Key observations from the NHLBI Asthma Clinical Research Network

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ABSTRACT

The National Heart, Lung and Blood Institute (NHLBI) Asthma Clinical Research Network (ACRN) recently completed its work after 20 years of collaboration as a multicentre clinical trial network. When formed, its stated mission was to perform multiple controlled clinical trials for treating patients with asthma by dispassionately examining new and existing therapies, and to rapidly communicate its findings to the medical community. The ACRN conducted 15 major clinical trials. In addition, clinical data, manual of operations, protocols and template informed consents from all ACRN trials are available via NHLBI BioLINCC (https://biolincc.nhlbi.nih.gov/studies/). This network contributed major insights into the use of inhaled corticosteroids, short-acting and long-acting ß-adrenergic agonists, leukotriene receptor antagonists, and novel agents (tiotropium, colchicine and macrolide antibiotics). They also pioneered studies of the variability in drug response, predictors of treatment response and pharmacogenetics. This review highlights the major research observations from the ACRN that have impacted the current management of asthma.

INTRODUCTION

The objective of this review is to summarise some of the seminal observations made by the investigative team of the National Heart, Lung and Blood Institute (NHLBI) Asthma Clinical Research Network (ACRN). When established in 1993, the stated mission of the ACRN was to perform multiple controlled clinical trials for treating patients with asthma by dispassionately examining new and existing therapies, and to rapidly communicate its findings to the medical community. This network contributed major insights into the use of inhaled corticosteroids (ICS), short-acting and long-acting ß-adrenergic agonists (SABAs, LABAs), leukotriene receptor antagonists (LTRAs), and potentially novel agents (tiotropium, colchicine and macrolide antibiotics). It also pioneered studies of the variability in drug response, predictors of treatment response and pharmacogenetics. The findings of many of the studies conducted by the ACRN are incorporated into the asthma guidelines. Finally, they provided a foundation for the design of future studies now being conducted in the NHLBI AsthmaNet, which is charged with conducting clinical trials in adults and children.

ORGANISING AN INFRASTRUCTURE FOR ASTHMA NETWORK STUDIES

Along the way, the programme established a model for organising a network of investigators that conducted clinical trials. The NHLBI of the National Institutes of Health (NIH) funded ACRN I from 1993 to 2003 with two grants and ACRN II from 2006 to 2011. These grants were structured with the initial award as a cooperative agreement (U10 funding mechanism) among several clinical centres and one data-coordinating centre. In addition to support for protocol budgets and core functions, the NHLBI also supported a Clinical Research Skills Development Core to foster the career growth of junior investigators.

The ACRN invoked the same organisational plan throughout both phases and was governed by its steering committee, which consisted of an independent chair, the NHLBI programme scientist, and the principal investigators of the participating institutions. The NHLBI formed two independent committees to oversee many of the ACRN activities. The Protocol Review Committee was responsible for reviewing and approving the scientific approach of every clinical trial protocol prior to its onset. The Data and Safety Monitoring Board was responsible for reviewing the informed consents, reviewing the study data to ensure the safety of study participants, and advising the NHLBI on the continuation, modification or termination of studies in progress.

The NHLBI charged the ACRN with designing and conducting multiple clinical trials to investigate the safety and effectiveness of current and novel interventions in adult asthma, and reporting the results of such trials in an expeditious manner to the scientific community and the public. The ACRN was successful in both endeavours. It conducted 15 major clinical trials during its 18-year existence and it typically presented reports of major results and ancillary studies at annual meetings of the American Thoracic Society and the American Academy of Allergy, Asthma and Immunology. The major publications from these 15 clinical trials appear as the first set of references to this article.[1–14] In addition, clinical data, manual of operations, protocols and template informed consents from all ACRN trials are available via NHLBI BioLINCC (https://biolincc.nhlbi.nih.gov/studies/). Studies in the ACRN were conducted primarily in adults, with several that included adolescents. In an effort to focus on childhood asthma as well, the NHLBI Childhood Asthma

Research and Education (CARE) Network was developed as a separate NIH asthma network to address the special needs of children.

