Protocol Title: Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.

Protocol Number:	AIR-SA 001
Short Title:	AIR-South Africa
Phase:	3
Sponsor Name:	Dr Pinkie Mekgwe Chief Operations Officer Africa Health Research Institute (AHRI)
Funder:	National Institute for Health and Care Research (NIHR) UK
Principal Investigator:	Professor Refiloe Masekela Department of Paediatrics and Child Health Africa Health Research Institute - Somkhele Via 618 to Hlabisa Somkhele Mtubatuba 3935

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Clinical Sub-Investigators	**Institution**
Professor Willem Hanekom	Africa Health Research Institute
Dr Sbekezelo Thembelihle Hlophe	University of KwaZulu-Natal
Dr Limakatso Lebina	Africa Health Research Institute
Dr Ngundu Behuhuma	Africa Health Research Institute
Dr Ngcebo Mhlongo	Africa Health Research Institute
Dr Suné Liebetrau	Africa Health Research Institute
Dr Lucica Thaver	Africa Health Research Institute
Non-Clinical Trial Sub-Investigators	
Professor Kevin Mortimer	University of KwaZulu-Natal and Cambridge University
Prof Josue Mbonigaba	University of KwaZulu-Natal
Nqobile Ndimande	University of KwaZulu-Natal
Clinical Trial Coordinators	
Dr Anne Derache	Africa Health Research Institute
Nompumelelo Ngobese	Africa Health Research Institute
Clinical Trial Pharmacists	
Kristien Bird	Africa Health Research Institute
Mnqobi Khumalo	Africa Health Research Institute
Buhle Nhlapo	Africa Health Research Institute

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.

I, the undersigned as National Principal Investigator agree that I have reviewed the application and protocol and will ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and South African legal, ethical and I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

1. I agree to personally conduct or supervise the study.
2. I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, as per any approved protocol amendments, as per International Conference on Harmonisation - Guidelines for Good Clinical Practice (ICH-GCP) and all applicable Regulatory Authority requirements and national laws.
3. I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Ethics Committee, and Regulatory Authority, except where necessary to prevent immediate danger to the participant.
4. I have read and understand the information in the relevant Summary of Product Characteristics, and I am familiar with the Investigational Medicinal Product (IMP); I also understand the IMP use, including its potential risks and side effects.
5. I agree to inform all participants that the IMPs are being used for investigational purposes and I will ensure that the requirements related to obtaining informed consent are in accordance with ICH-GCP Section and local requirements.
6. I agree to report adverse events that occur during the study to the Sponsor, to maintain adequate and accurate records and make those records available, in accordance with ICH-GCP, South African Good Clinical Practice and other local requirements. I agree to promptly report to the Biomedical Research Ethics Committee (BREC) all changes in the research activity and all unanticipated problems involving risk to the participants.
7. I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I will ensure that any qualified staff at my sites who are involved in the trial conduct are adequately trained regarding the IMP, the protocol, and their responsibilities for the foreseen duration of the trial to conduct the trial properly and safely. If I delegate any of my trial activities, I will provide the Sponsor with a Delegation of Activities Form. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in

meeting the above commitments.

8. I understand that the study may be terminated, or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interest of the participants.

14 Dec 2023

(signature) (date of signature)

Refiloe Masekela Principal Investigator
University of KwaZulu Natal

SPONSOR APPROVAL SIGNATURE PAGE

Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.

I, the undersigned have read this protocol and I approve the design of this trial:

Dr Pinkie Mekgwe

Pinkie. Mekgwe

14 Dec 2023

(name) (date of signature)

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1 Abbreviations and Definition of terms

Abbreviation	Definition
ABPI	Association of British Pharmaceutical Industry
ACDIS	Africa Centre Demographic Information System
ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
AHRI	Africa Health Research Institute
AHRI Link	Africa Health Research Institute Link
ATP	Adenosine Triphosphate
ATS	American Thoracic Society
AUC	Area Under the Curve
BMI	Body Mass Index
BREC	Biomedical Research Ethics Committee
cACT	Childhood Asthma Control Test
cAMP	Cyclic Adenosine Monophosphate
CDMS	Clinical Data Management System
COPD	Chronic Obstructive Pulmonary Disease
CTU	Clinical Trials Unit
CYP3A4	Cytochrome P450 3A4
DAIDS	Division of Allergy and Infectious Diseases
DMP	Data Management Plan
DPI	Dry Powder Inhaler
DSA	Demographic Surveillance Area
DSID	Directory Services Identifier
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Form
EOS	End Of Study
ERS	European Respiratory Society
EQ-5D-Y	Euro Quality of Life Youth version
FEV1	Forced Expiratory Volume in one second
GINA	Global Initiative for Asthma
HDSS	Health Demographic Surveillance System
HIV	Human Immunodeficiency Virus

HPA	Hypothalamus Pituitary Adrenal Axis
ICF	Informed Consent Form
ICH GCP	International Conference on Harmonization Good Clinical Practice
ICS	Inhaled Corticosteroids
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
Kg	Kilogram
LABA	Long-Acting Beta -2- Agonist
LMIC	Low to Middle Income Countries
MART	Maintenance and Reliever Therapy
MoH	Minister of Health
MRHDID	Maximum Recommended Human Daily Inhalation Dose
NCD	Non-Communicable Disease
NIHR	National Institute of Health and Care Research
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PEFR	Peak Expiratory Flow Rate
PIP	Population Intervention Platform
PIPSA	Population Intervention Program Surveillance Area
pMDI	Pressurised Metered Dose Inhaler
PRN	Pro Re Nata (As needed)
QALY	Quality Adjusted Life Year
QOL	Quality of Life
QTc	Corrected QT interval
SAE	Serious Adverse Events
SAGCP	South African Good Clinical Practice
SAHPRA	South African Health Products Regulatory Authority
SAP	Statistical Analysis Plan
SAPRIN	South African Population Research Infrastructure Network
SDG	Sustainable Development Goals
SOE	Schedule of Events
SPO2	Saturated Partial Pressure of Oxygen
SRC	Scientific Review Committee
SRT	SubRip Text
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event

TIE	Time, Inconvenience and Expense
TMC	Trial Management Committee
TMF	Trial Master File
TSC	Trial Steering Committee
SABA	Short Acting Beta-2- Agonist
SMART	Symbicort Maintenance and Reliever Therapy
UKZN	University of KwaZulu-Natal
US	United States
WHO	World Health Organisation

2 Protocol Summary

2.1 Synopsis

Protocol Title	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Phase 3 Randomised Open-Label Controlled Trial.
Short Title	AIR-SA 001
Rationale	Over the last two decades non-communicable diseases (NCDs) have been rising in sub-Saharan Africa, and NCDs are set to overtake communicable, maternal, neonatal, and nutritional diseases combined as the leading cause of mortality in sub-Saharan Africa by 2030.[1] Many NCDs have their roots in childhood with lifestyle changes in combination with an increasing median population age in Africa making a further dramatic rise in NCDs in Africa's near future highly likely.[2] The World Health Organization (WHO) now considers the prevention and control of NCDs as an urgent development issue and essential to the achievement of the Sustainable Development Goals (SDG) and this can only be achieved with childhood interventions.[3, 4] The 2018 WHO report on NCDs, reported 3.8 million deaths annually from non-communicable respiratory diseases (asthma and chronic obstructive pulmonary disease), with 78% of deaths in low-income and middle-income countries (LMICs). Asthma morbidity and mortality are preventable with inhaled therapies-however, there is lack of evidence on how to deliver these in an affordable and effective way The WHO highlights asthma as an under-appreciated cause of poverty in LMICs that retards economic and social development, erodes the health and well-being of those affected and has a negative impact on families and societies. Asthma aggravates poverty and poverty aggravates asthma.[5] Children miss out on education, adults lose days at work and the costs of drugs, emergency visits, and hospitalisation are major financial burdens, not only for individuals/families but also for struggling health systems. In South Africa, asthma is the most common NCD in childhood affecting 1 in 5 children with a prevalence of asthma symptoms at 21% in adolescence.[6] Despite the availability of asthma medicines in the Essential Medicines List, asthmatic children report having severe asthma symptoms in over 50% of those with asthma. South Africa still reports the fourth highest mortality rate globally.

	The core to asthma management includes use of chronic use of anti-inflammatory inhaled corticosteroids to address the inflammatory process in the airways (maintenance) and bronchodilators (relievers) for relief of the bronchospasm. Many studies have shown that asthma mortality is linked to poor use of anti-inflammatory inhaler treatment and over-reliance on short- acting β2 bronchodilator reliever therapy to treat asthma exacerbations. In many LMICs including South Africa, the use of controller treatment use of anti-inflammatory inhalers is limited, with only 40% of people with severe asthma symptoms using regular ICS for chronic asthma treatment, but with over 89% using their short-acting β2 agonists. There is a large body of evidence showing that overuse of SABAs is linked with asthma mortality and poorer outcomes. The combination treatment with budesonide/formoterol for the management of asthma has transformed asthma treatment in high-income countries (HIC), where it is recommended in the very first step of asthma treatment as both an anti-inflammatory and reliever therapy. With the “as needed” use of budesonide/formoterol, asthmatics benefit from the additional dose of a maintenance anti-inflammatory dose, which improves symptom control and reduces exacerbations. This approach has not been adopted in many LMICs related to access to budesonide/formoterol and its cost and therefore, people in LMICs are relegated to use of Track 2 of Global Initiative of Asthma (GINA) treatment which still suggests the use of separate anti-inflammatory and reliever inhalers. To address this gap, a large body of randomised controlled clinical trial evidence (SYGMA[7, 8], Novel START[9], PRACTICAL[7], and several trials of SMART[9, 10, 11, 12]), have shown that use of budesonide/formoterol as needed (for exacerbations) and for long-term controller treatment compared to separate inhaled corticosteroid and short-acting bronchodilators, reduces the number of asthma exacerbations and improves quality of life. The trials have though been limited in that there is no data on the cost-effectiveness of this approach in lower resourced settings and limited data from small studies participant numbers (<100) of this approach in children 6-11 years of age. Based on this, the approach of using budesonide/formoterol has not been recommended by the Global Initiative of Asthma (GINA) strategy for global asthma management in Step 1 and 2 of treatment in children 6-11 years of age both in HIC and LMICs, but rather on the higher steps of asthma treatment where symptoms are more severe. We therefore propose in a randomised controlled trial to assess the

	efficacy of budesonide/formoterol compared to the standard of care (separate inhaled corticosteroid and bronchodilator) inhaler approach to prevent asthma exacerbations, improve asthma control and quality of life and to also assess the cost-effectiveness of budesonide/formoterol compared to standard of care in children and adolescents in South Africa. The data will be novel as we will for the first time include a large number of children in a clinical trial comparing the two approaches, to provide definitive evidence of the efficacy and cost-effectiveness of this approach in children and adolescents.
Overall Design	This is a Phase 3 single-centre open label randomised controlled trial with two equal sized groups to assess the efficacy of budesonide/formoterol 80/4.5 (6-11 years) and 160/4.5 (12-18 years) compared to the standard of care in reducing asthma exacerbations over 52 weeks Children and adolescents with a diagnosis of asthma or newly diagnosed with asthma will be screened for eligibility for enrolment. Those who had an asthma exacerbation in the previous year will be randomised 1:1, to either receive budesonide/formoterol inhaler for both symptom relief and for chronic anti- inflammatory maintenance therapy or the standard of care which is separate inhalers for symptom relief (short acting bronchodilator salbutamol) and chronic maintenance therapy with inhaled corticosteroids (beclomethasone or budesonide) and/or long-acting beta agonists or montelukast as determined by treating physicians. All asthma exacerbations and clinic/hospital admissions will be recorded for the duration of the 52-week follow-up. Participants will be followed up at 13, 26, 39 and 52 weeks. The 13- and 39-week visit will be telephonic visits to capture the primary end-point i.e. asthma exacerbations. Adverse events and medication changes data will also be collected. An independent Data and Safety Monitoring Board (DSMB) will be convened for this study with expertise in asthma and asthma clinical trials. The purpose of the DSMB will be to monitor the study for safety and operational futility with pre-defined stopping criteria. In addition, a Trial Steering Committee (TSC) will also provide overall supervision of the trial and ensure the trial is delivered in accordance with ICH-GCP. The TSC has been established with an independent Chair and include additional independent members including an observer early career researcher. Representatives of the Trial Funder (NIHR) and Sponsor (AHRI) will be invited to all TSC meetings.

Sample population	Children and adolescents age 6-18 years with a diagnosis of asthma and at least one asthma exacerbation in the previous 12 months.
Sample size	1038 participants will be enrolled into the study (519 per treatment arm).
Recruitment	Participants will be recruited from the network of AHRI Somkhele CTU and its primary health care clinics (n=6). Participants who meet the eligibility criteria will be referred to the study staff for eligibility screening and enrolment in the trial.
Study Duration	52 weeks per participant
Inclusion criteria	• Age for inclusion children and adolescents 6-18 years at the time of consent • Known asthmatic on treatment. • Newly diagnosed asthma based on investigator review and/or medical report. • All patients will have their asthma diagnosis confirmed (both new or known asthmatic patients) by either spirometry with reversibility or excessive diurnal variability by PEFR twice daily over 2 weeks. • Ability to perform Peak Expiratory Flow rate and/or bronchodilator reversibility testing. • Only participants with mild, or moderate asthma , based on medical history • At least one exacerbation of asthma in the past year as defined by an event requiring treatment with systemic corticosteroids for ≥3 days and/or a hospitalisation/emergency room visit for asthma requiring treatment with systemic corticosteroids. • Written consent from the participant or parent/guardian and assent from study participants where applicable. • Participant and/or parent/guardian agrees to comply with the study procedures, including the completion of the visits and be available for contact for telephonically for the non-contact visits.
Exclusion criteria	• Tuberculosis (TB): active TB disease and contact with people with active TB disease in the last 6 months. • Chronic sputum expectoration, chest pain, shortness of breath, dizziness, or light-headedness in the last 2 months.

