CASE FOR ACTION-
PROPOSAL TO NHMRC
Targeted therapy for asthma

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Submitted by the Research Translation Faculty Asthma Steering Group
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The National Health and Medical Research Council (NHMRC) Research Translation Faculty (the Faculty) was established as a key advisory forum in 2012. The primary work of the Faculty for the 2013-15 Triennium has been to help NHMRC accelerate the translation of research by identifying the most significant gaps between research evidence and health policy and practice in each of the major health areas in the NHMRC Strategic Plan, and to propose to NHMRC possible action it could consider taking to address that gap – these are called Cases for Action. In April and May 2013, fourteen Faculty steering groups were established as NHMRC working committees to each oversee the development of a Case for Action.

The Faculty's Asthma Steering Group is comprised of a range of experts and includes primary (1°) and secondary (2°) representatives of NHMRC Health Care Committee (HCC), Prevention and Community Health Committee (PCHC) and Research Committee (RC). Further information is available at: www.nhmrc.gov.au/research/research-translation/research-translation-faculty/research-translation-faculty-steering-group.

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**Declaration of interests**

The declarations of interests of Steering Group members, authors and contributors are available at Appendix 2.

**Suggested citation**


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Title: Targeted therapy for asthma

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HCC – Health Care Committee; PCHC – Prevention and Community Health Committee; RC – Research Committee
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NHMRC Translational Faculty

Asthma Steering Group: the Case for Action

The Problem and Way Forward

Over the past 50 years, theories about asthma have determined approaches to treatment and consequent outcomes. While we have now achieved improved control for many, this has not been translated to all people with asthma, and additional problems have emerged such as over-diagnosis, over-treatment, and lack of ongoing improvement in outcomes. Few new therapies have been developed. Meanwhile, it is widely acknowledged that there is still a substantial global burden of asthma (1). The distribution of this burden reflects a paradox: the mortality and disability burden attributable to asthma in regions with the best access to modern medicines and medical care, such as Australia and New Zealand, Western Europe, and North America, is greater than in some regions with less access, such as Eastern Europe, parts of Asia and parts of Latin America (http://ihmeuw.org/26nm). Other low income regions have a very high burden of disease. These problems suggest that a new approach is needed.

The current dominant paradigm within clinical practice is that better outcomes can be achieved by using existing agents if patients and doctors rigorously adhere to current guidelines. This is encapsulated in the mantra ‘you can control your asthma’, which is the theme of much patient-focused health promotion activity (2). Sadly, it carries the unspoken implication that if your asthma is not controlled, then YOU are not doing enough. The limitation of this approach is seen in severe asthma, which, by definition, occurs in people whose asthma is uncontrollable using current strategies. No doubt there is some value to be gained by persisting with an emphasis on implementing control-based guidelines. However, this approach has been with us since 1989 and some might consider it had had sufficient time to have diffused into practice and achieved its maximum effect. We argue that it is now necessary to move beyond this approach in order to achieve better outcomes for people with this common disease.

Unfortunately, changes in clinical practice have not kept pace with new developments in respiratory science that relate to asthma. Scientists working in this field have recognised the limitations of the current approach and its failings when attempting to evaluate new asthma therapies. For example, a recent editorial in Nature Medicine reflected on the complex nature of asthma and stated that ‘Nowhere is this complexity more apparent than in the clinic, as asthma does not present as a single disease entity. Rather, distinct phenotypes of asthma are identifiable, and these distinct cohorts respond differently to medications, a fact that may account for the recent failure of several targeted biologics that were tested in large, unselected patient populations’ (3).

In responding to the NHMRC translation faculty’s call for action that has the potential to offer profound, game-changing and blue-sky outcomes, we are calling for a fresh perspective on asthma, for a new paradigm to approach asthma that is in line with the evidence emerging from the recent scientific studies. Targeted therapy has the potential to provide this.

Some History

The major therapeutic advances in the management of asthma during the 20th century (reviewed in 4) started in the 1920s when the use of adrenaline, by injection or inhalation, was recommended in medical textbooks (e.g. 5). Aminophylline was not widely recommended in textbooks until the late 1940s (e.g. 6, 7). Oral corticosteroid treatment was recommended for patients with asthma from the 1950s (8, 9).
Around this time, in the mid-20th century, asthma was considered a disease of allergic bronchospasm. Allergen bound to circulating IgE then cross-linked IgE receptors on mast cells leading to the release of bronchoconstrictor mediators from mast cells which, in turn, led to airway smooth contraction, wheezing and clinical asthma. The treatment approaches that were logically based on this theory were allergen avoidance and use of short-acting ß2 agonists (SABA). In addition, a novel therapy was identified, sodium cromoglycate (SCG), which blocked mast cell mediator release. Older people with lifelong asthma recall the immediate and spectacular effects of SABA during an acute asthma attack and currently people with asthma continue to experience the benefits of this therapy. Some people did gain substantial benefit from SCG (10, 11) and were able stop or reduce their reliance on long-term use of systemic corticosteroids (12), which had very undesirable side-effects, particularly in children.

The SABA-based approach provided effective rescue therapy for asthma but this was associated with two peaks of increased asthma mortality: in the late 1960's (13) and the 1980's (14) (Figure 1), possibly due to the unrecognised progression and persistence of airway disease or other pathology that was not responsive to bronchodilators. Additionally, limitations of SCG, particularly as therapy for asthma in adults, quickly became apparent (15). Unfortunately the same was true for allergen avoidance, which was never widely implemented.

Figure 1: Long-term time trend in death rate due to asthma in Australia (1911 to 2011). Peaks in 1966 and 1986 were attributed to excessive use of, or over-reliance on, beta-agonists. The cause of the rapid changes in the 1920s and late 1940s are unknown. From (16)

**A new approach was needed**

By 1990 scientists had begun to reformulate their understanding of asthma, regarding it as a disease of lymphocyte activation and eosinophilia (17-19). This subsequently evolved into a T-helper-2 (Th2) lymphocyte model. The new theory involved Th2 cells releasing cytokines, such as interleukin (IL)-5, leading to the recruitment of eosinophils into the airways and the clinical manifestations of asthma.

This improved understanding coincided with strengthening evidence about the beneficial effects of inhaled corticosteroids (ICS) in the management of asthma (20). This was coupled with improvements in self-management education (21-23) and what we now refer to as
implementation science. Guidelines were developed (for the first time in Australia and New Zealand (24) and then globally (25)) to promote a systematic, co-ordinated and step-wise approach to asthma management based on these new tools. A new phrase was co-opted into the guidelines to support this approach, namely ‘asthma control’.

While this approach provided better prevention of exacerbations and improved asthma control in many people with asthma, the limitations of this approach are now becoming apparent. Specifically:

- Improvements in asthma hospitalisation and mortality rates have plateaued, with no improvement in recent years; (Figures 1 and 2)
- Symptoms of asthma are not adequately controlled among people with asthma in many countries, especially in the most severe group; (Figure 3), and
- No new therapeutic classes have been successfully implemented. Importantly, the specific blockade of IL-5 in asthma based upon the untargeted therapy approach was ineffective when applied to a general population of people with asthma (26).