ICS: DOSE RESPONSE, VARIABILITY OF RESPONSE AND PREDICTORS OF RESPONSE—THE DICE, MICE, PRICE AND SMOG STUDIES

At the time ACRN began to discuss priorities, a major debate raged regarding the comparative efficacy and systemic effect of ICS. The ACRN decided that to address this question, the dose–response of individual ICS should be profiled for comparative efficacy, as measured by change in forced expiratory volume in 1 s (FEV_1) and airways hyperresponsiveness, and systemic effect, as measured by overnight plasma cortisol. A small pilot-feasibility study in adults entitled 'Measuring Inhaled Corticosteroid Efficacy' (MICE) was designed to compare the dose–response of two commonly used ICS.[6] Several key observations were made from this relatively small but important study. First, maximal FEV_1 response occurred with low-dose fluticasone propionate administered via a metered dose inhaler (FP-MDI) and medium-dose beclomethasone dipropionate via MDI (BDP-MDI) and was not further increased by treatment with high-dose fluticasone propionate via dry powder inhaler (FP-DPI). The same pattern was seen for methacholine concentration resulting in 20% reduction in FEV_1 PC_{20}. Both ICS caused dose-dependent cortisol suppression. Therefore, high-dose ICS therapy did not significantly increase the efficacy for these two measures but did increase the systemic effect measure, overnight cortisol suppression. Second, significant inter-subject variability in response occurred with both ICS. Good (>15%) FEV_1 response, in contrast to poor (<5%) FEV_1 response, was found to be associated with high exhaled nitric oxide (eNO), high bronchodilator response, and a low FEV_1/forced vital capacity (FVC) ratio before treatment. In contrast, excellent (more than three doubling dilutions) improvement in methacholine FEV_1 PC_{20}, in contrast to poor (<1 doubling dilution) improvement, was found to be associated with high sputum eosinophil levels and older age of onset of asthma.

At the same time, the ACRN conducted a study in adults with six ICS to define the dose response in systemic effect on overnight plasma cortisol in a study entitled 'Dose of Inhaled Corticosteroid with Equi-systemic Effect (DICE)'.[5] This study concluded that there were significant differences in the level of systemic effects among the ICS studied. Of interest, there was less systemic exposure in a dry powder formulation compared with the same ICS, fluticasone propionate, administered in a metered dose inhaler.

Based on the provocative results of the MICE study, the ACRN developed a follow-up study, the 'Predicting Response to Inhaled Corticosteroid Efficacy (PRICE)' trial, to evaluate potential biomarkers for predicting short-term (6-week) response to ICS in adults.[11] The key findings in this study included the following observations. First, although multiple baseline predictors had significant correlations with improvements for short-term ICS success, the only strong correlations ($r \geq 0.6$) were salbutamol (albuterol) reversibility, FEV_1/FVC and FEV_1 % predicted. Second, for the non-responders (<5% FEV_1 improvement), asthma control remained unchanged whether ICS were continued or were substituted with a placebo. Third, the good short-term responders (>5% improvement in FEV_1) maintained asthma control longer term only if maintained on ICS. This finding validated the use of change in FEV_1 as an indicator of ICS responsiveness, for it established a relationship between an ICS-induced improvement in this measure of maximal flow and ICS-induced protection against exacerbations. Another finding of this larger validation study was that eNO was not a predictive biomarker of ICS responsiveness in adults with mild to moderate persistent asthma as noted in the MICE study.

Therefore, we concluded from the PRICE study that short-term response to ICS with regard to FEV_1 improvement predicts long-term control. The clinical implications for these findings were that the decision to use long-term ICS could be based in part on a short-term trial, and that different therapeutic strategies would need to be established for non-responders. Unfortunately, other studies have suggested that the short-term FEV_1 responsiveness to ICS has not predicted complete freedom from exacerbations. Nonetheless, the change in lung function remains the best short-term predictor of ICS efficacy for individual patients.

ß-ADRENERGIC AGONISTS IN THE MANAGEMENT OF ASTHMA AND THE ROLE OF PHARMACOGENETICS

The ACRN investigation of the best approach to use β agonists illustrates the network's approach to asking clinically important questions in asthma treatment and how it has used its findings to explore new questions relevant to the best approaches to asthma treatments. The clinical questions we explored in relation to β agonists answered the initial questions posed and led us to investigate areas regarding personalisation of asthma treatment and pharmacogenomics. The BAGS (β-Agonists)[1] and BARGE (β-Agonist Response by Genotype)[7] trials, conducted in adults, have been previously reviewed,[15] and showed that as-needed albuterol was just as good as scheduled albuterol, but that participants with the Arg/Arg genotype affecting the 16th amino acid of the ß2 adrenergic receptor experienced a deterioration in peak flow, FEV_1, symptoms, and increased need for rescue inhaler when using albuterol regularly whereas the participants with the Gly/Gly genotype experienced an improvement in all these indices when using albuterol regularly. These data suggested that bronchodilator treatments avoiding albuterol may be appropriate for patients bearing the Arg/Arg genotype who are not using ICS.