	• Cardiac arrythmia. • Chronic conditions: thyrotoxicosis, phaeochromocytoma, cardiovascular disease, severe hypertension. • Uncontrolled diabetes mellitus • Patients with Peak Expiratory Flow Rate < 50% of predicted , as these would be classified as severe asthmatics. • Patients with any history of life-threatening asthma, defined as any history of significant asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma related syncopal episode(s). • Any use of biological therapy or immunomodulatory therapy such as methotrexate or regular oral prednisolone for the asthma management (STEP 5 GINA therapy). • Any surgical or medical condition that would significantly alter the absorption, distribution, metabolism or excretion of the IMP which may jeopardise the safety of the participants. The investigator should make this determination in consideration of the volunteer's medical history. • Any physical, mental or social condition, laboratory abnormality of history of illness that in the investigator's judgement might jeopardise the safety of the participant in the context of the study or might interfere with study procedures or the ability of the participant to adhere to and complete the study. The investigator should make this determination consideration of the volunteer's medical history. • Inability to present for follow-up or leaving the study area within 12 months of enrolment.
Investigational Product	Budesonide-formoterol fumarate dihydrate at two dose strengths 80/4.5 and 160/4.5 administered via a pressurized metered dose inhaler (pMDI) or dry powder inhaler (DPI), respectively. The dosing will be dependent on asthma symptom severity ranging from 1 dose as needed and titrated up or down depending on asthma control. • step 1-2: 1-dose as required. • step 3: 1 dose twice a day and 1 dose as required • step 4: 2 doses twice a day and 1 dose as required

Objectives	The primary objective is to assess the efficacy of a combination corticosteroid/rapid-onset long-acting ß$_2$ agonist (ICS/LABA) budesonide/formoterol inhaler 'as required' or, if clinically indicated, 'both as required, and regularly' to reduce asthma exacerbations compared to the standard of care for asthma.
Secondary objectives	The secondary objectives are to assess the cost-effectiveness of budesonide/formoterol compared to the standard of care from the individual, household, health system level and quality of life and to assess the impact of budesonide/formoterol compared to standard of care on quality of life.
Primary Endpoint	The primary endpoint will be the number of severe asthma exacerbations in the treatment year, defined as "events requiring systemic corticosteroids for three or more days and/or a hospitalisation/emergency room visit for asthma requiring systemic corticosteroids."
Secondary Endpoints	***Clinical Endpoints*** • Asthma Control Test (ACT) for ≥ 12 years or Childhood ACT (cACT) for children 6-11 years. • Paediatric Asthma Quality of Life Questionnaire (PAQLQ) • Peak Expiratory Flow Rate • School or work absence for carers/guardians • Adverse events (AE) • Serious Adverse Events (SAEs). ***Health economics Endpoints (N=200 participants)*** • Quality of survival estimates: time to first exacerbation, health-related quality of life using validated generic preference-based measures of health (EQ-5D-Y), adverse effects, school, work, household labour absences. • Household-level economic impact by socio-economic stratum (World Bank approach): out-of-pocket expenditures, loss of household productivity time and income (productivity losses), borrowing, and education losses. • Health system: health care costs related to in/out patient treatment of both the usual care and the intervention, including overhead costs, as well as cost savings from reduced exacerbations due to intervention and cost per quality-adjusted

	life year (QALY) gained. • Utility preferences as derived from the EQ-5D-Y questionnaire.

2.2 Schedule of Events

Table 1. Schedule of events

	Visit 1 ***Screening and enrolment***	***Visit 2*** ***First follow up (Telephonic)[1]***	***Visit 3*** ***Second follow up (Clinic visit)***	***Visit 4*** ***Third follow up visit (Telephonic)[1]***	***Visit 5*** ***End of study (Clinic visit)***
Visit week and study window	1	13 ± 2 weeks	26 ± 2 weeks	39 ± 2 weeks	52 ± 2 weeks
Informed consent	x				
Medical history and demographics	x		x		x
Vitals, weight and height	x		x		x
Physical examination	x		x		x
Inclusion/exclusion criteria check	x				
Randomisation	x				
Asthma review i) Asthma exacerbation (attacks) ii) Medication changes (including use of additional medications) iii) Days lost at school iv) Days lost from work for asthma parent(s)/guardian v) Serious adverse events vi) Adverse events	x	x	x	x	x

ACT/ cACT score[1]	x		x		x
PAQLQ	x		x		x
EQ-5D-Y ¶	x				x
Health economics questionnaires[2]	x		x		x
Spirometry and bronchodilator reversibility testing	x				
Spirometry	x		x		x
Peak Expiratory Flow rate (PEFR)[3]	x				
Written asthma action plan and diary assessments[4]	x		x		x
Inhaler technique assessment and demonstration	x		x		x
Dispense trial medication	x		x		x
Participant reimbursement	x		x		x

[1] *This is based on feasibility and the pragmatic design of the study. AHRI has an excellent telephonic system with experienced research nurses who are well equipment to conduct telephonic consultations with study participants and all participants who require assessment by the study team and the research doctors will be required to present to the research facility.*

[2] *EQ-5D-Y questionnaire only to sub-set of participants for follow-up (n=200), with health economics outcome data*

[3] *Peak expiratory flow rate (Measured with MicroLife AG Asthma Analyser electronic peak flow meter version 3.2.6)*

[4] *All participants will be provided and Asthma Action Plan (adapted from the Modified from Australian action plan with permission from National Asthma Council Australia and AstraZeneca Australia) the SMART Action Plan specifically for Budesonide/Formoterol and the National Asthma Education Program Action Plan (standard of Care).*

3 INTRODUCTION

3.1 Background

Africa comprises 15% of the world's population but bears 25% of the global disease burden and produces only 2% of the world's research output.[13] There is therefore, urgency to develop local research capacity to inform context-specific policy decisions. Asthma is the commonest chronic disease in children globally affecting 1 in 10 children and adolescents. South Africa has the highest asthma prevalence in Africa with 1 in 5 (21%) adolescents exhibiting asthma symptoms.[6]

The core to asthma management includes use of chronic anti-inflammatory inhaled corticosteroids to address the inflammatory process in the airways (maintenance) and bronchodilators (relievers) for relief of the bronchospasm. Many studies have shown that asthma mortality is linked to poor use of anti-inflammatory inhaler treatment and over-reliance on short-acting β2 bronchodilator reliever therapy to treat asthma exacerbations. In many LMICs, including South Africa, the use of controller anti-inflammatory inhalers is limited, with only 40% of people with severe asthma symptoms using regular inhaled corticosteroids (ICS) for chronic asthma treatment, but with over 89% using their short-acting β2 agonists. There is a large body of evidence showing that overuse of Short acting beta-2- agonist (SABA) is linked with asthma mortality and poorer outcomes.

The combination treatment with budesonide/formoterol for the management of asthma has transformed asthma treatment in high-income countries (HIC), where it is recommended in the very first step of asthma treatment as both an anti-inflammatory and reliever therapy. With the "as needed" use of budesonide/formoterol, asthmatics benefit from the additional dose of a maintenance anti-inflammatory dose, which improves symptom control and reduces exacerbations. This approach has not been adopted in many LMICs related to issues of access and affordability of budesonide/formoterol. Therefore, people in LMICs are relegated to use of Track 2 of Global Initiative of Asthma (GINA) treatment, which still suggests the use of separate anti-inflammatory and reliever inhalers.

There is a fundamental lack of clinical trial evidence to inform clinical care or policy for people with asthma in sub-Saharan Africa and South Africa. The proposed trial will provide important new clinical trial evidence about the clinical- and cost-effectiveness of a simple, pragmatic and intuitive approach with budesonide/formoterol compared to the standard of care in South Africa, and importantly assess the cost-effectiveness of this approach in a paediatric population where there is limited data and no recommendation for this approach in children 6-11 years of age.[14]

The experimental group participants will use a single inhaled corticosteroid/fast-acting long acting β2 agonists (budesonide/formoterol) inhaler initially just 'as required' and then titrated up to 'both as required, and regularly' if they remain symptomatic or have asthma exacerbations. This single ICS/LABA inhaler approach has the potential to transform asthma care by becoming the standard of care in South Africa, the wider sub-Saharan African region and other areas of

the world where asthma management is inadequate because of the multi-faceted consequences of resource limitations.[14]

3.2 Study Rationale

Over the last two decades non-communicable diseases (NCDs) have been rising in sub-Saharan Africa, and NCDs are set to overtake communicable, maternal, neonatal, and nutritional diseases combined as the leading cause of mortality in sub-Saharan Africa by 2030.[1] Many NCDs have their roots in childhood with lifestyle changes in combination with an increasing median population age in Africa making a further dramatic rise in NCDs in Africa's near future highly likely.[2] The World Health Organization (WHO) now considers the prevention and control of NCDs as an urgent development issue and essential to the achievement of the Sustainable Development Goals (SDG) and this can only be achieved with childhood interventions.[3, 4] The 2018 WHO report on NCDs, reported 3.8 million deaths annually from non-communicable respiratory diseases (asthma and chronic obstructive pulmonary diseases), with 78% of deaths in low-income and middle-income countries (LMICs). Asthma morbidity and mortality are preventable with inhaled therapies-however, there is lack of evidence on how to deliver these in an affordable and effective way.

The WHO highlights asthma as an under-appreciated cause of poverty in LMICs that retards economic and social development, erodes the health and well-being of those affected and has a negative impact on families and societies. Asthma aggravates poverty and poverty aggravates asthma.[5] Children miss out on education, adults lose days at work and the costs of drugs, emergency visits, and hospitalisation are major financial burdens, not only for individuals/families but also for struggling health systems. Of particular concern, is that asthma prevalence and burden is increasing across Africa as a consequence of urbanisation and westernisation. In Africa in 1990, about 11.7% (74 million including 34.1 million children) of the population had asthma; by 2010 this had increased to 12.8% (119 million including 49.7 million children).[1]

The WHO recognises that in Africa, asthma is underdiagnosed and undertreated and consequently the burden of severe asthma symptoms and mortality rates are disproportionately high.[11] In South Africa, half of all children with asthma symptoms have severe asthma symptoms with less than half of these using anti-inflammatory inhalers i.e. ICS for asthma management. Safe, effective inhaled asthma treatments were developed over half a century ago but a large proportion of children and adolescents with asthma in LMICs have yet to benefit, leading to ongoing avoidable morbidity and mortality. An important principle of asthma treatment is the step-wise approach whereby treatment is stepped up and down in response to asthma control and exacerbation risk. Current South African national asthma treatment approaches start with reliever medication (*e.g.* inhaled salbutamol) used 'as required' at the lowest step with the addition of regular preventer medication *(e.g.* ICS) and other therapies including long-acting β2 agonists (LABA) at higher steps or leukotriene receptor antagonists in children.[14] However, treatment can become complex especially when several inhalers are used which can affect

adherence, with over-use of SABAs being identified as a key barrier to achieving asthma control.[15]

Over the last decade a considerable body of clinical trial and clinical practice evidence has emerged supporting the efficacy and safety of combination inhalers containing an ICS and a rapid-onset LABA for maintenance and reliever therapy known as single maintenance and reliever therapy (SMART).[9, 10, 11, 12] In addition, the SYGMA 1 trial demonstrated that the use of 'as required' budesonide/formoterol compared with regular budesonide in patients aged ≥12 years, was non-inferior for asthma exacerbation prevention in patients with mild asthma.[9] The SYGMA 2 trial[10] and the more real-life pragmatic Novel START and PRACTICAL[15, 16] trials have provided further compelling evidence for the anti-inflammatory reliever approach and consequently, single ICS/LABA therapy from the outset of treatment initiation is now being used in HICs from the first step in asthma treatment. Although GINA recommends the use of this approach in adolescents, this is based on very small contributions of adolescents to the overall study populations.[14]

The proposed trial will evaluate, for the first time, a highly pragmatic approach to asthma treatment in a South African setting and in younger children 6-11 years, building on the findings of SYGMA[9, 10], Novel START[15], PRACTICAL[16], and several trials of SMART.[9, 10, 15, 16] Use of a single ICS/LABA inhaler in the way we propose, has the potential to improve compliance, reduce exacerbations, reduce the cost of long-term treatment and improve the quality of life for children and adolescents with asthma in South Africa, that can potentially be generalised to other low-resourced settings at a primary care level.

Relevant systematic reviews and the need for this trial in light of these

The fundamental lack of clinical trials of asthma treatments in the paediatric age group, mean there is also a lack of relevant systematic reviews of clinical trials evidence. Although also limited, we have a better understanding of the epidemiology of asthma in sub-Saharan Africa and this has been subject to systematic review: a 2013 systematic review of the prevalence of asthma in Africa concluded there were few studies and indications that asthma was both under-reported and increasing in prevalence.[1] In marked contrast, there is a substantial body of clinical trials evidence relating to asthma treatments in high-resource settings including multiple trials of maintenance and reliever therapy (MART) as summarised above. The most recent systematic review and meta-analysis of MART identified 16 randomised clinical trials involving 22,748 participants and found that MART, compared with the same dose of ICS and LABA as maintenance treatment, was associated with a reduced risk of asthma exacerbations (RR 0.68; 95% CI, 0.58 to 0.80).[8] Whilst it seems likely that such clinical benefits would be seen if MART was available in South Africa at the primary care level, the lack of clinical trial evidence relating to the clinical- and cost-effectiveness of MART is a major road block to informing clinical care and policy- and decision-making in South Africa and this means that adolescents with asthma do not benefit from this approach and it's not included in the South African Paediatric and

Adolescent guidelines.[17] Secondly, the lack of data of the use of this approach means that budesonide/formoterol is only recommended for children with moderate-severe asthma only from GINA Step 3, based on the lack of evidence of this approach in children 6-11 years of age.

The proposed AIR-South Africa-001 trial, offers the opportunity to change this situation and evaluate the MART approach in a highly pragmatic way with clear pathways to delivering a step-change in access to quality assured asthma treatments for the poorest in the South African population who may have the least access to regular asthma care. The setting where the study is conducted lends itself to the practicality of this approach to individuals in a primary care setting in a rural population.

High-quality clinical trial evidence of the health and economic impacts seen when children and adolescents with asthma adopt the proposed single inhaler-based approach to asthma management is needed to inform policy- and decision-making across health, commercial, development and community sectors at international, regional and local levels. The results of this trial will benefit international (*e.g.* WHO) policy- and decision-makers by contributing new evidence about the health and economic impacts of this approach to asthma management of broadly generalizable relevance. It will be relevant to Ministers of Health (MoH) in South Africa and other LMICs, and will have new effectiveness, economic data to guide decisions about funding asthma management programmes for improving lung health.

3.3 Investigational Medicinal Product

3.3.1 Budesonide/ Formoterol

The Investigational Medicinal Product (IMP) consists of a combination of Budesonide (corticosteroid) and Formoterol Furamate (fast-acting β2 agonist) dihydrate. The IMP is currently available and registered in dry powder form turbuhaler (Symbicort ®) and a pressurised metered dose inhaler (Vannair®).

The recommended doses are pMDI/DPI 80/4.5 1-2 puffs twice daily OR 1 puff as needed (a maximum daily dose of 8 puffs) for children 6-11 years of age and 160/4.5 1-2 inhalations twice daily or 1 puff as needed (a maximum daily dose of 12 puffs) for adolescents 12-18 years

Budesonide is a mixture of two isomers: Pregna-1,4-diene-3,20-dione,16,17-butylidenebis(oxy)-11,21-dihydroxy-,[11β,16α(R)] and Pregna-1,4-diene-3,20-dione,16,17-butylidenebis(oxy)-11,21-dihydroxy-,[11β,16α(S)]. Budesonide is a glucocorticosteroid and consists of a 1:1 mixture of two epimers, 22R and 22S. It is a white to off-white crystalline powder and is freely soluble in chloroform, sparingly soluble in ethanol, practically insoluble in water and in heptane. Budesonide melts at 224°C to 231.5°C, with decomposition. Budesonide is an agonist of glucocorticoid receptors. Among its effects are, it controls a) the rate of protein synthesis, b) depresses the migration of polymorphonuclear leukocytes and fibroblasts, c) reverses capillary permeability and d) stabilizes the lysosomes at the cellular

level to prevent or control inflammation. It has a potent glucocorticoid activity and weak mineralocorticoid activity.