Although failure to recognise, and prescribe ICS for people with asthma and related syndromes who would benefit from this class of treatment remains an ongoing problem (27), over-diagnosis and inappropriate treatment with ICS, among people who are unlikely to benefit from this treatment, has emerged as a significant problem (in settings where this class of drugs is readily available). A longitudinal study of people with asthma selected from the general population of eight cities in Canada established that ‘about one-third of obese and non-obese individuals with physician-diagnosed asthma did not have asthma when objectively assessed. This finding suggests that, in developed countries such as Canada, asthma is ‘over-diagnosed’ (28). Similarly, a primary care study from the Netherlands found that 30% of patients were using inhaled corticosteroids without a clear indication. The authors concluded that ‘Overtreatment with ICS in primary care seems to be considerable, which falsely labels patients as asthmatic and which generates unnecessary costs and possible side effects’ (29). Finally, Hawkins et al conducted a randomised controlled trial of ICS dose reduction in asthma and identified that a 25% ICS dose reduction (equivalent to 348ug/d beclomethasone) was possible without loss of control (30). Hence, there is evidence that, under the current approach to asthma management, therapy is poorly targeted.
Figure 2: Asthma Hospitalisations in Australia. Note the plateau, with no further reduction in hospital separations since 2002-2003. From (31)

Figure 3: Global asthma control. Summary of global asthma control surveys showing the percentage of patients with good/complete asthma control across different asthma severity levels and different world regions. With moderate and severe asthma, fewer than 50% of patients achieve control. (from Figure 2 in 32)

We believe that the development of guidelines in 1989 was the last big breakthrough in asthma management. For the reasons stated above, now it is time for the next big breakthrough in thinking about asthma management. Targeted therapy is a compelling option.
Could current asthma guidelines solve these problems?

This is unlikely and, in fact, continued focus on the current model of asthma guidelines may act as a barrier to making progress in improving asthma morbidity. There are several reasons for this:

1. Guidelines continue to promote the existing approach of one size fits all which leads to over-diagnosis and over-prescribing. They have been unable to successfully incorporate or address the issues described above. Specifically, existing guidelines are inconsistent with emerging data about the heterogeneous nature of the disease, since they tend to promote a common pathway for all patients who meet the diagnostic criteria for “asthma”. In this sense, they tend to value simplicity over validity and effectiveness for specific subgroups of patients. They promote an inefficient and sometimes inappropriate and ineffective use of therapy by ignoring heterogeneity and recommending the same therapy for broad groups of patients with asthma. This is despite the emerging evidence that it is likely to be ineffective in many within these groups. The current guidelines are likely to be inappropriate for non-allergic asthma, which is the most common phenotype in some parts of the world.

2. The processes used to develop current asthma guidelines are limited. Specifically:
   a. They are either directly industry-driven or indirectly industry-driven in that they are based on industry-sponsored large clinical trials. (This is a self-perpetuating phenomenon as much of the asthma research agenda is influenced by existing guidelines.)
   b. The processes for evidence review and synthesis are limited and do not always reach the same conclusions, despite having access to the same published data. For example, there have been four recent guideline statements of relevance to asthma. These are the Global Initiative for Asthma (GINA) guidelines update (GINA) (33, 34), the National Asthma Council’s (NAC) Australian Asthma Handbook (http://www.nationalasthma.org.au/handbook), the American Thoracic Society (ATS)/European Respiratory Society (ERS) Severe Asthma Task Force report (35), and the UK Government’s National Institute of Clinical Effectiveness (NICE) technology review (36). While all guidelines are based on a review of published evidence, the NICE and ATS/ERS documents used modern approaches to evidence identification, selection and synthesis (eg GRADE) and both made recommendations in favour of targeted therapy. NICE recommended dose adjustment of ICS based on monitoring of the fractional concentration of expired nitric oxide (FeNO) and the ATS/ERS task force recommended therapy adjustment in people with severe asthma using sputum eosinophils. In general, the GINA and NAC guidelines do not recommend these biomarker-based approaches to adjustment of therapy (targeted therapy).

3. Direct comparison of control-driven therapy (ie the current guideline approach) vs targeted therapy in randomised controlled trials shows that outcomes of the control-driven approach are inferior. For example, a randomised controlled trial of inhaled corticosteroid dose adjustment using a symptom control algorithm based on GINA guidelines was compared with FeNO-guided dose adjustment in 220 women with asthma during pregnancy (37). The symptom control algorithm was inferior, leading to 50% more asthma exacerbations, 50% more babies admitted to NICU, and higher average inhaled corticosteroid use (ie relative over-treatment). In an earlier randomised controlled trial, conducted in people with asthma, those who received guidelines-based treatment adjustment experienced a 50% higher rate of severe...
exacerbations compared with those whose ICS dose was titrated according to sputum eosinophil numbers (38).

4. Current guidelines recommend therapies and modes of management that are largely inaccessible and/or inappropriate for many people with asthma living in low and middle-income countries.

5. Control-based guidelines do not encourage the development and marketing of new therapeutics. In fact, when new drugs are evaluated in accordance with the current guidelines-based approach, their beneficial effects may be missed (see Box 1: The MEPO story).

6. Current guidelines are single-disease focused i.e. asthma guidelines focuses only on asthma yet many people with asthma have multiple diseases including concurrent airway disease such as COPD and bronchiectasis.

Box 1: The MEPO story

Mepolizumab is a humanised monoclonal antibody that was developed to block interleukin (IL)-5, as a natural development of the Th2 asthma concept. The drug was found to be safe and effective at blocking IL-5 when tested with in vitro systems and in vivo models.

A phase 3 trial was designed based around incorporating mepolizumab into a step-up guideline-based paradigm. Within this paradigm, mepolizumab was evaluated for its ability to reduce the frequency of disease exacerbations in patients with asthma who remained symptomatic on current inhaled corticosteroid therapy. Despite adequate power, this trial was unexpectedly negative. This led to much soul-searching and the near-abandonment of the drug.

Investigators who were familiar with the early forms of targeted therapy in asthma conducted two investigator-initiated studies (39, 40). Unlike the original phase 3 trial, these studies targeted MEPO treatment specifically to the asthma endotype with raised sputum or blood eosinophils. The results were spectacular with effect sizes of 50% and 80%, respectively (Box Figure).

Subsequently, GSK (the owner of the IP) conducted a further phase 3 trial using a targeted therapy design and reproduced the 50% effect size (41)....the rest is history(we hope!).

Box Figure: Comparative effect sizes expressed as odds ratio for asthma exacerbation rates for the use of mepolizumab 250mg for asthma, when applied using control-based paradigm(Unselected, (21)), and when used in a targeted therapy paradigm (Targeted, (35)). From systematic review by Liu et al (36)
Is the current approach meeting the needs of people with asthma in rural and remote region and of indigenous people?