Since albuterol is rarely used regularly by patients with asthma, except during exacerbations, we turned our attention to prolonged β-agonist stimulation that occurs with LABA use. We first genotyped participants who had been in our ACRN trials who had received salmeterol.[16] Although the numbers of participants were small, we found a significantly reduced peak flow with use of salmeterol compared with placebo (>50 litres/min) in Arg/Arg participants not concurrently using ICS compared with Gly/Gly participants. In those using ICS we found statistically significant deteriorations in FEV_1, symptom scores, and rescue inhaler use. These results led us to conduct a prospective, double-blind, genotype-stratified (Arg/Arg vs Gly/Gly) trial of salmeterol versus placebo in participants on moderate doses of ICS.[12] This trial, conducted in adults, was named the LARGE (Long-Acting β-agonist Response by Genotype) trial. In both genotypes peak expiratory flow (PEF, our primary outcome variable) improved when salmeterol was added to moderate doses of ICS. We did note an improvement in methacholine responsiveness in Gly/Gly participants compared with Arg/Arg participants who used salmeterol compared with placebo. Further, a post hoc analysis in the subset of self-identified black participants showed that in Arg/Arg black participants PEF did not improve with the addition of salmeterol. In contrast, in Gly/Gly black participants PEF did improve with salmeterol. These data suggested that, at the very least, there

was no genotype-specific response in airway calibre in reaction to regular use of LABAs in the setting of moderate doses of ICS. The significance of the genotype-specific differences in methacholine reactivity and the race-specific genotype remains to be determined and is being explored in ongoing trials.

How should the ACRN pharmacogenomic investigations be interpreted? It is clear that Arg/Gly polymorphisms at the 16th amino-acid position appear to have a significant effect on the response to regular use of SABAs. However, we now understand that these effects can be modulated substantially by environmental and gene–gene interactions. For example, smoking,[17] polymorphisms in other genes (eg, S-nitrosoglutathione reductase),[18] and race/ethnicity[19] have all been shown to modulate the effect of Arg/Gly polymorphisms and the response to β agonists. These interactions will need to be considered in developing personalised models for predicting therapeutic responses to these agents. Additionally, retrospective evaluations of clinical trials with LABAs used concomitantly with ICS have been consonant with the findings of the prospective LARGE trial in that they have not seen differences in the change in airway calibre by genotype. Further, they have not suggested increased rates of exacerbations, although they have not been powered to assess these effects by race.[20 21]

What did we learn from ACRN studies in terms of β agonists and asthma? The ACRN studies suggested that in a routine asthma population there is generally little benefit to using SABAs regularly. The Salmeterol or Corticosteroids Study (SOCS)/Salmeterol ± Inhaled Corticosteroids (SLIC) study, reviewed below, suggested that LABAs could not substitute for ICS in the treatment of asthma since they increased exacerbations while appearing to control symptoms. The exploration of the effect of polymorphisms in ß-adrenergic receptors really started the area of pharmacogenomic investigation in asthma. These studies identified one of the polymorphisms that continues to appear to have one of the strongest effects on β-agonist responses of any polymorphism identified thus far. It appears that Arg/Arg participants may be less likely to benefit if SABAs are used regularly. However, these studies also have made us aware that these genetic effects cannot be considered in isolation and need to be interpreted in the context of underlying behaviour, genetic background (race/ethnicity) and environment, including concomitant medications such as corticosteroids.