Formoterol is a relatively selective long-acting agonist of $beta_2$-adrenergic receptors, although it does carry some degree of activity at $beta_1$ and $beta_3$ receptors. $Beta_2$ receptors are found predominantly in bronchial smooth muscle (with a relatively minor amount found in cardiac tissue) whereas $beta_1$ receptors are the predominant adrenergic receptors found in the heart - for this reason, selectivity for $beta_2$ receptors is desirable in the treatment of pulmonary diseases such as chronic obstructive pulmonary disease (COPD) and asthma. Formoterol has demonstrated an approximately 200-fold greater activity at $beta_2$ receptors over $beta_1$ receptors. On a molecular level, activation of beta receptors by agonists like formoterol stimulates intracellular adenylyl cyclase, an enzyme responsible for the conversion of ATP to cyclic AMP (cAMP). The increased levels of cAMP in bronchial smooth muscle tissue result in the relaxation of these muscles and subsequent dilation of the airways, as well as inhibition of the release of hypersensitivity mediators (e.g. histamine, leukotrienes) from culprit cells, especially mast cells.

3.3.2 Summary of Preclinical studies

3.3.2.1 General toxicity

In animal reproduction studies, budesonide/formoterol (Symbicort®), administered by the inhalation route, was teratogenic, embryocidal, and reduced fetal weights in rats at less than the maximum recommended human daily inhalation dose (MRHDID) on a mcg/m^2 basis.[18]

Budesonide alone, administered by the subcutaneous route, was teratogenic, embryocidal, and reduced fetal weights in rats and rabbits at less than the MRHDID, but these effects were not seen in rats that received inhaled doses up to 4 times the MRHDID. Studies of pregnant women have not shown that inhaled budesonide alone increases the risk of abnormalities when administered during pregnancy. Experience with oral corticosteroids suggests that rodents are more prone to teratogenic effects from corticosteroid exposure than humans.[18]

Formoterol fumarate alone, administered by the oral route, was teratogenic in rats and rabbits at 1600 and 65,000 times the MRHDID, respectively. Formoterol fumarate was also embryocidal, increased pup loss at birth and during lactation, and decreased pup weight in rats at 110 times the MRHDID. These adverse effects generally occurred at large multiples of the MRHDID when formoterol fumarate was administered by the oral route to achieve high systemic exposures. No teratogenic, embryocidal, or developmental effects were seen in rats that received inhalation doses up to 375 times the MRHDID.[18, 19]

3.3.2.2 Carcinogenesis

No reported carcinogenesis has been found with exposure to budesonide/formoterol.[19, 20]

3.3.2.3 Mutagenesis

Formoterol

In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6-18, subcapsular cysts on the liver were observed in the fetuses at a dose 65,000 times the MRHDID (on a mcg/m^2 basis with a maternal oral dose of 60,000 mcg/kg/day). No teratogenic effects were observed at doses up to 3800 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 3500 mcg/kg/day).[18, 19]

3.3.2.4 Fertility

Budesonide

In a fertility and reproduction study, male rats were subcutaneously dosed for 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were dosed up until weaning of their offspring. Budesonide caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at doses less than the MRHDID (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and above). No such effects were noted at a dose less than the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 5 mcg/kg/day).[19]

Formoterol

In a fertility and reproduction study, male rats were orally dosed for 9 weeks and females for 2 weeks prior to pairing and throughout the mating period. Females were either dosed up to gestation day 19 or up until weaning of their offspring. Males were dosed up to 25 weeks. Umbilical hernia was observed in rat fetuses at oral doses 1600 times and greater than the MRHDID (on a mcg/m^2 basis at maternal oral doses of 3000 mcg/kg/day and higher).[19] Brachygnathia was observed in rat fetuses at a dose 8000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 15,000 mcg/kg/day). Pregnancy was prolonged at a dose 8000 times the MRHDID (on a mcg/m^2 basis at a maternal oral dose of 15,000 mcg/kg/day). Fetal and pup deaths occurred at doses approximately 1600 times the MRHDID and higher (on a mcg/m^2 basis at oral doses of 3000 mcg/kg/day and higher) during gestation.[19]

3.3.2.5 Development

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-16, budesonide/formoterol produced umbilical hernia in fetuses at doses less than the MRHDID (on a mcg/m^2 basis at maternal inhaled doses of 12/0.66 mcg/kg/day and above). Fetal weights were reduced at approximately 5 and 3 times the MRHDID, respectively (on an AUC basis at a maternal inhaled dose of 80/4.4 mcg/kg (budesonide/formoterol)). No teratogenic or embryocidal effects were detected at doses less than the MRHDID (on a mcg/m2 basis at a maternal inhaled dose of 2.5/0.14 mcg/kg/day).[19]

Budesonide

In an embryo-fetal development study in pregnant rabbits dosed during the period of

organogenesis from gestation days 6-18, budesonide produced fetal loss, decreased fetal weight, and skeletal abnormalities at doses less than the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 25 mcg/kg/day). In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-15, budesonide produced similar adverse fetal effects at doses approximately 8 times the MRHDID (on a mcg/m^2 basis at a maternal subcutaneous dose of 500 mcg/kg/day).[18, 19] In another embryo-fetal development study in pregnant rats, no teratogenic or embryocidal effects were seen at doses up to 4 times the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 250 mcg/kg/day). In a peri-and post-natal development study, rats dosed from gestation day 15 to postpartum day 21, budesonide had no effects on delivery, but did influence growth and development of offspring. Offspring survival was reduced, and surviving offspring had decreased mean body weights at birth and during lactation at doses less than the MRHDID and higher (on a mcg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.[18, 19]

Formoterol
In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation days 6-15, no teratogenic, embryocidal or developmental effects were seen at doses up to 375 times the MRHDID (on a mcg/m² basis with maternal inhalation doses up to 690 mcg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation days 6-18, subcapsular cysts on the liver were observed in the fetuses at a dose 65,000 times the MRHDID (on a mcg/m^2 basis with a maternal oral dose of 60,000 mcg/kg/day). No teratogenic effects were observed at doses up to 3800 times the MRHDID (on a mcg/m² basis at maternal oral doses up to 3500 mcg/kg/day).[18, 19]

In a pre- and post-natal development study, pregnant female rats received formoterol at oral doses of 0, 210, 840, and 3400 mcg/kg/day from gestation day 6 through the lactation period. Pup survival was decreased from birth to postpartum day 26 at doses 110 times the MRHDID and higher (on a mcg/m^2 basis at maternal oral doses of 210 mcg/kg/day and higher), although there was no evidence of a dose- response relationship. There were no treatment-related effects on the physical, functional, and behavioral development of rat pups.[19]

3.4 Summary of clinical studies

3.4.1 Pharmacokinetic properties

Absorption
The fixed-dose combination of budesonide and formoterol and the corresponding monoproducts have been shown to be bioequivalent with regard to systemic exposure of budesonide and formoterol, respectively. In spite of this, a small increase in cortisol suppression was seen after administration of the fixed-dose combination compared with the monoproducts. The difference is considered not to have an impact on clinical safety.

There was no evidence of pharmacokinetic interactions between budesonide and formoterol.[20]

Pharmacokinetic parameters for the respective substances were comparable after the administration of budesonide and formoterol as monoproducts or as the fixed-dose combination. For budesonide, AUC was slightly higher, rate of absorption more rapid and maximal plasma concentration higher after administration of the fixed combination. For formoterol, maximal plasma concentration was similar after administration of the fixed combination.[20]

Inhaled budesonide is rapidly absorbed and the maximum plasma concentration is reached within 30 minutes after inhalation. In studies, mean lung deposition of budesonide after inhalation via the powder inhaler ranged from 32% to 44% of the delivered dose. The systemic bioavailability is approximately 49% of the delivered dose. In children 6-16 years of age the lung deposition falls in the same range as in adults for the same given dose. The resulting plasma concentrations were not determined.[20]

Inhaled formoterol is rapidly absorbed and the maximum plasma concentration is reached within 10 minutes after inhalation. In studies the mean lung deposition of formoterol after inhalation via the powder inhaler ranged from 28% to 49% of the delivered dose. The systemic bioavailability is about 61% of the delivered dose.[20]

Distribution and biotransformation
Plasma protein binding is approximately 50% for formoterol and 90% for budesonide. Volume of distribution is about 4 l/kg for formoterol and 3 l/kg for budesonide. Formoterol is inactivated via conjugation reactions (active O-demethylated and deformylated metabolites are formed, but they are seen mainly as inactivated conjugates). Budesonide undergoes an extensive degree (approximately 90%) of biotransformation on first passage through the liver to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6-beta-hydroxy-budesonide and 16-alfa-hydroxy-prednisolone, is less than 1% of that of budesonide. There are no indications of any metabolic interactions or any displacement reactions between formoterol and budesonide.[20]

Elimination
The major part of a dose of formoterol is transformed by liver metabolism followed by renal elimination. After inhalation, 8% to 13% of the delivered dose of formoterol is excreted unmetabolised in the urine. Formoterol has a high systemic clearance (approximately 1.4 l/min) and the terminal elimination half-life averages 17 hours.[20]

Budesonide is eliminated via metabolism mainly catalysed by the enzyme Cytochrome P450 3A5 (CYP3A4). The metabolites of budesonide are eliminated in urine as such or in conjugated form. Only negligible amounts of unchanged budesonide have been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 l/min) and the plasma

elimination half-life after intravenous dosing averages 4 hours.[20]

The pharmacokinetics of budesonide or formoterol in children and patients with renal failure are unknown. The exposure of budesonide and formoterol may be increased in patients with liver disease.[20]

Linearity/Non-linearity
Systemic exposure for both budesonide and formoterol correlates in a linear fashion to administered dose.[20]

3.4.2 Safety

As the study drug contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side effects of β_2 agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment.[20]

Adverse reactions, which have been associated with budesonide or formoterol, are given below, listed by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000) and very rare (<1/10 000). The most common side effects include oral candidiasis, headache and tremor, palpitations, mild irritation in the throat, coughing, dysphonia including hoarseness. Rinsing of the mouth after use minimises risk of candidiasis and dysphonia.[20]

Table 2: Side effects of budesonide-formoterol(20)

System	**Frequency**	**Adverse Drug Reaction**
Infections and infestations	Common	Candida infections in the oropharynx, Pneumonia in COPD patients)
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g. exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Endocrine disorders	Very rare	Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Aggression, psychomotor hyperactivity, anxiety, sleep disorders

	Very rare	Depression, behavioural changes (predominantly in children)
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Eye disorders	Uncommon	Vision blurred
	Very rare	Cataract and glaucoma
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris. Prolongation of corrected QT (QTc) interval
Vascular disorders	Very rare	Variations in blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, dysphonia including hoarseness
	Rare	Bronchospasm
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps

Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity.[20]

Treatment with β_2 agonists may result in an increase in blood levels of insulin, free fatty acids, glycerol and ketone bodies.[20]

In paediatric participants budesonide-formoterol can affect growth and this will be monitored throughout the study.

3.4.3 Special populations

Budesonide-formoterol should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic sub valvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure. Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.[20]

Potentially serious hypokalaemia may result from high doses of β2 adrenoceptor agonists. Concomitant treatment of β2 adrenoceptor agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g., xanthine derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the β2 adrenoceptor agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances.
As for all β2 adrenoceptor agonists, additional blood glucose controls should be considered in diabetic patients.[20]

The need for, and dose of inhaled corticosteroids should be re-evaluated in patients with active or quiescent pulmonary tuberculosis, fungal and viral infections in the airways.

Pregnancy
For budesonide-formoterol or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-fetal development study in the rat, showed no evidence of any additional effect from the combination. There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels. Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide.[20] In animal studies glucocorticosteroids have been shown to induce malformations. This is not likely to be relevant for humans given recommended doses. Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.[20]

During pregnancy, budesonide-formoterol should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma

control should be used.[20]

Breast-feeding
Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of budesonide-formoterol to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.[20]

3.4.4 Drug to drug interactions

Potent inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible.[20]

The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose of 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only three-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose inhaled budesonide indicates that marked increases in plasma levels (on average four-fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 µg).[20]

3.4.5 Summary of potential risks and benefits

In a Phase 3 efficacy and safety study comparing budesonide-formoterol 160/9 pMDI vs. 160/4.5 pMDI vs. budesonide 160mcg pMDI in 279 children, budesonide-formoterol 160/9 but not 160/4.5 resulted in increased baseline FEV_1 changes compared to budesonide in children 6-12 year of age, p=0.015. Incidence of protocol-defined asthma exacerbations and improvements in asthma symptom-related and quality-of-life outcomes were similar across treatments. There were no notable safety differences among treatments.[21] In a safety, 12-week multi-centre randomised controlled trial comparing budesonide-formoterol pMDI and DPI compared to budesonide in 622 children 6-11 years of age, the pMDI showed equivalence to the DPI with regards to change in Peak Expiratory Flow Rates (PEFR) in both groups 29.5 vs 30.2 l/min, 95%CI 6:0 to 4:6; p=0:78.[22]

In a paediatric randomised controlled trial of 341 children aged 4-11 years, budesonide-formoterol reduced the number of exacerbations by 70-79% compared to high dose budesonide and also increased the time to first exacerbation, p=0.02. There was also improved quality of life with reduced night-time awakenings and increased growth in the

budesonide-formoterol group.[23] In a randomised controlled study by Pohunek *et al*, in 630 children, aged 4-11 years with asthma in a head-to-head study comparing; budesonide-formoterol 80/4.5 vs. budesonide 100 vs. budesonide 100 and formoterol 4.5 (separate inhalers); budesonide/formoterol significantly improved morning PEFR, evening PEFR and FEV_1 compared with budesonide (all $p < 0.001$); there was no significant difference between budesonide/formoterol and budesonide + formoterol in separate inhalers for these variables.[24]

With regards to cost-effectiveness, a recent study by Buendia *et a*l., comparing budesonide-formoterol SMART vs. budesonide-formoterol fixed dose combination and budesonide found mean QALY per patient was 0.57 and 0.56 QALYs per patient per year of SMART and fixed combination and 0.52 with fixed-dose budesonide.[24, 25] The total mean of discounted costs per patient per cycle were US$111 for SMART, US$133 for fixed combination, and US$67 for fixed-dose budesonide. The net monetary benefit of SMART was US$12,549, US$12278 for fixed combination, and US$11,380 for fixed-dose budesonide.[25]

Based on the above clinical trial data in young children 6-12 years of age and adult trial data which included adolescents 12-18 years in SYGMA, NOVEL START and PRACTICAL trials[9, 10, 15, 16,] the evidence of benefit for use of budesonide-formoterol to improve lung function, reduce the number of exacerbations and improve quality of life of asthmatic children and adolescents indicate the benefit that potential trial participants would gain from the use of budesonide-formoterol compared to the current standard of care.

To reduce the risk of complications and drug-to-drug interactions all volunteers with co- morbid conditions that will increase risk of side-effects from the IMP in a clinically significant way will be excluded from the study. All study participants will benefit from training on how to use the asthma devices i.e. pMDI and DPI and to rinse their mouths after medication use to minimise the most common side-effect of the IMP and standard of care inhaled corticosteroids, which is oral candidiasis. Appropriate inhaler technique and use of spacer devices in those on pMDI will also minimise the risk to study participants in both study arms for this most common side-effect.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, may cause a reduction in growth velocity in paediatric patients. This effect has been observed in the absence of laboratory evidence of HPA-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in paediatric patients than some commonly used tests of HPA-axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for “catch-up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5 to 12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1 centimetre reduction in growth compared with those

receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of 4 years, children treated with budesonide DPI and children treated with placebo had similar growth velocities.[26] Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of paediatric patients receiving orally inhaled corticosteroids, including Symbicort, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including Symbicort, each patient should be titrated to the lowest strength that effectively controls his/her asthma.