The available evidence suggests that, among people with asthma, those living in rural and remote regions and indigenous people, have worse outcomes that those living in metropolitan regions and non-indigenous people, respectively. The figures demonstrate this for deaths due to asthma 2009-2011 (16).
Similar trends are apparent for rates of hospitalisation among adults, but not children (31).

Population level data for other asthma outcomes are not readily available but these data for deaths and hospitalisations suggest that important disparities do exist with the current system of care for this disease.

**Is the current approach meeting the needs of consumers with asthma?**

Consumers' concerns and priorities for research are different from those of clinical researchers and involving consumers can improve the quality of research and research outcomes. Involving consumers in research is an important part of consumer engagement. Consumer input is also valuable in identifying and prioritising research issues, and consumer involvement in planning and managing projects is increasingly expected. The involvement of consumers in the development of a new model of care will ensure that issues which are important to consumers are identified and prioritised and that research does not just measure outcomes that are identified and considered important for professionals. It is not yet clear how targeted therapy will impact on consumer preferences for health care outcomes and health care delivery.

**The case for targeted therapy**

The goal of targeted therapy for asthma is:

Getting the

- Right therapy to the
- Right person at the
- Right time

**What is targeted therapy?**

This term has arisen from the cancer field, and refers to the development and use of drugs that interfere with specific molecules (targets) involved in the pathogenesis of the disease, which, in the case of cancer, refers to cell growth and survival. In this field it has delivered a substantial number of new therapeutics, and accompanying new diagnostic tests that are designed to ensure that the right treatment gets to the right person.

'As researchers have learned more about the gene changes in cells that cause cancer, they have been able to develop drugs that target these changes.' American Cancer Society

Targeted therapies have significantly changed the management of cancer over the last decade, delivering a multitude of new and effective treatment options for people living with cancer, with better survival rates and quality of life. We maintain that similar gains can be achieved for people with asthma by targeting existing therapies to those most likely to benefit from
them and by developing new therapies that target groups of patients whose disease cannot be adequately controlled with existing therapies.

**Box 2**

**US Food and Drug Administration (FDA)-Approved Targeted Therapies (42)**

The FDA has developed an evaluation programme for approval of a targeted therapy and its companion diagnostic tests. Several targeted therapies have already been approved for the treatment of cancer and the number will probably increase as research continues to take place. The targeted therapies listed below are approved by the FDA for specific cancer indications. These drugs continue to be studied in clinical trials for various types of cancer. For each generic drug name listed, the brand name is shown in parentheses. Additional information about these drugs can be found at [http://www.cancer.gov/cancertopics/druginfo/alphabetlist](http://www.cancer.gov/cancertopics/druginfo/alphabetlist).

Alemtuzumab (Campath-1H®)

Target: CD52 antigen (expressed on lymphocytes)

Indications: B-cell chronic lymphocytic leukaemia in patients for whom alkylating agents have failed

Bevacizumab (Avastin®)

Target: vascular endothelial growth factor (VEGF)

Indications: First-line treatment for metastatic colorectal cancer

Bortezomib (Velcade®)

Target: Proteasome (inhibitor)

Indications: Multiple myeloma relapsed after two prior treatments

Cetuximab (Erbitux®)

Target: epidermal growth factor receptor (EGFR)

Indications: E GFR-positive, irinotecan-refractory metastatic colorectal carcinoma

Gefitinib (Iressa®)

Target: Tyrosine kinase (inhibitor)

Indications: Third-line treatment of non-small cell lung cancer

Gemtuzumab (Mylotarg®)

Target: CD33 antigen (expressed on myeloid cells)

Indications: CD33-positive acute myeloid leukemia in patients older than 60 years who are not candidates for cytotoxic therapy
Ibritumomab tiuxetan (Zevalin®)
Target: CD20 antigen (expressed on mature B cells)
Indications: Low-grade and follicular B-cell non-Hodgkin lymphoma refractory to rituximab

Imatinib (Gleevec®)
Mechanism: Bcr-Abl and c-kit tyrosine kinases
Indications: Chronic myelogenous leukemia and gastrointestinal stromal tumors

Rituximab (Rituxan®)
Target: CD20 antigen (expressed on mature B cells)
Indications: Refractory low-grade and follicular B-cell non-Hodgkin lymphoma

Tositumomab (Bexxar®)
Target: CD20 antigen
Indications: Follicular non-Hodgkin lymphoma, with or without transformation (increased aggressiveness), that has relapsed after chemotherapy and is refractory to rituximab

Trastuzumab (Herceptin®)
Target: HER2
Indications: Metastatic breast cancer expressing HER2

**Targeted therapy for asthma**
Targeted therapy for asthma refers to a management approach where the treatment is applied based upon an assessment of the clinical features of the disease. Targeted therapy for asthma can include:

- Targeted current therapies guided by biomarkers,
- Targeted models of care, such as use of therapies targeted to specific populations, high risk groups, and/or specific settings. This may include identifying high risk groups eg., people in rural or remote areas; Aboriginal and Torres Strait Islander peoples, people from a non-English speak background; smokers; pregnant women; people who are obese and have asthma.
- Therapies targeted to problems identified by multidimensional assessment, and
- Application of newer agents that are targeted to a particular pathophysiological process or molecular target.

The analogy between cancer and asthma is useful. Corticosteroids, like chemotherapy, act on multiple cells and targets. While this results in correctly hitting the disease target, there are limitations such as 'off-target' effects, which cause significant toxicity. For example, corticosteroid induced growth suppression and adrenal suppression are major off-target effects of asthma treatment using corticosteroids. Since only about 50% of people with asthma exhibit the corticosteroid target pathology, that is Th2-high eosinophilia (43, 44),
many patients are exposed to the drug toxicity without any prospect of benefit. In addition, there are people with other airway diseases, not meeting classical criteria for the diagnosis of asthma, who do have airway or blood eosinophilia (45, 46) and may potentially benefit from ICS and other drugs active on the Th2 pathway. Optimising the use of ICS in people with airway disease involves using biomarkers both to select people for treatment with ICS and to adjust doses to an optimal level. There are already successful examples of this, showing superiority of this targeted therapy approach over an asthma control-based approach (37, 38).

The goal of targeted therapy in asthma is to deliver greater benefits for the patient with fewer adverse outcomes and lowest overall cost. The new approach has been called for in recent reviews (47, 48) and, over the past few years, there are successful examples of new therapies that have been evaluated and shown to be successful in a targeted asthma therapy paradigm. (Table).

Table: Newer therapeutic agents that have been successfully identified for asthma using a targeted therapy approach. The table lists the biomarker, treatment agent, and citation.