STEP-UP THERAPY: THE SOCS, SLIC AND SLIMsIT STUDIES

It is important to remember that the ACRN began in an era when the evidence base to guide therapy for patients needing more than rescue albuterol was incomplete. At that time, the use of LABA with or without concomitant ICS therapy (ie, monoLABA therapy) was considered a viable treatment option for step 2 treatment. To establish the proper positioning of LABA therapy in asthma treatment, three ACRN studies were conducted. These trials, were SOCS and SLIC studies conducted in adults and adolescents, and the Salmeterol and Leukotriene Modifier versus Salmeterol and ICS Treatment study (SLIMsIT), conducted primarily in adults.[3 4 10]

Key design features that were critical to positioning LABAs were that all three trials contained an element of ICS withdrawal for at least some participants, treatment failure as a primary endpoint with a well defined definition (including a decline in pre-bronchodilator PEF to ≤65%, or an increase in rescue albuterol use of 8 puffs/day over baseline), and a built-in treatment failure rescue algorithm for safety. SOCS and SLIC shared a common run-in on a medium dose of ICS. At the end of this period, participants whose condition was well controlled were randomised in SOCS, whereas those with suboptimal control entered SLIC. After establishing control with ICS during this run-in phase, the SOCS trial evaluated salmeterol as subsequent monotherapy compared with placebo or a continuation of ICS in a three-arm, parallel design.[3] By contrast, in SLIC, salmeterol was added to medium dose ICS and if participants did not experience a treatment failure after 2 weeks, half underwent an ICS reduction (half the previous dose) and elimination phases compared with the other half who maintained the ICS dose (all participants in these groups continued salmeterol).[4] The main results of these studies firmly established that LABAs should not be used as monotherapy and that in patients taking a LABA in addition to ICS, the ICS dose could be partially reduced but not eliminated.

Since LTRAs provide anti-inflammatory effects, the ACRN examined whether LTRAs, rather than ICS, could be used in combination with LABA to provide improved asthma control.[10] Participants with mild-to-moderate asthma entered a run-in period in which they received a low-dose ICS and an LTRA. During the treatment phases, all participants received add-on salmeterol and were then randomised to a crossover sequence such that each participant received ICS/LABA and LTRA/LABA combination therapy at some point, with a 4-week washout period in between. After a prespecified review of complete data from 50% of the intended sample size, the Data Safety and Monitoring Board halted the trial because the ICS/LABA treatment sequence was associated with a 3.5-fold longer time to the first treatment failure compared with the LTRA/LABA phase in the same participants.

Several important lessons can be extracted from the SOCS/SLIC and SLIMsIT data. First and foremost, monotherapy with a LABA (ie, step 2) has a higher rate of treatment failures than ICS and is not supported. Second, until we have better ways of identifying patients who preferentially respond to LTRAs, the combination of LTRA/LABA is inferior to ICS/LABA for the majority of patients. Finally, the SLIC results also raise an important question for future research. As pointed out by Sears,[23] the data from the ICS reduction phase of this study do not rule out the possibility that there is a dose dependence of the putative protective effect of ICS in terms of its ability to mitigate against potential risks conferred by LABA.

INTERMITTENT ICS AND BIOMARKER-BASED ASTHMA MANAGEMENT: THE IMPACT AND BASALT STUDIES

A key question for asthma practitioners is whether persistent asthma requires persistent, daily treatment to achieve optimal asthma control, prevent accelerated loss of lung function, or reduce the frequency of asthma exacerbations. The ACRN has addressed these questions with two seminal protocols conducted in adults: Improving Asthma Control (IMPACT)[8] and Best Adjustment Strategy for Asthma in the Long Term (BASALT).

In the IMPACT trial, 225 participants with mild persistent asthma were randomised to receive either placebo, daily inhaled budesonide (200 μg twice daily), or daily zafirlukast (20 mg twice daily) for a year, in conjunction with a symptom-based action plan that was used if asthma symptoms worsened. The symptom-based action plan (SBAP) included increasing β-agonist use and providing either 800 μg twice daily budesonide for 10 days, or 0.5 mg/kg prednisone for 5 days. The primary outcome was change from baseline in 2-week average morning PEF, and key secondary outcomes included the frequency of exacerbations, standard measures of asthma control and asthma quality of life. Adherence to the protocol exceeded 90% in all

arms. The primary outcome was not different among groups, with an increase in each group of about 32 litres/min PEF. Post-bronchodilator FEV_1, the proportion of exacerbations and time to first exacerbation, asthma quality of life, adverse events and missed school or work were not different among groups, despite the fact that the symptom-based action plan group used <90% the amount of ICS used by the regular treatment group. Asthma control score, and symptom-free days were significantly better in daily budesonide compared with either placebo or zafirlukast therapy, but not by a large margin. Despite the limitations inherent in applying a clinical trial to practice, IMPACT suggested that an appreciable proportion of subjects with mild asthma may not require daily ICS and rather could use them with impending exacerbations based on symptoms.