4 Objectives and Endpoints

4.1 Primary objective

The primary objective is to assess the efficacy of a combination corticosteroid/rapid- onset long-acting ß2 agonist (ICS/LABA) budesonide/formoterol inhaler ‘as required’ or, if clinically indicated, ‘both as required, and regularly’ to reduce asthma exacerbations compared to the standard of care for asthma.

4.2 Secondary objectives

The secondary objectives are:

a) To assess the cost-effectiveness of budesonide/formoterol compared to the standard of care from the individual, household, health system level and quality of life.
b) To assess the quality of life of children and adolescents on budesonide/formoterol compared to standard of care.

4.3 Primary Endpoint

The primary endpoint will be the number of severe asthma exacerbations in the treatment year, defined as “events requiring systemic corticosteroids for three or more days and/or a hospitalisation/emergency room visit for asthma requiring systemic corticosteroids”[27]. (ATS/ERS criteria for definition of asthma exacerbation for clinical trials). All participants will be given diaries to record any asthma related episodes as they occur. As an additional step to ensure that we capture all the primary endpoint data, as part of our data capturing all participants will receive SMS messages soliciting information about any exacerbations every month. A “yes” response to the SMS will trigger a call from the study team to capture the outcome data from the participants and capture any adverse events. A free call-me back system has also been developed where

participants can send a message should they experience an exacerbation.

4.4 Secondary Endpoints

Clinical Endpoints

The following clinical end points will be collected during visits 1, 2, 3, 4 and 5: any presence of asthma exacerbations, medication changes since the last visit, days lost from school for participants or work for parent(s) or legal guardians. Any presence of any adverse or serious adverse events will be reported.

For visits 1, 3 and 5 outcome data to be collected will include the growth parameters i.e. weight and height. For the asthma outcomes: Asthma Control Test (>12 years) or child Asthma Control Test (6-11 years), peak expiratory flow measurements (PEFR) with electronic peak flow meter (Microlife AG Asthma Analyser Version 3.2.6) and the Paediatric Asthma Quality of Life Questionnaires (PAQLQ) to assess quality of life (QoL) will be completed at these scheduled visits.

For the health economic endpoints in a sub-set of 200 participants i.e. 100 in each study arm, additional health economics questionnaire to capture data on time-to-first exacerbation, household labour absences, out-of-pocket expenditures, loss of household productivity time and income (productivity losses), borrowing, and education losses. Secondly, participants will complete the EQ-5D-Y to capture health-related quality of life using validated generic preference-based measures of health. We will use the EQ-5D-Y (and proxy) tool to collect the health profiles of respondents in our study sample. We will then use value sets pre-produced using standard preference (utility) elicitation methods. Each health profile of participants in our sample has a corresponding value set from the tables of values in the EQ-5D-Y. These values will then be used to analyse utility preference (quality of life that are weighted with preference (utility) weights) in the sample of interest.

For the health systems costs, data collected from the facility level and pharmacist will include: health care costs related to in/out patient treatment of both the usual care and the intervention, including overhead costs at visits 1,3 and 5. These will be utilised to derive cost-savings from the intervention or standard treatment arm and to derive cost per quality-adjusted life year (QALY) gained.

4.5 Exploratory objectives

To assess the change in FEV_1 in the two study arms, pre and post study.

5 Study Design

5.1 Overall Design

This is a Phase 3 single-centre, pragmatic open-label randomised controlled trial with two equal sized groups to assess the efficacy of budesonide/formoterol 80/4.5 (6-11 years) and 160/4.5 (12-18 years) compared to the standard of care in reducing asthma exacerbations over 52 weeks compared to the standard of care. The budesonide/formoterol will be given according to the severity of asthma symptoms for all asthma severities i.e. mild, moderate or severe asthma, with those with mild asthma using the study drug as needed and those who are more symptomatic i.e. moderate or severe asthma using the study drug twice daily and as needed titrated to need. Severity assessment will be based on GINA steps of asthma severity[14].

Children and adolescents with a diagnosis of asthma will be screened for eligibility for enrolment. Those who had an asthma exacerbation in the previous year will be randomised 1:1, to either receive budesonide/formoterol inhaler for both symptom relief and for chronic anti-inflammatory maintenance therapy or the standard of care which is separate inhalers for symptom relief (short-acting bronchodilator-salbutamol) and chronic maintenance therapy with inhaled corticosteroids (anti-inflammatory beclomethasone or budesonide) and/or long-acting beta agonists or montelukast as determined by treating physicians. All asthma exacerbations and clinic/hospital admissions will be recorded for the duration of the 52-week follow-up. Participants will be followed up at 1,13, 26, 39 and 52 weeks. The 13- and 39- week visits will be telephonic visits to capture the primary end-points i.e. asthma review which will include: exacerbations, changes in medication, days lost at school or work for caregivers/guardians and serious adverse events and adverse events.

An independent Data and Safety Monitoring Board (DSMB) will be convened for this study with expertise in asthma and asthma clinical trials. The purpose of the DSMB will be to monitor the study for safety and operational futility (see section 10.1.5)

In addition to the usual regular required reporting to SAHPRA and the biomedical research ethics committee (BREC) of the University of KwaZulu-Natal (UKZN), a Trial Steering Committee (TSC) will also provide overall supervision of the trial and ensure the trial is delivered in accordance with South African Guidelines for Good Clinical Practice (SA GCP). The TMC will be established with an independent Chair and include additional independent members including an observer early career researcher, representatives of the Trial funder (NIHR) and Sponsor (AHRI) will be invited to all TMC meetings.

5.2 Investigational Product

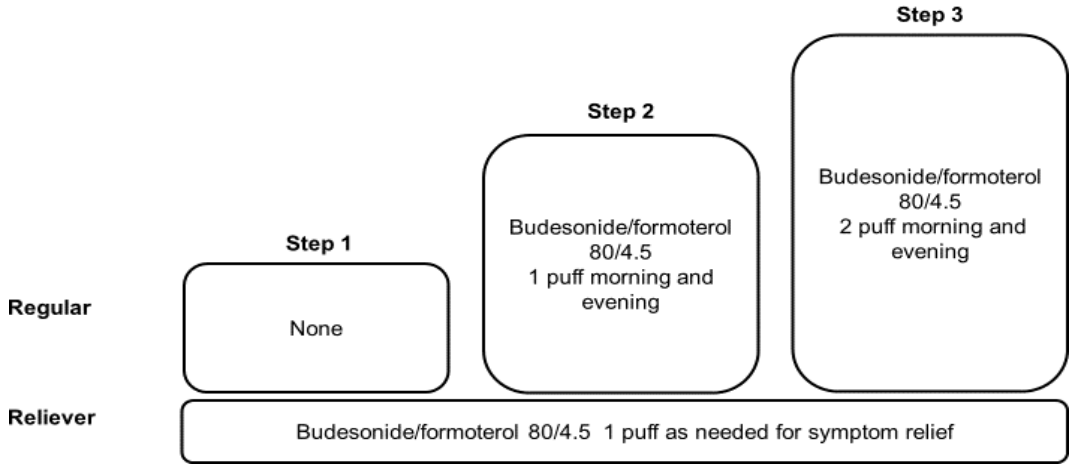
The study is an open label study with the comparator group being asthmatics on standard of care according to DOH guidelines.

Age group	**Inhaler and dose**
6-11 years	Budesonide formoterol 80/4.5 pMDI/DPI

12-18 years	Budesonide formoterol 160/4.5 DPI

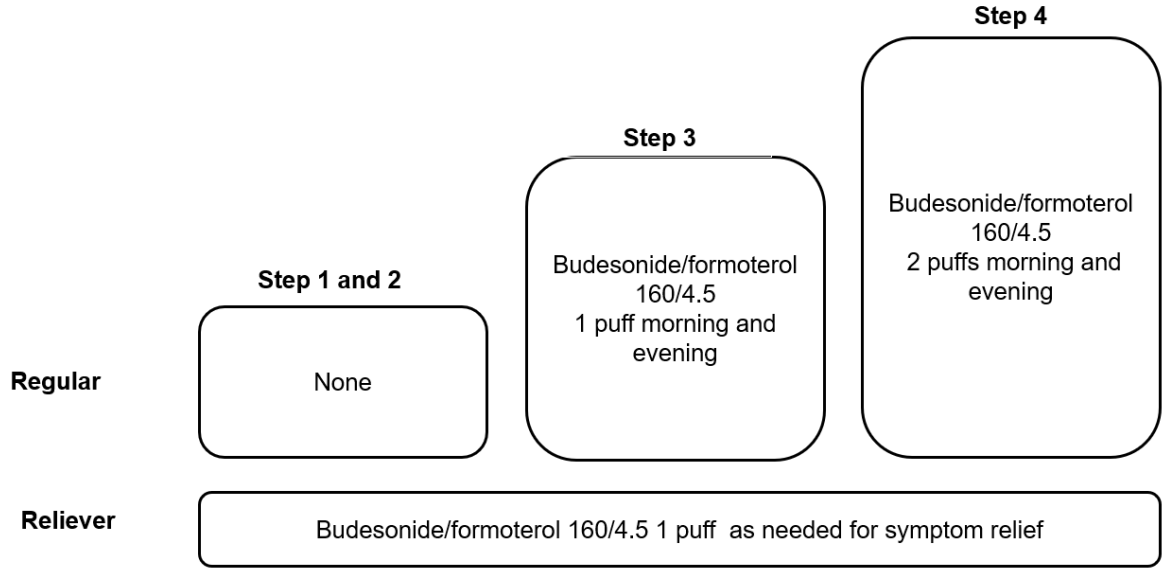
For children 6- 11 years of age, the medication will be stepped up and down depending on asthma control every 6 months as per Figure 1.

Figure 1: Protocol for treatment children 6-11 years of age



For adolescents 12-18 years, the medication dosing will be stepped up or down depending on symptom severity and asthma grading every 6 months as per Figure 2.

Figure 2: Protocol for treatment for adolescents 12-18 years of age



5.3 Comparator

Standard of care for children 6-11 years and adolescents 12-18 years. In the current Essential

Medicines List in South Africa the available drugs are as chronic anti- inflammatory agents: Budesonide or Beclomethasone, Fluticasone/Salmeterol (ICS/LABA) and Montelukast (leukotriene receptor antagonist). With the pragmatic nature of the trial, similar to the NOVEL and START trials[15, 16] , the treatment options of medications used in the comparator arm will be at the discretion of the investigator. The comparator arm will be the standard therapy the patient is receiving and stepping up/down will be as per the GINA guidelines and the treating doctor's assessment (track 2)

For the standards of care arm treatment will be stepped up or down based on GINA track 2 guidelines[14].

a) Children 6-11 years

Step 1: Inhaled corticosteroid (Beclomethasone 100mcg OR Budesonide 100mcg) 2 puffs PRN and bronchodilator (Salbutamol 100mcg) 2 puffs PRN.

Step 2: Inhaled corticosteroid (Beclomethasone 100mcg Budesonide 100mcg) 2 puffs twice daily and bronchodilator (Salbutamol 100mcg) 2 puffs PRN.

Step 3: Inhaled corticosteroid (Beclomethasone 200mcg OR Budesonide 200mcg) 2 puffs twice daily and bronchodilator (Salbutamol 100mcg) 2 puffs PRN

OR
Leukotriene receptor antagonist (montelukast) 4mg Per os daily AND Inhaled corticosteroid (Beclomethasone 100mcg OR Budesonide 100mcg) 2 puffs twice daily and bronchodilator (Salbutamol 100mcg) 2 puffs PRN.

OR
Fluticasone/Salmeterol 25/50 2 puffs twice daily

b) Adolescents 12-18 years

Step 1 and 2: Inhaled corticosteroid (Beclomethasone 200mcg OR Budesonide 200mcg) 2 puffs PRN and bronchodilator (Salbutamol 100mcg) 2 puffs PRN.

Step 3: Inhaled corticosteroid (Beclomethasone 200mcg Budesonide 200mcg) 2 puffs twice daily and bronchodilator (Salbutamol 100mcg) 2 puffs PRN OR Fluticasone/Salmeterol 25/125 2 puffs twice daily

Step 4:
Fluticasone/salmeterol 50/250 2 puffs twice daily and salbutamol 100mcg 2 puffs BD

OR

Inhaled corticosteroid (Beclomethasone 200mcg OR Budesonide 200mcg) 2 puffs twice daily and bronchodilator (Salbutamol 100mcg) 2 puffs PRN AND Leukotriene receptor antagonist (montelukast) 4mg Per os daily

Uncontrolled asthma

Before considering any step up, we will first confirm that the symptoms are due to asthma and identify and address common problems such as inhaler technique, adherence, allergen exposure, multimorbidity and provide patient education. For adolescents, the preferred Step 3 treatment is the Track 1 regimen with low-dose ICS-formoterol maintenance -and-reliver therapy (MART). This reduces the risk of severe exacerbations, with similar or better symptom control, compared with maintenance treatment using a combination of an ICS and a LABA as controller, plus as-needed SABA. If needed, the maintenance dose of ICS-formoterol can be increased to medium (step 4) by increasing the number of maintenance inhalations. MART is also a preferred option at Step 3 and 4 for children 6 – 11 years, with a lower dose ICS-formoterol inhaler. Hence, for the study participants in the intervention arm, they will benefit from use of this drug compared to the standard of care.

5.4 End of Study and Study Duration

The study duration is 52 completed weeks per study participant.

6 Study Population

Children and adolescents (6-18 years) with asthma have had ≥1 asthma exacerbation in the preceding 12 months. An exacerbation of asthma will be defined as an event requiring treatment with systemic corticosteroids for ≥3 days and/or a hospitalisation/emergency room visit for asthma requiring treatment with systemic corticosteroids. Participants will be enrolled if they have asthma of any severity i.e. mild, moderate or severe asthma.

Written consent from a parent or guardian and assent from all the study participants. A **“**Parent/Guardian/Caregiver: will be regarded as the child's primary parent/Guardian/Caregiver if they are an adult who assumes the most responsibility in caring for the health and well-being of the child by providing for their food, shelter and clothing needs. In most instances, the Parent/Guardian will be the biological mother but may be the father, other legal guardian, grandparent or a child over 18 heading a household.”

All participants who agree to comply with the study procedures, including the completion of the visits and be available for contact for telephonically for the non-contact visits.

6.1 Site and Participant Recruitment

Study participants will be recruited from a single centre the AHRI CTU with 6 satellite sites that will be located in 6 primary care clinics. AHRI CTU also has a group of general practitioners who practice in the study area, who will be contacted about the study protocol for the referral of potential study participants to the nearest clinic.