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<thead>
<tr>
<th>Biomarker</th>
<th>Treatment agent</th>
<th>Reference</th>
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<tr>
<td>Allergen-specific IgE</td>
<td>omalizumab</td>
<td>(49)</td>
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<tr>
<td>Eosinophils – IL-5</td>
<td>mepolizumab</td>
<td>(39-41)</td>
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<td>Eosinophils – IL-5</td>
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<td>Eosinophils – IL-5</td>
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<tr>
<td>Eosinophils</td>
<td>dupilumab</td>
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<tr>
<td>FeNO</td>
<td>inhaled corticosteroid</td>
<td>(37)</td>
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<tr>
<td>Periostin – IL-13</td>
<td>Lebrikizumab; IL4-IL13 R blockade</td>
<td>(51)</td>
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In addition to the ICS and molecular targeted therapies discussed above and listed in the table, other old and new therapies for asthma, such as theophylline and other phosphodiesterase inhibitors, macrolides (52), SCG, and leukotriene receptor antagonists (53), as well as non-drug therapies including bronchial thermoplasty (54), may also be used more effectively and safely if applied in a targeted manner. Existing evidence about the relevant markers for these therapies, and how best to use them in a targeted way, is very limited.

In applying this approach it is important to recognise that, while asthma is a chronic disease, it does not occur in isolation. This is especially the case among older people with airway disease. Indeed, a multidimensional assessment of 100 consecutive outpatient attendees with obstructive airway disease found an average of 10 clinically significant problems per person (55). These problems included associated comorbidities, risk factors (such as obesity and smoking), and behavioural issues (including poor self-management skills). Each clinical problem was associated with a clinically significant impairment in health status. This argues for a multidimensional assessment and treatment approach, as is used in geriatric medicine. A strategy based on this approach has been developed for asthma in older people (56). Clinical problems are assessed in 4 domains that address the airway component, comorbidity, risk factors and behavioural issues. Each problem is then managed using targeted approaches. The strategy, which targets problems in several clear domains and links treatment of these to the specific problem (Figure 4), demonstrated significant benefits when applied in a pilot controlled clinical trial (57).
Clinical problems are assessed in 4 domains (boxes) and managed using targeted approaches (quadrants of the circle). Comorbidity management may require a customised approach to deal with multiple comorbidities in severe asthma. From (56)

**Box 3: The role of Australian discoveries**

There are some significant Australian discoveries that are relevant in the targeted asthma therapy area. The challenge to reconceive asthma as a disease with multiple molecular subtypes has been eloquently described by Professor Gary Anderson (58). He identifies the need to recognise endogenous asthma phenotypes, termed endotypes, that are based on specific molecular pathways relevant to asthma. The prototypic studies that have driven this re-evaluation in asthma involve a drug that blocks IL-5. (see box 1, ‘the MEPO story’). IL-5 was discovered as an eosinophil active cytokine by an Australian researcher, Colin Sanderson (59). At the John Curtin School of Medicine, Paul Foster and Ian Young performed the pivotal studies showing that IL-5 gene knockout abolished the asthmatic response in dynamic model systems.

**The claims for targeted asthma therapy**

Since targeted therapy is proposed to address the limitations of a symptom-control based approach, it is appropriate to ask, have there been direct tests of these claims?

The targeted therapy paradigm has been assessed in several settings, including with RCTs to directly compare the 2 approaches. Each of the claims of targeted therapy has been assessed, including improved outcomes (reduced exacerbations; better diagnostic accuracy; less overtreatment) and delivery of new therapeutic agents (Table). Targeted therapy can improve outcomes: several RCTs have shown reduced asthma exacerbations when using a targeted therapy approach (37-41). This has been demonstrated when evaluating newer agents (Table), and also when evaluating use of inhaled corticosteroid in a targeted therapy vs symptom-guideline based approach (37,38). Two recent systematic evidence reviews have recommended targeted therapy in certain areas:
NICE have recommended FeNO-based management, the ATS/ERS severe asthma task force has recommended sputum-guided therapy for severe asthma (36).

Diagnostic accuracy: Guideline-recommended tests for asthma diagnosis (bronchodilator responsiveness, and peak flow variability) were compared with tests based on a targeted therapy approach (using FeNO and sputum eosinophils)(60). FeNO measurements and induced sputum analysis were superior to conventional approaches. Sensitivities for each of the conventional tests (0-47%) were lower than for FeNO (88%) and sputum eosinophils (86%). Overall, the diagnostic accuracy when using FeNO and sputum eosinophils was significantly greater. Results for conventional tests were not improved by incorporation of a trial of corticosteroid therapy (to assess steroid responsiveness) into the diagnostic process.

Overtreatment: A targeted therapy approach to ICS dose adjustment resulted in 20-25% less ICS overtreatment in 2 RCTs (37, 60)

What are the barriers to targeted therapy?

- Lack of targets and biomarkers for some available therapies
- Lack of new therapies
- Lack of access to existing biomarkers and therapies in many settings
- Current guidelines that limit the application of this approach
- Lack of a realistic implementation program

What is needed?

- New targets and biomarkers
- Feasible and accessible tools for measuring these biomarkers
- Safe, effective and affordable therapies directed at new targets
- Clinical methods: algorithm
- Proof of efficacy: RCTs
- General application beyond guidelines
- Engagement with clinicians and patients on implementation strategies
- Identifying at what point simple guidelines hinder clinical care

We are recommending a new approach that addresses how to select the right therapies in the right dose for the right person. This will require:

- technological advances
- a change in concepts of how asthma is managed
- both basic and applied research to discover and develop new targets, biomarkers, therapies, tools and implementation approaches
- education and training of the health and medical workforce
- updated information and education for asthma sufferers

Is this targeted-therapy approach feasible for people with asthma who are living in rural or remote regions or who are indigenous?

In general terms, we see no reason why this approach would not be feasible in all people with asthma, regardless of location of residence or indigenous status. Some of the challenges faced by people living in rural and remote communities and by indigenous people include limited access to services, particularly specialist services. The targeted therapy approach should simplify treatment decisions for people with asthma and may reduce the need for specialists to be involved in care, thereby making optimal care more accessible to people in rural and remote regions and to indigenous people. It is important, however, that this new model of care considers the best methods of delivery in these settings, and adapts the model of care to these requirements.
Consumer Issues: how does targeted therapy address consumer needs and what is the impact of this model of care on consumers?

These are important considerations that will need to be addressed during the development and implementation of targeted therapy. Including consumers in decision making about a new therapy increases the likelihood it will successfully be adopted and translated into practice. Consumers are among the first to be aware of the need for change. Involving end users in research provides information on the consumption behaviours and purchasing decision-making process of individual and group users. Group users include the government, enterprises, and medical and education institutions. With the promotion of patient self-management, patients involved in the development of new models of care will contribute to ensuring successful design of the model and uptake of the product.

In wanting patient input it will be necessary to design processes that speak to their reality and provide a choice of pathways for participation e.g. development of the study, information they want to provide, assist with data collection (i.e. focus groups, conduct individual interviews or survey their membership). This process will include patients and caregivers at the outset in crafting the processes and communications that relate to them. It will be precise about what will be done with the information that is requested and how and when it will impact the decision-making process. All language in communication will be purged of jargon and user appropriate. There will in addition be pathways for consumers to provide input and more time for them to do so.

