funding a Centre of Research Excellence in Treatable Traits. The Centre of Excellence in Treatable Traits is a global consortium of world-renowned clinicians, researchers and key respiratory organisations who are collaborating to improve healthcare outcomes for people with chronic lung diseases such as asthma and COPD. Our mission is to revolutionise the management of chronic lung diseases by testing and implementing the "Treatable Traits" approach.

Furthering the research and implementation of "Treatable Traits" will depend on answering a two fundamental questions in regard to study design and outcome measures.

Study Design

The first question is to determine if "Treatable Traits" based research questions need to be answered using efficacy trial designs, or effectiveness trial designs. As "Treatable Traits" is a complex intervention, the traditional randomised controlled trial design may not be sufficient to address efficacy outcome measures. Additionally, the trait interventions that form part of the Treatable Traits model of care, are likely to already have efficacy data, for example treatments for airway inflammation, or treatments for anxiety already have a sufficient evidence base. Given this, Treatable Traits based effectiveness trials, including implementation trials may be more appropriate. Effectiveness trials are designed to examine the degree of benefit of an intervention in the real-world setting. Useful examples from implementation science that can be used to assess effectiveness include: stepped wedge designs, hybrid I, II and III effectiveness studies and configurational comparative methods.

Another promising approach is the use of Adaptive trial designs. Adaptive trials use the data generated throughout the study to modify the trial, making it more efficient. This may be an appropriate trial design to examine a complex intervention, such as Treatable Traits, however further thought is required to define how that may operate.

Treatable Traits Outcome Measures

In clinical trials outcome measures (otherwise known as dependent variables) are used to determine the effectiveness (or efficacy) of the intervention, procedure, process or medication. Since "Treatable Traits" is a complex intervention, which acts on many aspects of a person's health and wellbeing, determining which outcome to use is crucial to be able to determine the effectiveness of the Treatable Traits Model of Care, but is somewhat challenging. One potential solution which has been used in other disease groups, such as chronic kidney disease and COPD exacerbations to this is the development of a core outcome set. A core outcome set is an agreed upon, standardised group of outcomes to be reported by all clinical trials conducted within that area of study. Core outcome sets can include core sets which are essential for all studies, but can also include an extended version of outcomes, which may be appropriate for a subgroup within the broader disease group. This onion-type layer approach allows for the

expansion of the core outcome set, and enables the core outcome set to grow and expand as the field of research grows and expands. The elements of a proposed core outcome set for Treatable Traits could include quality of life measures, exacerbation events, disease control and quality adjusted life years.

Another potential outcome which could be used in Treatable Traits research could be "Life Participation". Life participation, generally measured as a patient reported outcome is a high priority outcome for consumers and clinicians alike. Currently there is no such measure which would be appropriate for use across the spectrum of respiratory diseases which are encompassed by the "Treatable Traits" model of care.

The Future

The pathway forward for furthering the research and implementation of "Treatable Traits" will depend on addressing the complex challenges of study design and outcome measures. Effectiveness trial designs, along with an aggregate of outcome measures, albeit not without its own limitations, may provide a promising direction.