In addition, active case finding will be employed. As an additional recruitment strategy, we will select a number of primary and secondary schools in collaboration with the local school health programs, where we will screen children for asthma symptoms with an internationally recognised asthma screening questionnaire (Global Asthma Network questionnaire addendum). Participants who are screened positive for asthma will be reviewed by the trial investigators who can confirm or exclude an asthma diagnosis in the potential participants and assess them for eligibility.

We will recruit participants from the AHRI Somkhele Research Campus clinical trials unit (CTU) which is based in a poor rural community in uMkhanyakude in KwaZulu-Natal. AHRI operates a health and demographic surveillance system (HDSS)[23] as part of the South African Population Research Infrastructure Network (SAPRIN) funded by the South African Department of Science and Innovation. AHRI's HDSS follows approximately 20 000 households (140 000 household members) longitudinally, contacting them three times a year to update the status of each household member and to record any new births, in- or out-migrations, or deaths to establish and maintain a very accurate database containing every individual in the HDSS and assigns a unique Directory Services Identifier (DSID) to each person.

Historically, population-based research at the Africa Centre for Population Health centred on a demographic surveillance system referred to as the Africa Centre Demographic Information System (ACDIS). ACDIS was established in 2000 to describe the demographic, social and health impact of the HIV epidemic in a population going through the health transition, and to monitor the impact of intervention strategies on the epidemic. The Africa Centre Demographic Surveillance Area (DSA) is situated in the Mtubatuba local municipality in the uMkhanyakude district of KwaZulu-Natal and within the Hlabisa health sub-district. The area is 438km^2 in size and in mid-2015 there were approximately 90 000 (61 000 resident) household members of 11 000 households in this area. Three primary subjects are observed longitudinally in ACDIS: physical structures (e.g. homesteads, clinics and schools), households and individuals.

Since 1 October 2016 the DSA has been expanded, and a new structure referred to as the population intervention platform (PIP) has been established. PIP is a population-based platform for epidemiology and intervention research focused primarily on human immunodeficiency virus (HIV) and tuberculosis (TB). The HDSS incorporates a rural area of approximately 845 km^2 with a mid-year population of 151 441 in 2015. The platform builds on the health and demographic surveillance system established in 2000 in this area. The purposes of this longitudinal platform are firstly to obtain accurate measures of population dynamics, disease burden, and utilisation of health and other services; secondly to measure clinical phenotypes and manifestations of ill health; and thirdly to provide a framework for the implementation and evaluation of individual

and population level interventions. The HDSS is served by 11 primary health clinics and one hospital.

Written consent is obtained from all households to contact them both in person and telephonically to recruit household members into research studies conducted by AHRI. Two of the three households contacts are done telephonically using a modern call centre technology, this facility is available to all studies at AHRI to follow-up study participants where physical visits are not required. The homesteads where households are resident are all accurately geo-coded to allow easy navigation to selected households when physical contact is required.

We intend to enrol participants from the AHRI CTU and at the following 6 Satellite Sites to ensure we reach the required sample size for the study:

a) Hluhluwe Clinic
b) Somkhele Clinic
c) KwaMsane Clinic
d) Mpukunyoni Clinic
e) Mtubatuba Clinic
f) Nkundusi Clinic

The study will be enrolling children from 6 to 18 years therefore, most of the children are still at school. The pre- screening of potential participants be conducted in schools and qualifying participants will be referred to the enrolling clinic. On assessment by the investigator the diagnosis of asthma will be confirmed from the medical history with performance spirometry with bronchodilator reversibility testing and/or 2-week diurnal variation on peak flow measurements to confirm the diagnosis of asthma. Based on previous evidence, only 40% of children with an asthma diagnosis will have bronchodilator reversibility, a lack of bronchodilator reversibility will not be an exclusion criterion as almost 60% of children with asthma lack objective evidence of bronchodilator reversibility as per ERS asthma diagnosis guideline 2022. Below are the schools where the pre-screening for the potential participants will take place:

Table 2. List of schools and linked clinics for pre-screening

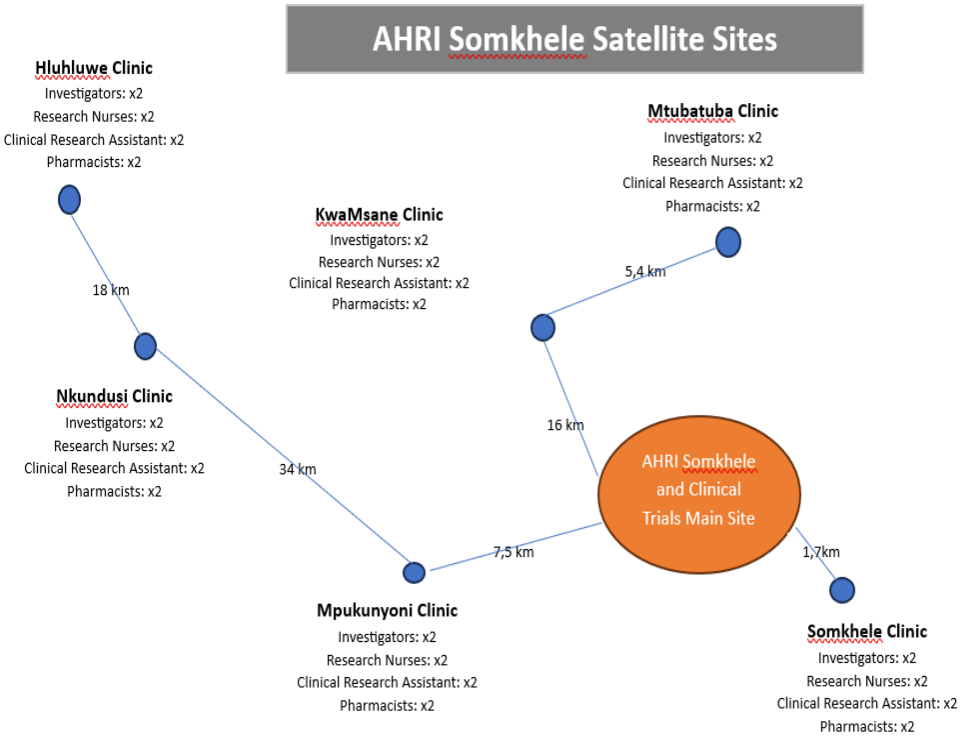
KwaMsane Clinic	***Somkhele Clinic***	***Mpukunyoni clinic***	***Nkundusi clinic***	***Hluhluwe clinic***	***Mtubatuba clinic***
Mnotho Primary School	Nomathiya High School	Mpukunyoni Primary School	Chwebebeni Primary School	Isihosabadletshe High School	Mtubatuba Primary School
Nqiwaneni Primary School	Mgwazeni High School	Veyane Primary School	Mfekayi High School	Duma Primary School	Mfolozi Primary School
Umfolozi High School	Somkhele Primary School	Nkodibe High School	Ntulifakazi Primary School	Safari Primary School	Kingdom Christian College
Zitike Primary School	Mehlokubheka High School	Ndukebandla High School	Mchakweni High School	Bush Lands Primary School	Combined School
Nkosikayingangathi High School	Mtuba Primary School	Mandlesizwe Primary School	Mfekayi Primary School	Siyembeni Nkonyane Primary School	Mtuba Christian Academy
Hill 70 Primary School	Ntikili Primary School		Gilonki High School	Sphelele Primary School	Combined School
Ngweni Primary School	Welani Primary School			Asiphikelele Primary School	
Ikusasalethu High School	Phola Primary School				
Siyathuthuka Primary School	Umsizi wama Crestu				
Syiyaqala High School	Njojo Primary School				
Ophaphasi Primary School	Baswazini Primary School				
	Mcebo Primary School				
	Siyaphambili High School				

The study will be conducted at the AHRI CTU and 6 Satellite Sites. The HDSS incorporates a rural area of approximately 845 km^2 with a mid-year population of 151 441 in 2015. The platform builds on the health and demographic surveillance system established in 2000 in this area. The number of children between 6-18 years is 31 729 in 2021. With an asthma prevalence of 13% (i.e. an estimated 4 124 asthmatics) in the population, for the study to be feasible we need to

cover a large geographic area.

The satellite sites are equipped and capacitated with appropriately trained personnel to conduct this clinical trial. The participants will be recruited and enrolled at each of the satellite site each with a full complement of trial staff i.e. trial investigators (x2), research nurses (RN) (x2), clinical research assistants (CRA) (x2), drivers, pharmacists. The satellite sites is supported by the full IT support infrastructure which is already in existence at all the 6 sites. IT provide oversight technical support to the clinic staff.
IMP will be stored at the AHRI CTU pharmacy according to GCP and GPP guidelines. IMP will be dispensed to the enrolled participant once randomisation has been done and a prescriptions has been received. IMP (prepared or unprepared) will be transported (within the recommended temperature range) to the satellite clinics. If the IMP was not prepared for the participant at the CTU pharmacy the IMP will be prepared at the satellite clinic (by the pharmacist) once a prescription is received. The IMP will be issued to the participant by the pharmacist A data team of two data managers is set up to monitor the data systems of the study.

Figure 3: Map of Satellite sites for the study



Equipment and resources

- Vehicle to transport the participants.
- Each site will have a room for screening and enrolment procedures.

- Calibrated Scales
- Calibrated blood pressure machines
- Calibrated Thermometer
- Calibrated Oximeter
- Bed for examination
- Lockable cupboards for participants' information
- Computers and tablets to capture patient information
- Access to AHRI network and data bundles for backup
- Stationery will be provided to satellite sites
- Working site files will be kept at each enrolling clinic
- Screening and enrolment logs will be kept at each enrolling clinic
- Emergency trolley with paediatric size equipment

Emergency trolley for satellite sites

- The satellite sites will all have emergency trolleys with paediatric specific resuscitation equipment provided by AHRI.
- Emergency trolley checklist will be done on weekly basis and the RNs will email the emergency trolley checklist to the SC.

Site monitoring and evaluation

Clinical Research Satellite Sites will be monitored by an internal monitoring team according to AHRI Internal Monitoring Plan and the external monitoring will be contracted to a Clinical Research Organisation. The monitoring visits will be structured according to the following types of visits that will be done in combination and varied according to the observed risks, the stage of the study and the protocol requirements.

Table 3. Site Monitoring Plan

Monitoring activity	**Frequency**	**Approach**
Investigators meeting	1	Remote
Site Evaluation visit	1	Remote
Site Initiation visit	1 (2 days)	Onsite
First 18-24 participants enrolled in the study at each site (100% Review) (~3 per satellite site)	3- 4 days	Onsite
Scheduled monitoring (10-20% Review of source -data verification, and 60-80% ICF review)	Every 8 weeks in Year 1 (while recruiting) and every 12 weeks thereafter	Remote and onsite (alternating)
Adverse event (100% Review)	Per occurrence	Remote and onsite
For-cause-visit	Per occurrence (budget 2)	Remote and onsite

- Study Coordinator (SC) will be responsible for certifying and filing of the emergency

trolley checklists while the satellite sites keep the original electronic copies.

- SC will be responsible for operational meetings for the study to give an update and the progress of the study.
- SC and the quality team will be responsible for ensuring that the study sites are prepared for monitoring visits
- PIs and SC will be responsible for providing feedback and progress report to the partners (DOH), CAB, and the sponsor.

6.2 Inclusion criteria

1) Age for inclusion children and adolescents 6-18 years at the time of consent
2) Known asthmatic on treatment
3) Newly diagnosed asthma based on investigator review and/or medical report
4) All patients will have their asthma diagnosis confirmed (both new or known asthmatic patients) by either spirometry with reversibility or excessive diurnal variability by PEFR twice daily over 2 weeks.
5)
6) Ability to perform spirometry and Peak Expiratory Flow rate and/or bronchodilator reversibility testing.
7) Only mild, or moderate asthma severity, based on medical history
8) At least one exacerbation of asthma in the past year as defined by an event requiring treatment with systemic corticosteroids for ≥3 days and/or a hospitalisation/emergency room visit for asthma requiring treatment with systemic corticosteroids.
9) Written consent from the participant or parent/guardian and assent from study participants where applicable.
10) Participant and/or parent/guardian agrees to comply with the study procedures, including the completion of the visits and be available for contact for telephonically for the non-contact visits.

6.3 Exclusion criteria

1) Tuberculosis: active TB disease and contact with people with active TB disease in the last 6 months.
2) Chronic sputum expectoration, chest pain, shortness of breath (without any asthma symptoms), dizziness, or light- headedness in the last 2 months.
3) Cardiac arrythmia
4) Chronic conditions: thyrotoxicosis, phaeochromocytoma, cardiovascular disease, severe hypertension.
5) Uncontrolled diabetes mellitus
6) Patients with Peak Expiratory Flow Rate < 50% of predicted , as these would be classified as severe asthmatics.
7) Patients with any history of life-threatening asthma, defined as any history of significant asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma related syncopal episode(s).

8) Any use of biological therapy or immunomodulatory therapy such as methotrexate or regular oral prednisolone for the asthma management (STEP 5 GINA therapy).
9) Any surgical or medical condition that would significantly alter the absorption, distribution, metabolism or excretion of the IMP which may jeopardise the safety of the participants. The investigator should make this determination in consideration of the volunteer's medical history.
10) Any physical, mental or social condition, laboratory abnormality of history of illness that in the investigator's judgement might jeopardise the safety of the participant in the context of the study, or might interfere with study procedures or the ability of the participant to adhere to and complete the study. The investigator should make this determination consideration of the volunteer's medical history.
11) Inability to present for follow up or leaving the study area within 12 months of enrolment

6.4 Justification of inclusion and exclusion criteria

The eligibility criteria were chosen to ensure that the study population selected include participants with asthma diagnosis or symptoms and no other chronic lung diseases in which asthma therapies are not recommended and may potentially be harmful.

6.5 Participant identification

All volunteers who are screened for eligibility to participate in the study will be allocated a unique sequential screening number. On enrolment the study participants will be allocated participant identifier number for the duration of the study.

6.6 Screen Failures

All participants who fail the screening process will be continued on the normal care at the clinics and hospital. Those who may be symptomatic identified at the schools will be referred to the local clinic or hospital for management of asthma symptoms and follow-up care.

6.7 Co-enrolment

Participants will be considered for enrolment in this study if they are involved in other research studies that are observational or include behavioural interventions only. Participants who are enrolled in other clinical trials will be excluded unless prior approval is provided after review by the Principal Investigators. BCEPS and IDS are put in place to prevent co-enrolment. Participants will be required to produce their identity documents and fingerprints to verify that they are not enrolled in another clinical trial.

6.8 Endpoint Case Definitions

The primary endpoint will be the number of severe asthma exacerbations in the treatment year, defined as "events requiring systemic corticosteroids for three or more days and/or a hospitalisation/emergency room visit for asthma requiring systemic corticosteroids." based on

medical history or records. The primary end point will be assessed at every visit, for the preceding 3 months. Participants will be offered diaries at the initial visit so they can record all exacerbations. There will be a study monitor in place to review all study safety and clinical data monthly in conjunction with the PI. The DSMB board is also in place to review for any safety concerns on a 6-monthly basis. As per the SAHPRA requirements any SAE and AEs will be reported and reviewed by the PI and study monitor and should any safety concerns arise, these will be immediately reported to all ethical committees, SAHPRA and the DSMB.