Economics of targeted therapy for asthma

Asthma creates a significant disease burden in terms of costs to the patient, healthcare system and the community. The Australian Institute of Health and Welfare (AIHW) estimated the direct health care costs associated with asthma at $655 million in 2008-09 ($747 million in 2014 dollars). These costs are mainly attributable to use of medications (50%), out-of-hospital medical care (30%) and inpatient hospital care (20%) (61, 62). Indirect costs are not included in the AIHW cost estimate. One strategy to value indirect costs is to measure ‘disability adjusted life years’ (DALYs). DALYs take into account both years lived with a disability (YLD) and years of life lost (YLL) due to premature mortality. Asthma accounted for nearly 117,000 DALYs representing 2.3% of all DALYs in Australia, i.e. 2.3% of the total Australian disease burden. In 2004 the AIHW applied a financial value (63) to the number of DALYs attributable to asthma and estimated that the cost of disability and premature mortality was approximately $4.3 billion (64) ($5.6 billion in 2014 dollars) (65).

Reducing the burden of asthma and more efficient (targeted) use of medications for the disease would reduce the resources that are consumed for this disease. Cost-of-illness calculations provide an estimate of the resources that would be available for use elsewhere, under various assumptions about the effect of targeted therapy in both reducing the burden of illness and improving the efficiency of use of medications (66). Assuming additional treatment costs do not exceed downstream costs avoided, we have estimated that the potential direct health care cost savings that would flow from better targeted treatment for asthma in Australia range from $129 million to $1,288 million. These net savings represent costs avoided over a 10 year period (see Appendix 1). The potential savings in health care costs are not just theoretical. We have shown that, even before better targeting of treatment among people who do have asthma, there are large savings to be made by avoiding use of combination ICS/LABA therapy in people who do not have asthma or COPD (67).

The broad range of estimated health cost savings due to better targeted therapy for asthma is due to uncertainty about the net proportion of health care costs that could be saved by this approach. This uncertainty range could be narrowed by more extensive review of evidence.
and modelling. Improved patient outcomes reduced risk of death and disability would have a substantial impact on indirect health costs (DALYs) but the magnitude of this additional benefit cannot be quantified at this stage.

**A framework to direct research to support this new approach**

![Diagram of research framework]

- **Descriptive and mechanistic studies:** phenomenology, phenotypes and mechanisms
  - **Cohort Studies:** aetiology
  - **RCTs:** prevention
  - **Health services research:** integrated care, global health solutions

- **Biotechnology and engineering:** affordable and feasible tools for phenotyping in clinical practice

- **Policy and advocacy**
**Actions proposed for the NHMRC**

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<tr>
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<th>TIMELINE</th>
<th>STAKEHOLDERS</th>
<th>BENCHMARKS/KPIs</th>
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<td>Commission a systematic review of the evidence that is relevant to the recommendations contained in this Case for Action</td>
<td>6 months after Council adopts CFA</td>
<td>NHMRC</td>
<td>Evidence review produced</td>
</tr>
<tr>
<td>Commission an economic analysis of the potential benefits of targeted therapy. This should be include estimates that include targeting low cost drugs (eg steroids, macrolide antibiotics etc) and high cost drugs (that is, biologicals)</td>
<td>6 months after completion of evidence review</td>
<td>NHMRC</td>
<td>Economic analysis produced</td>
</tr>
<tr>
<td>Issue position paper for targeted therapy for asthma, and related diseases, to stimulate and guide future research and research translation</td>
<td>6 months after completion of evidence review</td>
<td>Consumer groups: Asthma Australia, LFA; Professional groups: TSANZ, AZCIA, RACGP, NAC; Indigenous reference groups; Health care providers: Commonwealth, State and territory health depts.; Pharmaceutical: PBAC; Pharma industry;</td>
<td>Website hits, Downloads, Comments</td>
</tr>
<tr>
<td>Sponsor a multi-disciplinary workshop to promote collaboration among experts in respiratory science, clinical practice and biotechnology and engineering, and industry to promote the research agenda outlined above</td>
<td>2 months after completion of evidence review</td>
<td>Experts in respiratory science, clinical practice and biotechnology and engineering, and industry</td>
<td>Publication of a research agenda arising from this workshop</td>
</tr>
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| Commission research to extend the CFA targeted model of care to high risk groups including:  
  - people in rural or remote areas;  
  - Aboriginal and Torres Strait Islander peoples,  
  - people from a non-English speaking background; and  
  - pregnant women | 12 months after completion of evidence review | Indigenous reference groups;  
Health care providers: Commonwealth, State and territory health depts.;  
Consumer organisations | Publication of targeted models of care for asthma in high risk groups and for geographically diverse settings. |
| Work with consumer groups to identify performance measures to monitor progress with improving prevention and management of asthma. | 12 months after completion of evidence review | Asthma Australia | Performance measures identified |
| Provide input into the new national Asthma Strategy being developed by National Asthma Council and Asthma Australia | Within two months of Council adopting CFA | National Asthma Council  
Asthma Australia  
NHMRC | A meeting held between the stakeholders  
A response from National Asthma Council and Asthma Australia to the recommendations contained in the Case for Action |
References


64. Australian Centre for Asthma Monitoring. Health care expenditure and the burden of diseases due to asthma in Australia. Canberra: AIHW, 2005 Contract No.: Cat. No. ACM 5.


Appendix 1: The economics of targeted therapy for asthma patients

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Locked Bag 1000
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Andrew Searles
Chris Doran
Simon Deeming
The economics of targeted therapy for asthma

This document complements a case for action paper on targeted therapy for asthma prepared by the NHMRC Asthma translation Group. Consequently, a formal introduction is not provided nor is it broken into standard sections we might otherwise use: intro / methods / results / discussion etc.

This Appendix addresses three points related to the economics of targeted therapies for asthma. It provides:

1. A brief overview of the costs associated with asthma;
2. A summary of insights gained from economic evaluations of targeted therapies in the field of cancer;
3. A simple modelling exercise to provide guidance on possible cost savings through the introduction of effective personalised medicine for asthma.

The cost of asthma

Asthma creates a significant disease burden in terms of costs to the patient, healthcare system and the community. Cost-of-illness calculations provide an estimate of the resources that would be available for use elsewhere, if the disease did not exist.1

Costs can be separated into direct and indirect costs. Direct costs include those associated with the provision of healthcare and patient out-of-pocket expenses. For asthma they include diagnostics (screening tests, pathology) and disease management (medications, ambulance, emergency rooms, inpatients, patient out-of–pocket costs etc.). Indirect costs include lost wellbeing, reduced productivity due to work and school absenteeism, as well as care givers’ leave. Internationally, a key driver of asthma related costs has been medication and inpatient expenses.2

The Australian Institute of Health and Welfare (AIHW) estimated the direct cost of asthma to be $655 million in 2008-09 ($747 million in 2014 dollars). The key cost drivers in Australia are medications, out-of-hospital expenses and inpatient care.3,4 In 2011-12, asthma was responsible for 39,000 hospitalisations with an average length of stay of 5.1 days.5 The rate of hospitalisation was highest for those aged 0 to 14 years. In this age category males were most likely to be hospitalised, but this trend reversed in older age groups with females more likely to become inpatients.5

Indirect costs are not included in the AIHW cost estimate. A strategy to value indirect costs is to place a dollar on ‘disability adjusted life years’ (DALYs). DALYs take into account both years lived with a disability (YLD) and years of life lost (YLL) due to premature mortality. Disability from asthma is caused from narrowing of the airways resulting in shortness of breath, chest tightness and wheezing. As the onset of asthma can be in early childhood, a substantial proportion of a patient’s life can be spent with asthma-related disability.5,6 Asthma accounted for nearly 117,000 DALYs representing 2.3% of all DALYs in Australia, i.e. 2.3% of the total Australian disease burden. Of all lung diseases, asthma is the leading cause of disability because it affects all age groups.5 In terms of mortality, Australian death rates from asthma are higher than reported in many other countries.7
In 2004 the AIHW applied a financial value to the number of DALYs attributable to asthma and estimated that the cost of disability and premature mortality was approximately $4.3 billion ($5.6 billion in 2014 dollars).