The aims of the BASALT trial were to extend the findings of IMPACT to patients with asthma with somewhat greater degree of asthma severity, and to assess the possible benefit of using a putative biomarker of airway inflammation, eNO, to guide anti-inflammatory therapy. We randomised 342 patients with mild–moderate asthma to three arms: provider-assessment based adjustment (PABA), a close implementation of the existing US NHLBI NAEPP guidelines; biomarker based assessment (BBA) using eNO as an index of airway inflammation; and symptom-based adjustment (SBA), in which participants took inhaled steroids each time their symptoms were sufficient to warrant use of their rescue β-agonist inhaler. Inhaled steroids were started at 200 μg twice daily for all participants, and were adjusted by PABA or BBA at the time of clinic visits 6 weeks apart, and participants followed the regimen for 44 weeks. For those on SBA, beclomethasone 400 μg was administered only at the time of rescue albuterol use. The primary outcome was time to first treatment failure, a clinically relevant worsening of asthma control used in several ACRN trials. Important secondary outcomes included FEV_1, methacholine responsiveness, validated symptom and quality-of-life questionnaires, and sputum eosinophils. As presented at the 2011 American Academy of Allergy, Asthma and Immunology Annual Meeting by Dr. William Calhoun on behalf of the ACRN (manuscript in review), three treatment groups did not differ significantly for the primary outcome, or most of the secondary outcomes, and the frequency and rates of treatment failure and exacerbations were smallest in the SBA group. The cumulative dose of inhaled beclomethasone was significantly smaller in SBA compared with either PABA or BBA. BASALT suggests that in patients with mild–moderate persistent asthma controlled on a low dose of inhaled steroids, symptom-based adjustment of steroid administration at the time of use of β agonists is reasonable.

EXPLORING NEW TREATMENT APPROACHES: THE CIMA, MIA, TALC STUDIES

When the ACRN was created, its charge directed members of the network to dispassionately examine new and existing therapies for asthma. During its 18-year history, three trials examined novel treatment approaches.

The Colchicine in Moderate Asthma (CIMA) trial tested the hypothesis that in patients with moderate asthma who use ICS for control of symptoms and lung function, colchicine would offer therapeutic benefit as measured by maintenance of control when ICS were discontinued.[2] This 10-week, double-blind, randomised, placebo-controlled trial involved 71 adult patients with moderate asthma treated with ICS who tolerated 2 weeks of open-label colchicine, and who were then randomised, in a double-blind fashion, to either colchicine or placebo, with the concomitant discontinuation of the ICS for a 6-week observation period. For this trial, a novel endpoint of time to 'treatment failure' was developed and employed. Participants could 'fail treatment' by any one of several ways: by a deterioration in lung function (FEV_1 or PEF), through an excessive increase in the use of rescue β agonist, or by refusing to continue with study drugs because of lack of satisfaction with the treatment regimen. The goal was to allow patients to become uncontrolled, without developing a true asthma exacerbation which would require systemic corticosteroid use. While colchicine showed no benefit in this protocol (60% of participants receiving colchicine and 56% of those receiving placebo failed to complete 6 study weeks of treatment because of treatment failure), the trial suggested that the 'treatment failure' endpoint was both robust and safe, and paved the way for its use in other ACRN protocols, including SLIC, SLIMsIT and BASALT.[4 10]

The Macrolides in Asthma (MIA) trial tested the hypothesis that the addition of a macrolide antibiotic to an inhaled corticosteroid would improve asthma control over that achieved with ICS alone, in a stratification by PCR design in two separate groups of participants, those with and those without evidence of *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* in bronchial biopsies sampled by fibreoptic bronchoscopy.[13] The 20-week trial included 16 weeks of double-blind, placebo-controlled treatment with clarithomycin, and enrolled 92 adult patients with asthma, 12 with evidence of *M pneumoniae* or *C pneumoniae* and 80 without. The primary outcome, the seven-item Asthma Control Questionnaire (ACQ) score evaluated at the time of randomisation and after 16 weeks of treatment with study drug, was evaluated independently in each PCR stratum and showed no significant change in either stratum. Because only 12 of the 92 randomised participants (13%) displayed evidence of *M pneumoniae* infection, this stratum was underpowered for the primary endpoint, but suggests that the incidence of infection might be lower than reported by others.[23]

The Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) trial tested two hypotheses, that the addition of tiotropium bromide to patients whose condition was inadequately controlled on low-dose ICS alone would be superior to doubling the dose of ICS, and not inferior to the addition of a long-acting β agonist (salmeterol) in terms of asthma control.[14] This double-blind, double-dummy, three-way crossover trial, a companion of the BASALT trial, randomised 210 adults for 14-week treatment periods, followed by 2-week run-out/run-in periods between randomised treatment periods. It demonstrated superiority of tiotropium plus 1×ICS to 2×ICS in terms of am PEF (primary outcome), pm PEF, trough FEV_1, proportion of asthma control days, daily symptoms, ACQ score and FEV_1 after four puffs of albuterol; non-inferiority to salmeterol plus 1×ICS in terms of am PEF, pm PEF, proportion of asthma control days, daily symptoms, ACQ score; and superiority to salmeterol plus 1×ICS in terms of trough FEV_1, and FEV_1 after four puffs of albuterol. These data suggest that long-acting anticholinergic agents might be an alternative to LABAs and other controllers in patients whose condition is inadequately controlled on an ICS alone.

The ACRN experience with novel approaches for treating asthma was, in general, quite positive with one trial showing positive results (TALC), one trial addressing an important issue in asthma treatment with a negative outcome (MIA), and one trial demonstrating the usefulness of a novel, robust and safe asthma outcome, time to treatment failure (CIMA). In addition, the ACRN also reported the differential effect of smoking on the response to ICS and LTRAs in adults in the Smoking Modulates

Box 1 Significant contributions from Asthma Clinical Research Network studies

- Response to inhaled corticosteroids (ICS) is variable but can be associated with the level of pulmonary function and bronchodilator response and the response to a short-term trial.
- Long-acting ß-adrenergic agonists (LABAs) should not be used as monotherapy in the treatment of asthma.
- To verify observations related to pharmacogenetic markers defined from retrospective data analysis, prospective, randomised studies must be conducted.
- Leukotriene receptor antagonists should not be substituted for ICS therapy when combined with LABAs.
- Patients with mild asthma may be managed with intermittent ICS and may not require daily therapy.
- Symptom-based administration of ICS may be more effective than provider-based or biomarker-based adjustments in therapy.
- Inhaled long-acting anticholinergic agents might be an alternative to LABAs and other controllers in patients whose condition is inadequately controlled on an ICS alone.

Outcomes of Glucocorticoid Therapy (SMOG) trial, showing that LTRAs provided a better response than ICS in patients with asthma who were also smokers.[9]

THE IMPACT OF ACRN ON OTHER NIH ASTHMA NETWORK STUDIES

As summarised above, the ACRN advanced the field of asthma care in a number of ways (box 1). Box 2 indicates some reasons why the NHLBI ACRN worked so well to contribute landmark studies and some tasks that remain to be continued in the work of future asthma multicentre collaborative efforts. The ACRN also had a significant effect on studies conducted in other NIH asthma networks. Several investigators in the ACRN were also investigators in the NHLBI CARE Network. Studies conducted in the ACRN influenced the evaluation of ICS, LTRA and LABA in children. The combination of experience in ACRN and CARE has also provided a strong base for the design of studies that will be conducted in the NHLBI AsthmaNet Network. This new asthma network is charged with conducting studies in children and adults along with cross-age studies when possible. Therefore, the work of the ACRN in developing a clinical research infrastructure and refining procedures has set the stage for future clinical studies that will continue to improve the management of asthma and lead to a personalised medicine approach.

Box 2 Lessons learnt from the National Heart, Lung and Blood Institute (NHLBI) Asthma Clinical Research Network

What went well?

- A strong base of funding from the NHLBI to set up the infrastructure to manage and conduct the multiple clinical trials.
- Strong leadership from established investigators to develop and implement the clinical trials.
- A spirit of collaboration to assure the success of major clinical trials, to address information gaps or to innovate care.

What can future networks address?

- Identify ways to collaborate to meet the needs of children, adolescents and adults in one asthma network.
- Consider methods to prevent the onset of asthma at a very early stage and to prevent asthma exacerbations and progression.
- Develop new tools, such as genetics, epigenetics and biomarkers, that will advance the personalised approach to asthma care at a clinical level.
- Continue to find ways to quickly apply research findings to clinical care.

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