6.8.1 Clinical Endpoints

a) Asthma exacerbations (visit 1-5)
b) Asthma Control Test (ACT) for ≥ 12 years and Childhood ACT (cACT) for children 6-11 years (Visit 1,3 and 5)
c) Paediatric Asthma Quality of Life Questionnaire (PAQLQ) (Visit 1, 3 and 5)
d) Peak Expiratory Flow Rate (Visit 1)
e) Spirometry (Visit 1,3 and 5)
f) School absence for participants (Visit 1-5)
g) Work absence for parents/guardians to take care of children due to asthma. (Visit 1-5)
h) Adverse events (AE) (Visit 1-5)
i) Serious Adverse Events (SAEs) (Visit 1-5)

6.8.2 Health economics Endpoints (N=200 participants).

These endpoints will be collected in a sub-set of a convenience representative sample 200 participants i.e. 100 in each study arm at study entry and exit. Questionnaires will be administered to the study participants to capture the relevant economic data including the completion of the EQ-5D-Y tool (Addendum B).

j) Quality of survival estimates: time to first exacerbation, health-related quality of life using validated generic preference-based measures of health (EQ-5D-Y), adverse effects, school, work, household labour absences. (Visit 1,3 and 5)
k) Household-level economic impact by socio-economic stratum (World Bank approach): out-of-pocket expenditures, loss of household productivity time and income (productivity losses), borrowing, and education losses. (Visit 1, 3 and 5)
l) Health system: health care costs related to in/out patient treatment of both the usual care and the intervention, including overhead costs, as well as cost savings from reduced exacerbations due to intervention and cost per quality-adjusted life year (QALY) gained. (Visit 1,3 and 5)
m) Utility preferences as derived from the EQ-5D-Y (Visit 1, 3 and 5)

7 Discontinuation/Withdrawal

A study participant may withdraw from the study at any time and for any of the following reasons:

a) At the participant's request (withdrawal of consent), irrespective of the reason for this.

b) At the request of the parent or guardian, irrespective of the reason for this.
c) At the discretion of the investigator if he/she believes that the continuation of the participant in the study will be detrimental to their well-being in any way.
d) At the discretion of the REC, SAHPRA, Funder or Medical monitor if they believe that continuation in the study would be detrimental to the participants well-being in any way.
e) Any protocol non-conformance that results in a significant risk to the participants safety.

The investigator will make every effort to determine the primary reason for the participant's withdrawal from the study and record this information in the electronic case report form (eCRF). If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data before such withdrawal of consent. For those participants who withdraw, if possible and agreed to, all the Visit 5 assessments (week 52) will be completed at the time of discontinuation. Participants who withdraw or are withdrawn will not be replaced if the participant has completed at least 6 months follow-up time in the study.

7.1 Loss to Follow-up

Participants lost to follow-up or who fail to return will be considered to be withdrawn from the study under the following scenarios:

a) Missed two consecutive study visits.
b) Study team unable to contact via three telephone calls or one home visit.

All attempts to contact the participants, parents and or guardians will be recorded in the source documents. The investigator will make every effort to determine the primary reason for the participants to be lost to follow-up and will attempt to trace the participant and will demonstrate due diligence by documenting all the steps taken to contact the participant.

8 Study assessments and procedures

No study-specific assessments will be performed, or information gathered, until the potential participant or parent/guardian has given written, informed consent for screening procedures and (if found to be eligible) for procedures and assessments to be conducted during the study period. The timing of all assessments and procedures is detailed in the Schedule of Events (Section 1).

8.1 Screening and Baseline Assessments

Screening evaluations will be completed, and the results reviewed by the investigator to confirm eligibility of participants. Screening and enrolments can be completed on the same day, unless there are further evaluations required to confirm asthma diagnosis by the investigator.

8.1.1 Demographics

Demographic and baseline characteristic data to be collected for all participants includes but not limited to: age, sex, self-reported ethnicity.

8.1.2 Relevant medical and surgical history/current medical conditions including treatment

Information related to past and current relevant medical conditions and surgical procedures will be collected, including age at diagnosis of asthma and current asthma medication. At screening a list of chronic diseases and current medications both over the counter and prescribed medication will be recorded.

No special investigations or laboratory measures will be performed as part of study procedures.

8.2 Safety Assessments

8.2.1 Physical examination

Abbreviated, symptom-directed physical examinations will be performed at screening, at the end of study (EOS) visit, and during unscheduled visits if deemed necessary by the investigator or primary health care nurse. At a minimum these examinations will include: general appearance, skin, blood pressure, chest and lungs. Significant findings present at screening will be recorded in the relevant medical history/current medical conditions section of the participant's eCRF. At follow-up visit significant findings, or worsening of pre-existing findings, detected after dosing will be recorded as AEs in the participant's eCRF.

8.2.2 Height and weight

Height in centimetres (cm) and body weight (to the nearest 0.1 kg in light indoor clothing, but without shoes) will be measured. The stadiometer available at all the clinic and hospital research sites will be used.

Body Mass Index (BMI) will be calculated using the formula: BMI = weight (kg) / height $(m)^2$.

8.2.3 Vital signs

Vital signs include body temperature, pulse rate, blood pressure assessments and SpO2. Blood pressure, pulse rate and SpO2 will be measured after the participant has been at rest for at least 5 minutes. An appropriately sized cuff will be used to ensure accurate blood pressure determination.

8.3 Efficacy Assessments

8.3.1 Patient Reported Outcomes

For each participants the following questionnaires will be completed:

a) Study designed questionnaire (All visits)
b) Paediatric asthma quality of life questionnaire (visit 1, 3 and 5)
c) EQ-5D-Y (visit 1 and 5)
d) Asthma Control Test (ACT or cACT) score (visit 1, 3 and 5)

e) Health economics questionnaire (Visit 1,3 and 5)

These questionnaires will be completed on e-source or paper-based source documents. Participants will be contacted via telephone call or text/direct messaging or web-based conference on visits 2 and 4 by the study team to confirm any AE occurrence, general well-being and record of asthma review.

9 Study treatment/Investigational products/devices

9.1 Budesonide-Formoterol

Budesonide-formoterol is a combination of a corticosteroid and a fast acting long acting β2 agonist. Budesonide is an agonist of glucocorticoid receptors. Among its effects are it controls the rate of protein synthesis, depresses the migration of polymorphonuclear leukocytes and fibroblasts, reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation and it has a potent glucocorticoid activity and weak mineralocorticoid activity. Formoterol is a relatively selective long-acting agonist of beta2-adrenergic receptors, although it does carry some degree of activity at beta1 and beta3 receptors. Beta 2 receptors are found predominantly in bronchial smooth muscle (with a relatively minor amount found in cardiac tissue) whereas beta1 receptors are the predominant adrenergic receptors found in the heart - for this reason, selectivity for beta 2 receptors is desirable in the treatment of pulmonary diseases such as asthma. Formoterol has demonstrated an approximately 200-fold greater activity at beta 2 receptors over beta1 receptors. On a molecular level, activation of beta receptors by agonists like formoterol stimulates intracellular adenylyl cyclase, an enzyme responsible for the conversion of ATP to cyclic AMP (cAMP). The increased levels of cAMP in bronchial smooth muscle tissue result in relaxation of these muscles and subsequent dilation of the airways, as well as inhibition of the release of hypersensitivity mediators (e.g. histamine, leukotrienes) from culprit cells, especially mast cells.

The IMP that will be administered in the study either in dry powder form (Symbicort ®) turbuhaler and a metered dose inhaler pMDI (Vannair®).

9.1.1 Packaging, labelling, storage and accountability

There will be adequate quantities of budesonide-formoterol (both DPI and pMDI) supplied to the study site in sufficient amounts with each participant being provided with at least a 6-month supply of medication to cover for all physical once approvals from SAHPRA and UKZN BREC have been obtained. The drug will be packed, labelled, and shipped together with the respective Certificates of Analysis containing the batch numbers. The label content will be in accordance with South African legal requirements.

The PI is responsible for ensuring that the study drug is stored in a secure location with restricted access to unauthorised personnel. Budesonide-formoterol should be stored at room

temperature. Storage conditions will be adequately monitored, and appropriate temperature logs maintained throughout the study at the trial pharmacy.

Upon receipt of the budesonide-formoterol shipment, the study pharmacist (or designee) will immediately inspect the shipment for damage, acknowledge receipt and confirm the shipment condition and content. Any damage or discrepancies from the packing list will be documented and promptly discussed with the supplier and study monitor to determine the appropriate action.

The study pharmacist (or designee) is responsible for maintaining accurate study drug accountability records. Instructions and the necessary forms for completion will be detailed in the Pharmacy Manual. Study drug accountability records will be reviewed by the study monitor during interim site visits and upon completion of the study. On study completion, copies of all study drug management records will be provided to the Sponsor. The originals must be maintained at the study site with the rest of the study records.

9.1.1.1 Cohorts

Eligible participants will be randomised 1:1 to receive either Budesonide-formoterol or Standard of Care for a total duration of 52 weeks.

9.1.1.2 Blinding

This study is an open labelled study but the PI (or designee) who will be assessing the AEs will know the treatment assignment of the participants.

9.1.1.3 Dispensing

The study drug will be dispensed by the study pharmacist and dispatched to the clinic for administration to study participants.

9.1.1.4 IMP administration

The study drug are inhalers both pMDI and DPI. All the participants will be trained on how to use the pMDI (Vannair) which will be administered together with a spacer device for participants who are unable to co-ordinate inhalation of the medication and actuation at the same time. For the participants who will be receiving Symbicort Turbuhaler, all participants will be taught how to use the DPI and technique will be confirmed with the use of a DPI training device. The technique for device use will be checked at each physical study visit to ensure correct technique. For the participants in the control arm, similar checks on correct use of inhaler devices and provision of spacer devices will be checked at all physical study visits to ensure good inhaler technique.

9.1.1.5 Treatment adherence

The trial medication adherence of participants who require chronic use of medication as well as the comparator arm will be reviewed at all study visits. With each visit, the study staff will enquire on whether use of medication is as needed and this will be recorded in the source documents.

9.1.2 Overdose

An overdose of formoterol would likely lead to effects that are typical for β_2 adrenoceptor agonists: tremor, headache, palpitations. Symptoms reported from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting. Supportive and symptomatic treatment may be indicated. A dose of 90 micrograms administered during three hours in patients with acute bronchial obstruction raised no safety concerns.

Acute overdosage with budesonide, even in excessive doses, is not expected to be a clinical problem. When used chronically in excessive doses, systemic glucocorticosteroid effects, such as hypercorticolism and adrenal suppression may appear. As per the budesonide/formoterol package insert, for adolescent a maximum of 12 doses per day and for children 6-11 year 8 doses per day. Should participants overdose, as per regulatory requirements, any adverse events will be reported to the regulator and ethics committees should adverse events occur and the study participants will have a SMART action plan with maximum daily allowable doses stated.

Treatment of overdose is supportive measures and correction of electrolyte abnormalities.

9.1.3 Returns

After completion of the study, any study drug that is remaining will be returned to the Sponsor. Empty and returned pumps will be destroyed according to Good Pharmacy Practice Guideline and destruction certificate will be filed.

9.1.4 Concomitant treatments

Participants will be asked about any concomitant medication at the screening evaluation. At each contact visit i.e. telephonic and physical visits the investigator will question the participants on any medication takes (including over-the-counter) or prescription medication, vitamins or other supplements they may be taking. Participants will be assessed and depending on whether the over-the-counter drug causes drug-to-drug interactions with any of the drugs mentioned in section 3.4.4.

9.1.5 Post-trial access

There will be no post-trial access to the study drug for any of the participants as this is an

investigator-initiated study. Should the findings of the trial be positive for the budesonide-formoterol arm including the cost-effectiveness analysis, these findings will be shared with the Department of Health in particular the Ministry of Health Chronic Diseases Unit, as part of advocacy efforts to improve access to the budesonide-formoterol.

The PI will also ensure that should that advocacy efforts to allow for access to the treatment post -trial. The advocacy efforts nationally will include recommendation of the addition of the use of budesonide/formoterol in the South African Paediatric Guidelines for chronic asthma treatment. Global efforts will include recommendation of use of this approach through the GINA Scientific Committee and through the WHO Integrated Management of Childhood Illnesses (IMCI) Guideline Development Group.

9.2 Research Capacity Strengthening

This study will provide much needed research capacity by graduation of 3 PhD students through this clinical trial. These will be two South African PhD students (Black African) with a PhD (Health economics) and two PhD (Paediatrics).

10 Safety Considerations

10.1 Responsibilities for Ensuring the Safety of Study Participants

10.1.1 Principal investigator

The PI has a personal responsibility to closely monitor the study participants and an inherent authority to take whatever measures necessary to ensure their safety, including ensuring that procedures and expertise are available to cope with the medical emergencies during the study. The PI has the authority to terminate, suspend or require changes to a clinical study for safety concerns and may pause or delay the administration of the study drug to an individual or across the study. If the PI has concerns that the study drug may place participants at significant risk.

10.1.2 Study Sponsor

The Sponsor (AHRI) has the institutional responsibility to ensure participant safety and undertakes to promptly notify the concerned Investigator/Ethics committee and SAHPRA of findings that could adversely affect the safety of participants included in the study, impact the conduct of the study, alter the BREC's approval of, or favourable opinion to continue the study. This included the expedited reporting to these parties of all adverse events that are both serious and unexpected.

10.1.3 Study Funder

The Funder National Institute of Health and Care Research (NIHR) has a responsibility to

immediately inform the Sponsor and PI of any existing risk assessment of the study or new information that could impact adversely on the participant safety.

10.1.4 Safety Review Committee

The Medical Monitor, in consultation with the Safety Review Committee (SRC). The SRC will comprise of at least the following personnel:

a) The Principal Investigator
b) The Medical Monitor
c) The Safety Physician
d) Another medically qualified paediatrician

The timing of the SRC data review and a detailed description of the operational aspect of the SubRip Text (SRT) will be documented in the SRT Charter.

10.1.5 Data and Safety Monitoring Board

An independent DSMB will be convened for this study with expertise in asthma clinical trials. A biostatistician will also form part of the DSMB. The purpose of the DSMB is to monitor the study for safety and operational futility. The board will provide recommendations to the Sponsor regarding ongoing study conduct.

Roles and responsibilities of the DSMB

The DSMB is responsible for reviewing study documentation (e.g., study protocol, the informed consent and other participant handouts, etc.) and ensuring that it has adequate information to assess the safety of the study participants and the efficacy of the intervention during both the treatment and follow-up periods. The DSMB will review the data and safety monitoring plan, safety and operating procedures. The DSMB will meet six-monthly or earlier should recruitment targets be faster with at least one mid-study interim analysis meeting or safety concerns. The DSMB must ensure that the data and safety monitoring plan is sufficient given the complexity of the study and patient population. The Board shall have the option for expedited meetings to review unexpected SAE or other urgent issues that may arise during the course of the trial. Unscheduled meetings may be recommended and initiated by the DSMB Chairperson, the clinical trial Sponsor, or the PI. Clinical trial documentation and data will be available to the Board members at least two weeks prior to the meeting.