The economic rationale for undertaking targeted therapy in asthma is driven by a need to improve patient outcomes and raise the efficiency and cost-effectiveness of healthcare delivery. Targeted therapies can improve outcomes for subgroups of asthma patients who do not respond to existing treatments. Evidence indicates that there is substantial heterogeneity in human asthma. While many patients can adequately manage their asthma using available treatments, there is an unmet need for medical care in a smaller patient group who are unable to control their disease. This group accounts for a disproportionate amount of asthma-related direct cost, disability and mortality. In a systematic review of asthma-associated costs, twenty-two studies suggested severity of disease was an important factor related to higher cost. One of these reported that the per patient cost of asthma was up to five times higher amongst those reporting ‘severe’ asthma compared those reporting with ‘mild’ asthma.

Economic evaluations of targeted therapy: insights from cancer

The economics of targeted therapies is quickly developing in cancer. Better precision from genomic treatments are expected to deliver benefits to cancer patients in the form of improved health and productivity. They are also expected to reduce healthcare costs by avoiding unnecessary treatments and adverse reactions. Conceptually, economic evaluations should be capturing these benefits yet there is evidence these evaluations need refinement. For example, a systematic review of economic evaluations of Herceptin showed that there was a lack of consistency in the assumed length of time patients’ would benefit from treatment – a major parameter for the calculation of cost-effectiveness. The short-term view of some studies suggested a need for long-term follow-up. Problems were also identified with the evidence on which the evaluations were based. Cost data tended to be, appropriately, extracted from sources related to actual practice. However, outcome data (effectiveness and utilities) were sourced from the literature.

Economic evaluations of targeted therapies need to recognise the shift in technology from a blunt ‘one size fits all’ therapy, to those that target treatments to patient phenotypes. This shift in technology brings evidence and ethical challenges when assessing cost against effectiveness; new approaches for economic evaluations may be needed. Randomised controlled trials (RCTs) are suited to interventions where heterogeneity of effect size is unlikely to be a problem within the patient sample. However, without sufficient sample sizes they do not necessarily provide the best evidence for personalised medicines, where only sub-groups of patients will report benefit. This raises an issue for healthcare payers when assessing whether targeted therapies are likely to provide value for money. Cost-effectiveness studies of targeted therapies based on RCTs may underestimate clinical and, therefore, economic benefit. An example is the cancer drug erlotinib, found to be marginally cost-effective amongst all patients, until re-analysed using genomic data to select patient sub-groups – cost-effectiveness improved greatly. One response to this problem is ‘value-based pricing’ that assesses efficacy as well as broader societal impacts although it does not alleviate the need to understand clinical (and economic) outcomes for the sub-groups of patients who benefit from targeted therapy.
Targeted therapy and possible cost savings in asthma

The aim of this exercise was to identify the potential benefits through the use of targeted therapies to identify and manage asthma. The modelling was conducted in Microsoft Excel and is based on projections of avoided direct healthcare costs due to more effective identification and management of asthma patients. It is assumed that the profile of asthma direct costs, as reported by the AIHW in 2008-09, remains stable over the ten years of projections. All costs are expressed in 2014 financial values; adjustments for changes in the value of money were based on the consumer price index. The modelling is designed to provide an understanding of what cost savings may be possible with targeted therapy. More sophisticated modelling would take account of expected therapeutic advances; and, time lags between research and development, and potential patient outcomes. It would also capture potential improvements in wellbeing and productivity benefits.

The rationale for obtaining savings through cost avoided is based on the expectation that there will be a reduction in airways-related exacerbations. Patient outcomes can be improved through better diagnostics and disease management. Optimising diagnosis and management has flow-on impacts for patients and, consequently, efficiency impacts for the health system through the reduction of the unnecessary use of medications, emergency departments and inpatient services. There is already evidence of targeted therapies helping to reduce the overuse of medications by ensuring patients receive appropriate therapies. Proteomics have been used to develop blood-based biomarkers to help identify patients with asthma and/or COPD. For ensuring the effective and efficient use of medications, trials have already shown the response to inhaled corticosteroids (ICL) and leukotriene receptor antagonists (LTRAs) varies among asthma patients and biomarkers have been identified that predict the development of allergic asthma in children from three years of age.

Six ten-year scenarios were modelled. The first three scenarios assumed an initial (Year 1) cost avoided of 1.5% of direct asthma expenditure that was attributable to targeted asthma therapies. To provide a range of possible costs avoided, scenarios four, five and six assumed an initial (Year 1) cost avoided of 15% of direct asthma expenditure that was attributable to targeted asthma therapies. There was no literature to guide these estimates. However, clinical trials in targeted therapies for cancer suggest that these estimates are probably modest. For example, melanoma patients with the BRAF V600E mutation had a significantly better response to vemurafenib compared with existing treatment dacarbazine: a relative reduction of 63% in risk of death and a reduction of 74% in the risk of either death or disease progression (P<0.001 for both comparisons).

The modelling assumes that additional treatment costs associated with targeted therapy do not exceed downstream costs avoided. While the starting point for the modelling varied (between 1.5% and 15% cost avoided in Year 1), all scenarios are based on annual increases in savings. This provides an allowance for new technology to be adopted throughout the community. The annual unit of increase differed between scenarios. The low growth scenarios (#1 and #4) assumed a 0.0005 percentage point increase each year after year 1; moderate impact scenarios (#2 and #5) assumed a 0.0025 percentage point increase; and high impact scenarios (#3 and #6) assumed a 0.005 percentage point increase. The modelling included a sensitivity analysis.
for each scenario by adjusting the discount rate. Three discount rates were used: 0%; 3%; and 5%.