The DSMB will evaluate participant safety data throughout the duration of the trial; evaluate the efficacy of the study intervention(s) at intervals specified in the DSMB charter; and independently provide recommendations to the study Sponsor to either continue, amend or terminate a clinical trial based on this information. The presence of early unanticipated therapeutic results, side effects, or AE are all reasons that a DSMB might recommend termination of a clinical trial early due to safety or efficacy matters.

In addition, the DSMB is responsible for monitoring the performance of each clinical site (e.g., protocol violations, improper participant enrolment criteria, slow accrual rate, low participation rate, failure of randomisation, inadequate treatment adherence, inadequate follow-up rate, severely compromised validity). The DSMB will independently make recommendations for improving the performance of the clinical trial or terminating the trial if it determines the study would be unable to provide useful data, regardless of modifications. A summary of each board meeting and the board recommendation will be provided to the clinical trial sponsor for distribution to each participating clinical site.

In addition to meeting at pre-determined, scheduled time points, the DSMB will also be called upon to perform evaluations of relevant data should any of the study pause criteria be met at any stage, and make recommendation about study stopping or continuation, or amended circumstances under which the study may proceed.

The objectives and responsibilities of the DSMB will be detailed in the DSMB Charter which will be ratified by the DSMB members prior to the study start.

DSMB
Chair: Prof Chen-Yuan Chiang (Taiwan)

Members:
Prof Richard Van Zyl Smit (UCT-Asthma expert and Pulmonologist)
Mr Jacob Busang: Biostatistician
Prof Marielle Pijnenburg (Netherlands- Paediatric pulmonologist expert in asthma clinical trials) (TBC)
Dr Sanelisiwe Ngaka (Early career researcher and observer non-voting member)

The objectives and responsibilities of the DSMB will be detailed in the DSMB Charter which will be ratified by the DSMB members prior to the study start.

AHRI the Site, NIHR the Funder, the PI, UKZN BREC and Regulatory Authority independently reserve the right to discontinue the study at any time for safety or other reasons. This will be done in consultation with the Funder, Sponsor and PIwhere practical.

Trial Steering Committee
Chair: Prof Chakaya Muhwa (Kenya) Members
Prof Refiloe Masekela (Principal investigator) Prof Kevin Mortimer (UK)
Prof Asma El-Sony (Sudan)
Dr Rebecca Nantanda (Uganda)
Dr Reratilwe Mphahlele (Early career researcher and observer non-voting member) Lay member: Mtubatuba Community Advisory Board Member

10.2 Adverse events

10.2.1 Definitions

The following definitions are based on those described in the SAHPRA Safety Reporting Guidelines for Clinical Trials conducted in South Africa.

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical trial participant administered an investigational product that may present during treatment with that investigational product, but which does not necessarily have a causal relationship with this treatment.

A **treatment emergent adverse event (TEAE)** is any new AE that begins, or any pre- existing condition that worsens in severity, after at least one dose of study product has been administered.

An **adverse drug reaction (ADR)** is a response to a medicine in humans which is noxious and unintended,
and which occurs at any dose, and which can also result from overdose, misuse, or abuse of a medicine. “Response” in this context means that a causal relationship between a medicine and an adverse event is at least a reasonable possibility.

A **serious adverse event (SAE)** is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)

- Requires inpatient hospitalisation or prolongation of existing hospitalisation unless this is for:
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the trial and has not worsened since the start of the investigational product
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
    - An acute asthma exacerbation
    - cosmetic surgery or for social reasons or respite care in the absence of any deterioration in the participant’s general condition

- Results in persistent or significant disability/incapacity

- Results in a congenital anomaly/birth defect

- Is medically significant or important event or reaction.

An **Unexpected Adverse Drug Reaction** is one in which the nature, specificity, severity, and outcome is not consistent with the applicable product information. An expected ADR with a fatal outcome should be considered unexpected.

A **suspected unexpected serious adverse reaction (SUSAR)** is an unexpected adverse drug reaction which also meets the criteria for a serious adverse event.

10.2.2 Assessment and recording of adverse events

All AEs regardless of seriousness or relationship to the study drug are to be recorded in the eCRF. AEs can be spontaneously reported by the participant, observed by the investigator (either directly, or through an objective assessment) or elicited by general questioning. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis.

The following information will be recorded for each AE:

a) a description of the adverse event (verbatim term)
b) the dates of onset and resolution of the event (and whether the event started prior to or after start of study drug)
c) the characteristics of the event (seriousness, severity)
d) the action taken in response to the event (including treatment required)
e) the outcome of the event
f) the relationship of the event to the study drug (causality assessment).

Vital signs abnormalities will be recorded as AEs only if they are considered clinically significant, are symptomatic, require corrective treatment or fulfil a seriousness criterion. Day-to-day fluctuations in pre-existing conditions that do not represent a clinically significant change in the participant's status (including fluctuation in symptoms of asthma) will not be reported as AEs.

10.2.2.1 Reporting time period

For the purpose of this study, all non-serious AEs will be reported from the time of granting main study informed consent until the participant's EOS visit (Week 52). Events reported prior to this will be recorded as medical history unless the symptoms worsen during the follow-up period.

SAEs will be reported for the same period. SAEs occurring after the reporting period that the Investigator becomes aware of will be reported to the Sponsor within 24 hours of being aware of the event.

10.2.2.2 Severity grading

The medical assessment of AE severity will be recorded in accordance with the classification detailed in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events Version 2.1, Jul 2017.[25]

AEs not specifically referenced in the DAIDS classification will be graded in accordance with the following general guidelines detailed in the classification document:

- Grade 1: Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated
- Grade 2: Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated
- Grade 3: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalisation indicated
- Grade 4: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
- Grade 5: Death related to the AE.
-

10.2.2.3 Relationship to study drug

The investigator will assess the relationship of each event to the study drug and decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study drug. This should be documented in the participant's source documentation and eCRF.

The following may guide this assessment:

- *Related:*
  - The event has a reasonable temporal relationship to study drug administration
  - The event is more likely to be explained by the study drug than by another cause
  - This includes events considered possibly related to the study drug
- *Not related:*
  - Events not meeting the "related" criteria.

Where possible, a distinction will be made between events considered related to the study

drug and those related to study-specific procedures.

10.2.2.4 Outcome

The investigator will follow up all AEs wherever possible until they have attained an acceptable outcome.

The date of the outcome will be recorded, and the course of the AE will be assessed in accordance with the following classification:

- *Recovered/resolved*: the AE has resolved, and the participant returned to their condition prior to onset
- *Recovered/resolved with sequelae*: the AE resolved, but the participant has sequelae
- *Recovering/resolving*: the AE has almost resolved, and the participant is returning to his condition prior to onset
- *Death*: the participant died
- *Not recovered/not resolved*: the AE had not resolved, and the participant's condition remained unchanged at the last time of observation.

In case of death from a different cause, events ongoing at the time of death will be classified as such.

10.2.2.5 Action taken and follow-up of events

All adverse events will be followed up by the Investigator until:

- the event is resolved, or stable
- no further medically relevant information in relation to the event can be expected, and
- the investigator considers it justifiable to terminate the follow-up.

Events that are ongoing at the time of the participant's EOS visit should be indicated as "not recovered/not resolved" or "recovering/resolving" (whichever applicable) if considered unrelated to the study drug. AEs that are considered related to the study drug and are ongoing at the time of the participant's EOS visit will continue to be followed up by the Investigator until the event has resolved or the Investigator, Sponsor and Medical Monitor consider it justifiable to terminate the event follow-up.

All AEs should be treated appropriately. The Investigator will decide upon the appropriate action to be taken in response to an AE, which may include one or more of the following:

- no action taken (i.e., further observation only)
- administration of a concomitant medication or other treatment
- hospitalisation or prolongation of current hospitalisation (event to be reported as an SAE)
- other.

10.2.3 Reporting of serious adverse events

The investigator will report all SAEs to the Sponsor within 24 hours of the site personnel becoming aware of the event in accordance with the procedures described in the Safety Management Plan. The report should be in writing by email with the Medical Monitor on copy and documented on a standard SAE Reporting Form. In addition to this, fatal or life-threatening SAEs must be reported immediately to the Sponsor and the Medical Monitor, irrespective of the extent of available AE information.

For all SAEs, the investigator is obligated to pursue and provide information in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE case report form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a participant death, a summary of autopsy findings (if available) must be submitted as soon as possible to the Sponsor.

All SAEs will be followed-up until resolution, or until in the opinion of the PI and the Medical Monitor, no further improvement can be reasonably expected on medical grounds.

The UKZN BREC and SAHPRA will be notified of all SAEs in accordance with their requirements. Reporting and follow-up procedures are described in the Safety Management Plan (SMP).

All the research sites have an emergency trolley which is checked daily, and a log of the equipment is kept on site to ensure that all the emergency equipment and medication is available in case of an emergency.

10.2.4 Pregnancy

All women of reproductive potential will be advised on contraceptives. Should a participant become pregnant during the study (at any stage), she will be counselled regarding the use of budesonide-formoterol during pregnancy or asthma standard of care.

Pregnancies occurring in participants enrolled in this study will be reported. Follow-up will include, but is not limited to, the following:

- Ultrasound at approximately 20 weeks' gestation
- Pregnancy complications
- Outcome ascertainment
- Information related to live births
- Follow-up of infants to approximately 3 months of age.

Reporting will be performed using a standard Pregnancy Reporting Form. The reporting procedure follows that described for SAEs in Section 10.2.3.

Pregnancy alone is not regarded as an AE. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalisation for normal delivery of a healthy Newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated outcome that meets one or more of the SAE criteria. Spontaneous abortions should always be reported as SAEs.

Any pregnancy outcome considered to be an SAE should be reported within the timelines and using the procedures described in Section 10.2.3.

10.2.5 Assessment and recording of adverse events

All AEs regardless of seriousness or relationship to the study drug are to be recorded in the eCRF. AEs can be spontaneously reported by the participant, observed by the investigator (either directly or through objective assessment) or elicited by general questioning. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis.

11 Study Limitations

The study will be limited due to it not being double-blind but open label in design. The pragmatic nature of the study comparing standard of care and budesonide-formoterol necessitates this methodology, as well as being similar to other real-world studies NOVEL and START studies. The reliance on self-reporting for our outcomes and study end-points. There may also be recall bias

due to timing of the study visits. Lastly, there may be social desirability bias by study participants and parents/guardians from the self-reporting of symptoms.

12 Statistical considerations

We will enroll 1038 participants. Assuming a 10% loss to follow-up, 1142 participants will complete the trial (571 experimental, 571 control; 286 children, 286 adolescents). Sample size has been performed for the primary endpoint of severe asthma exacerbations based on the assumption that approximately 40% of participants under the standard of care will experience at least one such exacerbation in a 52-week period giving an anticipated rate of 0.7 severe exacerbations per year (conservative assumptions). The severe exacerbation rate of 0.7 in the control group was estimated based on studies with similar study populations. A recent meta-analysis reported a 36% reduction in exacerbations with ICS/LABA.[28] The sample size calculations was based on a clinically relevant 25% reduction in severe exacerbations (equivalent to average rate of 0.525 severe exacerbations/year) between the control and experimental groups. Sample size was calculated using the negative binomial distribution with the "power.nb.test" function in R, based on work by Zhu and Lakkis.[29, 30] The negative binomial allows a degree of 'over dispersion' meaning that individuals differ in their underlying propensity to (i.e. rate of) exacerbations. This over dispersion is reflected by the dispersion parameter k.[30] At 90% power, a two-sided significance level of 0.05, and assuming k =0.7, a minimum sample size of n = 519 subjects per arm. Calculations were undertaken with different estimates of k to ensure robustness (k= 0.9, 646 per arm; k = 0.5, 544 per arm) and noting that we are powered for a relatively small rate reduction, if the true dispersion is 0.9 then at n = 443 subjects per arm we will retain 85% power to detect a 25% reduction and 95% power to detect a 30% reduction in severe asthma exacerbations. A sample size of n = 387 per arm will have 80% power to detect a 25% difference in the rate of severe exacerbations between arms. For the study analysis plan the following populations are defined and will be described in greater detail in the trial Statistical Analysis Plan (SAP). An intention to treat analysis approach will be adopted to on all enrolled randomised participants. A per-protocol analysis plan will be performed for all participants who completed the study protocol procedures without any major protocol deviations. For the safety analysis, all participants who received at least one dose of the study drug will be analysed.

Based on previous GAN data of 3957 children in Durban, the asthma prevalence of adolescents age 12-14 year of age is 13.8%.[3] Based on this and from engagement with the AHRI Biostatistician, the population of uMkhanyakude, we will therefore recruit children and adolescents in AIR-South Africa from all the Somkhele Research Campus from 6 drainage clinics and the Hlabisa District Hospital which serves a community of 137 000 which has been followed up for the past 20 years as part of the Health and Demographic Survey System (HDSS) with excellent data management systems. This is a relatively stable population with low levels of migration in a rural community in uMkhanyakude. The current paediatric population of 6–18-year-olds is 31 729 children. Based on our calculations we should have a minimum of 4 128 asthmatic

children in the population, and we will be using an active recruitment strategy at schools to identify any undiagnosed children in the community. Based on this, we should be able to recruit the required sample size.

13 Ethical considerations

13.1 Regulatory and Ethical Considerations

The study will be done according to South African GCP Guidelines , the Belmont Report, the Declaration of Helsinki, and South Africa legal requirements regarding clinical trials.[31] The study protocol and relevant supporting documents will be submitted for review and approval by SAHPRA and UKZN BREC. The study protocol has been registered with the South African National Clinical Trial Registry (www.sanctr.gov.za), National Human Research Ethics Committee (www.ethicsapp.co.za) and www.ClinicalTrial.gov. Six-monthly progress reports will be submitted to SAHPRA and BREC for the duration of the study, and as requested. Upon completion or premature termination of the study, the investigator will provide BREC and SAHPRA with a summary of the study's outcome, and any reports required. Administrative approvals will also be requested from the district and provincial departments of health and education.

13.2 Informed Consent Process

The principles of informed consent in the current edition of the Declaration of Helsinki will be implemented before any protocol-specified procedures or interventions are carried out. The active case finding consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

As per the South African National Department of Health guide on "Ethics in Health Research: Principles, Processes and Structures (2015)," all participants <18 years of age will have to provide assent and consent from the parent or Parent/Guardian. In South Africa, children ≥18 years of age are able to independently consent for medical and surgical procedures. In the South African context, "Parent/Guardian" means a person who factually cares for a child (s 1 Children's Act, 38 of 2005; a Parent/Guardian is obliged (in terms of s 32(1)) to safeguard the child's health, well-being and development; and to protect the child from abuse and other harms. Further, a Parent/Guardian may exercise the parental right to consent to medical examination or treatment of the child (in terms of s 32(2)). We will adhere to the guidelines for all minors (children and adolescents) considering, amongst others, special precautions for children (including orphans) living in child headed households and children who are taken care of by a legal guardian. Furthermore, parental permission and permission from orphans without legal guardians, will be obtained according to the guidelines. We do not envisage that child headed households and orphans without legal guardians would be recruited into this study based on our previous experience conducting studies in this setting. If a child turns 18 years during the course of the study, he/she will be re-consented to obtain their permission to continue participation in

this study. According to South African law, an unmarried minor mother may not agree to the participation of her child in research without assistance. Her guardian (usually her parent) is also the guardian of her child while she is a minor and must consent to the child's participation. In other words, pregnancy and childbirth do not change the legal status of the minor mother. When the mother reaches the age of majority (18 years), she may consent to her child's participation in research. However, we do not anticipate recruiting mothers who are also minors based on previous experience in this setting.