The modelling (see Table 1 and Table 2) suggests that under highly conservative assumptions (scenario 1) savings in the direct cost of asthma of $130 million over ten years are possible. After applying discount rates of 3% and 5%, the savings over ten years are estimated at $109 and $98 million, respectively. Relaxing the assumptions (scenario 6) identifies that the potential savings could be in the order of $1.3 billion over the ten year time frame. After applying discount rates of 3% and 5%, the savings over ten years are estimated at $1 billion and $0.9 billion, respectively. Note that under the most optimistic scenario, number 6, the increase in assumed savings from 15% in Year 1 reaches a maximum of 22% by Year 10. While representing substantial cost avoided, this estimate may be achievable if targeted asthma therapies result in effect sizes of similar magnitudes to that observed for some cancer therapies.
Table 1: Estimates of direct costs* avoided through the increased use of targeted therapies for the diagnosis and management of asthma, Australia - savings start at 1.5% of direct costs

### Scenario 1: Low impact of targeted therapy for asthma

Scenario details: Summation of a 10 year projection; cost avoided starts at 1.5% of asthma expenditure; assume increase of 0.0005 percentage points in savings each year

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<tr>
<td>0% discount rate</td>
<td>3% discount rate</td>
<td>5% discount rate</td>
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<td>($m)</td>
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- **Cost avoided through better use of medications**: $64, $55, $49
- **Cost avoided through improved patient outcomes leading to reduced out of hospital costs**: $39, $33, $29
- **Cost avoided through improved treatment leading to reduced inpatient days**: $26, $22, $20

**Total cost avoided**: $129, $109, $98

### Scenario 2: Moderate impact of targeted therapy for asthma

Scenario details: Summation of a 10 year projection; cost avoided starts at 1.5% of asthma expenditure; assume increase of 0.0025 percentage points in savings each year

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<td>($m)</td>
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- **Cost avoided through better use of medications**: $98, $82, $73
- **Cost avoided through improved patient outcomes leading to reduced out of hospital costs**: $59, $49, $44
- **Cost avoided through improved treatment leading to reduced inpatient days**: $39, $33, $29

**Total cost avoided**: $196, $163, $146

### Scenario 3: High impact of targeted therapy for asthma

Scenario details: Summation of a 10 year projection; cost avoided starts at 1.5% of asthma expenditure; assume increase of 0.005 percentage points in savings each year

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- **Cost avoided through better use of medications**: $140, $116, $102
- **Cost avoided through improved patient outcomes leading to reduced out of hospital costs**: $84, $69, $61
- **Cost avoided through improved treatment leading to reduced inpatient days**: $56, $46, $41

**Total cost avoided**: $280, $231, $205

* All financial figures in 2014 dollars
Table 2 Estimates of direct costs* avoided through the increased use of targeted therapies for the diagnosis and management of asthma, Australia - savings start at 15% of direct costs

**Scenario 3: Low impact of targeted therapy for asthma**
Scenario details: Summation of a 10 year projection; cost avoided starts at 15% of asthma expenditure; assume increase of 0.0005 percentage points in savings each year

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<td><strong>Cost avoided through better use of medications</strong></td>
<td>$568</td>
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<td><strong>Cost avoided through improved patient outcomes leading to reduced out of hospital costs</strong></td>
<td>$341</td>
<td>$291</td>
<td>$263</td>
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<tr>
<td><strong>Cost avoided through improved treatment leading to reduced inpatient days</strong></td>
<td>$227</td>
<td>$194</td>
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<td><strong>Total cost avoided</strong></td>
<td>$1,137</td>
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**Scenario 5: Moderate impact of targeted therapy for asthma**
Scenario details: Summation of a 10 year projection; cost avoided starts at 15% of asthma expenditure; assume increase of 0.0025 percentage points in savings each year

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<td><strong>Cost avoided through better use of medications</strong></td>
<td>$602</td>
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<td><strong>Cost avoided through improved treatment leading to reduced inpatient days</strong></td>
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<td><strong>Total cost avoided</strong></td>
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**Scenario 6: High impact of targeted therapy for asthma**
Scenario details: Summation of a 10 year projection; cost avoided starts at 15% of asthma expenditure; assume increase of 0.005 percentage points in savings each year

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<td><strong>Cost avoided through improved patient outcomes leading to reduced out of hospital costs</strong></td>
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<td>$1,288</td>
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* All financial figures in 2014 dollars
Points for further research

A commissioned paper is recommended to explore the issues associated with the economics of targeted therapies in asthma care. The paper should (a) examine the potential costs and benefits of targeted therapies in asthma care and (b) investigate the implications for economic evaluations of targeted therapies, including the impact on cost-effectiveness analyses and the viability of cost-benefit analysis.
References


## Asthma Case for Action - Declarations of Interests

The declarations of interests of Steering Group members, authors and contributors to this Case for Action are listed below.

<table>
<thead>
<tr>
<th>Name and Role[s]</th>
<th>Interests declared</th>
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<td>• Steering Group Co-Chair</td>
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<tr>
<td>• Author</td>
<td>• Holds several NHMRC grants</td>
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<td>• The Woolcock Institute of Medical Research has received research funds from AstraZeneca and from AIHW.</td>
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<tr>
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<td>• NHMRC Senior Principal Research Fellow</td>
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<td>• Director of AIHW Collaborating Unit</td>
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<td>• Vice-President, International Union Against Tuberculosis and Lung Disease.</td>
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<td>Prof Peter Gibson</td>
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<tr>
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<td>• Holds NHMRC grants and may apply for same during the period of committee membership. Holds an unrestricted educational grant from Novartis to provide postmarketing safety and efficacy data on an asthma product.</td>
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<td></td>
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<td>• Steering Group member</td>
<td>Consultancy fees/honorarium</td>
</tr>
<tr>
<td>• Author</td>
<td>• Honorarium received as member of GlaxoSmithKline (GSK) Respiratory Advisory Panel.</td>
</tr>
<tr>
<td>Prof Carol Armour</td>
<td></td>
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<tr>
<td>• Steering Group member</td>
<td>Grants</td>
</tr>
<tr>
<td>• Author</td>
<td>• Holds grants relating to asthma, NHMRC grants.</td>
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<td></td>
<td>Speeches/lectures</td>
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<tr>
<td></td>
<td>• Has given lectures on the needs in asthma.</td>
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<tr>
<td>Prof Anne Chang</td>
<td></td>
</tr>
<tr>
<td>• Steering Group member</td>
<td>Grants</td>
</tr>
<tr>
<td>• Author</td>
<td>• Institutional funding received from GlaxoSmithKline (GSK) for an investigator-led clinical study on non-typeable Haemophilus influenzae infections in children</td>
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<td></td>
<td>• Holds/has received NHMRC grants</td>
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<td></td>
<td>• Holds current peer-reviewed grants from other non-pharmaceutical granting bodies,</td>
</tr>
<tr>
<td>Name and Role(s)</td>
<td>Interests declared</td>
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| **Prof Anne Chang**  
**Speeches/lectures; support for travel/accommodation**  
- Has given three talks on the management of chronic cough in children to paediatricians in China. The airfare and accommodation were provided by Johnson & Johnson (J&J). The products of J&J were not mentioned any in any of these talks. |
| **Clin Prof Alan James**  
- Steering Group member  
- Author | **Relationships**  
- Member of the Thoracic Society of Australia and New Zealand, the Asia South Pacific Society of Respirology, The American Thoracic Society.  
**Consultancy fees/honorarium**  
- Honoraria have been received from pharmaceutical companies for educational lectures delivered by the member. These companies manufacture therapeutic products for asthma.  
**Grants**  
- Research funding from NHMRC (past and current), Asthma Foundation of Western Australia and institutional funding for asthma-related work. Investigator-initiated grant from Pfizer (2012). |
| **A/Prof Anne Wilson**  
- Steering Group member  
- Prevention and Community Health Committee (PCHC) primary contact  
- Author | **Consultancy fees/honorarium**  
- Chief Investigator, NHMRC Project Grant  
- Chief Investigator on Department of Health and Ageing (DOHA) Grants  
- Researcher in new sensor device not funded by NHMRC  
- Investigator on current and past NHMRC Project Grants.  
**Other**  
- Fellow of the Australian College of Nursing (Ongoing).  
**Employment**  
- Since May 2012 – Associate Professor Research, Paramedics, School of Medicine, Flinders University. |
| **Prof Lin Fritschi**  
- Steering Group member  
- Research Committee contact  
- Author | **Grants**  
- Chief Investigator on NHMRC Project Grant grants, NHMRC Partnership Project Grant  
- Current, past and likely future application to NHMRC for research and people support  
- Current holder of a Senior Research Fellowship in the area of occupational cancer  
- Potential applicant to Global Alliance for Chronic Diseases (GACD) next call.  
**Employment**  
- Employee of Curtin University of Technology.  
**Activities**  
- Member of the guideline development committee on "Health Effects of Environmental Noise" for enHealth  
- Chair of Research Committee of the Cancer Council of Western Australia. |
| **Prof Claire Wainwright**  
- Steering Group member  
- Health Care Committee (HCC) primary contact  
- Author | **Board membership**  
- Thorax Editorial Board  
- Associate Editor Respirology  
- International Advisory Board Vertex Pharmaceuticals.  
**Grants**  
- Chief Investigator on NHMRC project grants  
- Income on a per patient basis derived from pharmaceutical studies as listed below:  
  - 2007, Merck Sharp and Dohme: Treatment of Episodic Asthma in Children  
  - 2008, Novartis Pharmaceuticals Corporation: Trial to Assess the Safety of Tobramycin Inhalation Powder Compared to TOBI® in Cystic Fibrosis Subjects  
  - 2008-2009, Gilead Sciences Inc.; three studies relating to Aztreonam Lysine for Inhalation in patients with cystic fibrosis, mild lung disease and P. aeruginose  
  - 2009-2011, Inspire Pharmaceuticals Inc.; two studies: (1) Efficacy and Safety Study |
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<tr>
<th>Name and Role(s)</th>
<th>Interests declared</th>
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</table>
| **Prof Claire Wainwright**<br>...continued | of Denufosol Tetrasodium Inhalation Solution in Patients with Cystic Fibrosis Lung Disease and FEV1>/ 75% but < 110% (2) Study of Denufosol Tetrasodium Inhalation Solution in Patients with Cystic Fibrosis Lung Disease  
- 2010-2014, Vertex Pharmaceuticals Inc.; five studies: (1) Study to Evaluate the Efficacy and Safety of VX 770 in Subjects with Cystic Fibrosis and the G551D Mutation" (2) Study to Evaluate the Pharmacokinetics, Efficacy and Safety of VX 770 in Subjects aged 6 – 11 Years with Cystic Fibrosis and the G551D Mutation (3) Study to Evaluate the Long Term Safety and Efficacy of VX 770 in Subjects with Cystic Fibrosis (4) Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination with Ivcacaftor in Subjects Aged 12 Years and Older with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation (5) Study to Evaluate the Safety and Efficacy of Long-term Treatment with Lumacaftor in combination with Ivcacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation"  
- 2011-2014, Boehringer-Ingelheim; three studies: (1) A trial to confirm the efficacy and safety of tiotropium administered via the Respimat B device in patients with cystic fibrosis; (2) A trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler in children with severe persistent asthma; (3) A trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler in adolescents with severe persistent asthma  
- 2010-2012, GlaxoSmithKline: Analysis of BronchoalveolarLavage (BAL) fluid from children with respiratory disorders  
- 2012 - 2013, Novo Nordisk Pharmaceuticals Pty Ltd - Cystic Fibrosis - Insulin Deficiency, Early Action (CF-IDEA) Research Grant. |

**Consultancy fees – honorarium**
- Other presentations with reimbursements / activities as listed below:  
  - Novartis Pharmaceuticals Corporation: (1) TOBI® supplied by Pathogenesis, Chiron, and Novartis for the ACFBAL study between 1999 and 2009; (2) Acted on international Drug Advisory Board for Novartis regarding TOBI/TIP European CF meeting Valencia 2010; (3) Presented for the Novartis sponsored CF Symposium at European CF meeting Valencia 2010 (1 night’s accom. provided); (4) Economy flight return Brisbane to Melbourne to present to PBAC 9th March 2011; (5) European CF Conference Lisbon July 2013 - return travel and accommodation to present symposium; (6) Honorarium to present symposium at Australasian CF Conference in August 2013  
  - L.E.K Consulting: Consulting Interview regarding CF Studies  
  - Vertex Pharmaceuticals Inc.: (1) Consultant on the Vertex Physician Paediatric CF Advisory Board; (2) May 2013 - San Francisco return flight and accommodation as Investigator in Lumacaftor (104) study  
  - Guidepoint Global: Phone consultation regarding recent CF Trials  
  - Gilead Sciences Inc.: AZLI Advisory Board Honorarium  
  - Medscape: Consultation interview regarding CF Studies 2012. |

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<tr>
<th>Prof Graham Mann</th>
<th>Employment</th>
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</table>
| - Steering Group member  
- HCC secondary contact | - An employee and a senior academic of the University of Sydney in Sydney Medical school  
- Receives occasional honoraria for lectures, examination of theses and ad hoc committee work. |

**Activities**
- Holds unremunerated appointments as a researcher at Westmead Millennium Institute for Medical Research (WMIMR) and Melanoma Institute Australia (MIA), where his laboratories facilities of his research program are located, and where some staff that he
<table>
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<tr>
<th>Name and Role(s)</th>
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<tr>
<td><strong>Prof Graham Mann</strong> ...continued</td>
<td>supervises are employed. He is a member of the Faculty of WMIMR and is co-director of research at MIA.</td>
</tr>
<tr>
<td><strong>Grants</strong></td>
<td>• Holds research grants as Chief Investigator from NHMRC, Cancer Institute NSW, NSW Health, the Cancer Council NSW and Bioplatforms Australia.</td>
</tr>
<tr>
<td><strong>Direct or indirect pecuniary interest</strong></td>
<td>• Other than as part of managed superannuation funds, has no investments or assets relevant to the work of the Committee.</td>
</tr>
<tr>
<td><strong>Prof Chris Doran</strong></td>
<td>• Nil interests to declare.</td>
</tr>
<tr>
<td><strong>Conj A/Prof Andrew Searles</strong></td>
<td>• Nil interests to declare.</td>
</tr>
<tr>
<td><strong>Mr Simon Deeming</strong></td>
<td>• Nil interests to declare.</td>
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</table>