Participants and or guardian/parent will be counselled about the available data regarding the efficacy of budesonide-formoterol in improving asthma control and preventing exacerbations but also that data is limited in children between the age of 6 and 11 years of age. Potential participants and or guardian/parent will have the opportunity to have any questions answered before and after signing the informed consent forms (ICFs). The informed consent process and all questions raised will be documented.

The study staff who conduct the informed consent process will also sign the ICFs. A copy of the consent form(s) will be given to the participant and or guardian/parent, and this fact will be documented in the participant's record.

Any participant who is rescreened should be re-consented and eligibility for the study must be re-checked prior to enrolment with regard to all other screening procedures.

13.3 Study Records and Confidentiality

The study site will establish a standard operating procedure for confidentiality protection. The site will ensure that study records including administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the study, including ICFs, locator forms, case report forms, notations of all contacts with the participant, and all other source documents are stored in a secure manner.

All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring, and auditing by the Regulatory Authority or the Institutional Review Board (IRB)/ BREC.

The PI or designee and all employees and co-workers involved with this study may not disclose or use, for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study.

- Electronic source documents will be kept in the designated secured server which is password protected.
- All computers used during the study conduct will be password-protected, and records will only be accessible to authorised study staff delegated on the delegation log.

13.4 Compensation for Injury

The Sponsor will ensure that compensation is provided for reasonable medical expenses incurred because of study-related injury, illness, or death, as determined according to the guidelines laid down by the Association of the British Pharmaceutical Industry (ABPI) compensation guidelines Version 2014, and Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.[32]

13.5 Participant Remuneration

For each day of protocol-related study procedures, the participants will receive compensation for travel costs to and from the clinic and inconvenience incurred, as per local regulating body recommendations at R400 per clinic visit for the participant and parent/guardian for any scheduled visit which is less 3 hours as per SAHPRA Guideline for clinical trial participants time, inconvenience and expense (TIE) Compensation model July 2022. Should the visits extend beyond 3 hours participants and parents/guardians will be provided with an additional R50 to cover meals.

13.6 Budget

The Research site will be funded by NIHR for the clinical trial for a total amount of ZAR 42 885519.00 for 5 years. UKZN has sub-contracted the AHRI Clinical Trials unit as Sponsor and an independent clinical trial monitor has been commissioned to assist with trial oversight. AHRI will be compensated by UKZN for all trial related renumeration including site staff, equipment, consumables and infrastructural requirements.

The PI will not receive any renumeration for the study as her salary is recycled through the grant for payment of a clinician to assist with her clinical duties and as a PhD student.

1. UKZN PhD students (100% FTE):
    a. 1 Clinical salary: for 5 years (R 1 304 023/year)
    b. 1 Health economics PhD salary for 3 years (R 1 05 000/year)
    c. 1 clinical PhD for 3 years (R 1 308 000/year)
    d. 1 Clinical PhD for 3 year (R 1 160 000/year)

2. AHRI salary: Staff costs
    a. CTU administrator (FTE 25% year 1 and 50% year 2-5): R356 168 per year
    b. Trial co-ordinator (50% FTE): R 715 000 per year

    i). Medical officers (25% FTE): R 317 311 per year (year 1-5)
    ii). Enrolled nurses (FTE 300%): R 1 7 00 234 per year (Year 1-5)
    iii). Research pharmacists (25% FTE): R 144 4500 per year (Year 1-5)
    iv). Database manager (25% FTE): R 356 168 per year
    v). Clinical research assistants (300% FTE): R 738 312 per year (Year 1-5)
    vi). Grants officer (5% FTE): R 30 607

3. Trial monitor: R1 808 860.00 monitoring professional and pass-through costs.
4. Trial insurance: R219 537.00 annual premium for 1038 participants.

The investigator-initiated research approval for funding the supply of IP and spacers has been approved by the AstraZeneca Global team, so we have secured funds for the IP.

We will randomise 519 study participants to the active arm. The study drug requested for participants is for 260 pMDI (6-11-year-old) and 260 DPI (12-18 adolescents)

a) Vannair 80/4.5 pMDI= a total of (130 X 12) 1560 of 3120
b) Vannair 160/4.5 pMDI = total of (130X 12) 1560 of 3120
c) Symbicort 160/4.5 DPI = total of (260 X 12) 3120
d) Spacers = 519.

Should there be the requirement to source additional IP, the budget would accommodate additional purchasing of IP.

13.7 Protocol Amendments

Any protocol amendments will be prepared by the Sponsor and submitted to UKZN BREC and SAHPRA in accordance with local requirements.
Approval must be obtained from the UKZN BREC and SAHPRA (as required) before the implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants, or changes that involve logistical or administrative aspects only (e.g., change in contact information).

13.8 Clinical Data Records

A log of names, signatures and initials of all staff authorised to enter data into a participant's clinic file and eCRF will be kept.

The investigator will maintain paper or electronic source documentation in a locked place and password encrypted electronic device for all study participants. Protocol-specific participant information will be captured in an eCRF. The Clinical Data Management System (CDMS) will comply with regulatory guidelines and requirements for electronic systems. Data validation and quality control procedures will be detailed in the Data Management Plan (DMP).

All deviations from this study protocol will be documented in the Trial Master File (TMF) and included in the final study report. An assessment of the significance of each protocol deviation will be presented in the clinical study report.

13.9 Record Retention

All source data and clinical records relating to the study will be archived for a minimum 15 year-

period after completion of the study in accordance with South African GCP guidelines, Sponsor and Funder requirements. Data will be available for retrospective review or audit by arrangement with the appropriate representative at the archiving organisation (e.g., Sponsor Head). Written agreement from the Funder NIHR, must precede destruction of the same.

13.10 Discontinuation of the Study

AHRI the Sponsor, NIHR the Funder, the PI, UKZN BREC and Regulatory Authority independently reserve the right to discontinue the study at any time for safety or other reasons. This will be done in consultation with the Funder, Sponsor and PI where practical. In the event of premature termination or suspension of the study, the above-mentioned parties will be notified in writing by the terminator/suspender stating the reasons for early termination or suspension (with the exception of the Sponsor's responsibility for notifying the Regulatory Authority). Following such a decision, the Sponsor and the investigator will ensure that adequate consideration is given to the protection of the participants' interest and safety. All ongoing participants will be followed up for a minimum of 28 days post initiation of the study drug and will be scheduled for an EOS visit. At this visit all assessments scheduled in accordance with the Schedule of Events will be performed.

13.11 Publication Policy

A dissemination plan will be developed with all project partners prior to study completion. After study completion, results will be disseminated using the following strategies: written methods (i.e., publications in peer reviewed scientific journals), presentations at scientific conferences and workshops, in person dissemination of results to the research participants, the ministry of health and using electronic methods such as the project website and electronic media to publish results.

13.12 Study Audits

Audits may be carried out by the Sponsor quality assurance representatives, local authorities, or authorities to whom information on this study has been submitted. All documents pertinent to this study must be made available for such inspections after adequate notice of the intention to audit is provided.

14 References

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15 APPENDICES

15.1 Appendix 1: Study screening questionnaire

Unique Study ID Number:	
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1; 21 Aug 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela, uMkhanyakude
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*

We would like to invite your child to consider taking part in a research study called "Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial".

We are currently recruiting participants for a trial involving budesonide/formoterol and regular asthma therapy. The purpose of the study is to check whether using a newer asthma pump (Budesonide/formoterol) will lead to reduced asthma attacks compared to the normally used asthma pump in South African children and adolescents and to see if this will reduce the costs of asthma care.

Would you be willing for your child to be part of the study?

Yes ☐

No ☐

If No, please sign below.

If you are willing for your child to participate, you will be asked some questions about your child for us to check if he/she would be a potential participant for the study.

If you decide for your child to take part in this study, you will be given the document about the study and be guided through the next steps. You will also be given a copy to keep and refer to.

PARENT/GUARDIAN:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

WITNESS (If applicable):

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

_____

Printed Name(s) and Surname

_____

Signature Date and Time

15.2 Appendix 3: Patient information and consent form

PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT

Each **participant** must receive, read and understand this document **before** any study-related procedure is performed

Study Uniqe ID :	
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1 21 Aug 2023;
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

To the potential participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

ICF administration starting time: _____ ICF administration finish time: _____

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*
I would like to invite you to consider having your child taking part in a research study called "Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial. "

- Before you decide if you want your child to be part of this study, we would like to give you information to help you decide if you would like to be part of the study.
- Please take the time to think through the following information and discuss it with others if you wish. Knowing what is involved will help you decide if you want your child to take part.
- If you have any questions, do not hesitate to ask me.
- You should not agree to take part unless you are happy about all the procedures involved.
- Please be open with me regarding your child's health history since you may otherwise harm your child by taking part in this study.
- If you decide for your child to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will also be given a copy to keep and refer to.
- Should you agree for your child to take part in the study we will do so without revealing his/her study identity.

What is the purpose of the study?

- The purpose of the study is to check whether using a newer asthma pump will lead to reduced asthma attacks compared to the normally used asthma pump in South African children and adolescents and to see if this will not cost a lot of money.

Why has my child been invited?

- Your child have been selected to participate in this study because he/she has asthma symptoms and have been diagnosed with asthma. We got your child's details from Somkhele Campus of the African Health Research Institute (AHRI) database which includes all people living in your area. We are planning to include 1142 participants who will be divided into 2 age groups (6 -11 years) and (12 – 18 years). Your child will either be in the group that will be taking normal asthma medication dispensed at the clinic (standard medication) or he/she will receive the study asthma pump (new medicine called Vannair or Symbicort)

Does my child have to take part?

- Taking part in this study is entirely voluntary. You do not have to have your child take part if you would not like to. If you choose to have your child take part and you change your mind later about participation in the study, you can withdraw from the study at any point, without giving a reason. Withdrawal from the study will not affect your child's clinical care at the clinic or hospital and you will not incur any penalties

What will happen to me if I decide for my child to take part?

- When you decide to have your child take part, you will be asked to sign the consent form to confirm that you have received enough information about the what the study is about and that and you are willing for him/her to take part.
- You will be asked few questions so that we get to know you and your child's background better.
- Your child will be allocated one of the groups then be given asthma pump (standard one or new one) to use for his/her asthma management.
- Once allocated, your child will stay in that group for the duration of the study.
- The number of participants in the standard asthma pump and the new asthma pump will be the same.
- Your child will be involved in this study for 12 months. During this period, he/she will have checkups every 3 months. The check-up will be either by one of the nurses/investigator at the clinic/hospital or will be done telephonically.
- The checkups are to check how he/she is feeling and whether he/she has had any asthma attacks or any undesired harmful effects from the medication or any concerns.
- Your child can go to the clinic at any point if he/she is unwell or you have any concerns, you don't have to wait for the scheduled appointments.

What should I consider?

- Your child cannot participate in the study if he/she do not have asthma or if he/she has active tuberculosis on treatment. If he/she is taking any other medication, you will be expected to let us know what these are. If he/she is taking the medicine that can interact with any medicine in the new pump, he/she will not be expected to participate in the study. If your child is involved in any other research studies, we will request that you let us know as this ma also not allow us to enroll your child in this current study without discussion with the principal investigator of that study.

Are there any possible disadvantages or risks from taking part?

- The risks expected during the study are adverse events (side-effects) from the drugs being given, otherwise the project itself is not associated with any risks.

For the new medication that we will be giving for the study.

- The medicine is already recommended for use for the moderate to severe asthma treatment for children 6 to 11 years and for mild asthma treatment in adolescents over the age of 12 years.
- There may be side effects from the drugs. The most common side effects are minor and well-described and include headache, throat irritation, nausea, vomiting, diarrhoea, blocked nose, changes in voice, oral candidiasis, nasopharyngitis and upper respiratory tract infections. These side effects especially the throat irritation, change in voice and candida can be avoided by rinsing out the mouth after using the medicine.

What are the possible benefits of taking part?

- All trial participants will benefit from the asthma education and training provided at all health centres, from individualised advice about what action to take in the event of deteriorating asthma and an asthma attack. Your child will also be guaranteed availability of first-line asthma treatments during the study. If the study findings are positive, we will use the findings to recommend to the health policy makers to make the new medicine available for all children in South Africa.

Will my family doctor/ General Practitioner be informed of my child's participation?

- Your family doctor (should you have one) will be provided with the study information sheet and will be informed that your child is taking part in the study. We will require him/her to fill out information for us should your child experience an asthma attack and present to him/her for treatment.
- Your family doctor may be contacted if there are any other health concerns that may be picked up during the study.

Will my child's taking part in the study be kept confidential?

- Your child's participation to the study will be known by the relevant people such as clinical team at the clinic you will be attending.
- All trial staff will protect the rights of your child's information and privacy of his/her information will be maintained, including the informed consent or assent.
- Arrangements have been made to ensure that information is kept secure, in a locked cupboard accessible on the to the study team.
- Devices with participants details will be encrypted with the password. AHRI and UKZN will maintain all trial records and documents and retain these for at least 15 years.
- For the analysis of data, all direct identifiers to your child will be removed, and participants will be identified only by numbers.

Will me and my child be reimbursed for taking part?

- You will be reimbursed for travel expenses and inconvenience for you and your child. Your child's involvement in the study should not cost you any amount.

What will happen to the data?

- The information received will be kept in a password crypted devices. Numbers will be used instead of personal identifiers during the data analysis and reporting. The information will be kept by the UKZN and AHRI for 15 years.
- We will be using information from AHRI to undertake this study. Research is a task that we perform in the public interest.
- We will use the minimum personally identifiable information.
- We will keep identifiable information about your child for 15 years after the study has finished.
- We will store the anonymized research data and any research documents with personal information, such as consent forms, securely at UKZN and AHRI.

You can find out more about how we use your information by contacting UKZN 031 26 04399/ masekelar@ukzn.ac.za or AHRI 035 251 0650 .

What will happen if I don't want to carry on with the study?

- Participation is voluntary and you may change your minds at a later stage.
- Withdrawal will not affect the care you receive from any health service
- If you withdraw from the study, we will destroy all identifiable samples, but will use the data up to your withdrawal.

What happens at the end of the study?

- Your child will not be identified from any report or publication placed in the public domain.
- We intend to publish the findings of the study, present it at conferences and give feedback to the community and policy makers.
- Some of the research being undertaken will also contribute to the fulfilment of an educational requirement (e.g. a doctoral thesis).

What if we find something unexpected?

- If there are unexpected clinical findings, your child will be referred to the local clinic/ district hospital. We will need to report these findings, so please inform the study team should these happen.

What if there is a problem?

- In the event of any problems or concerns/questions you may contact Professor Masekela, at 031 260 4399/ masekelar@ukzn.ac.za or the UKZN Biomedical Research Ethics Committee and the South African Health Regulatory Authority on the contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2602486 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY:

The Chief Executive Officer
South African Health Products Regulatory Authority
Loftus Park
Building A
402 Kirkness Street
Arcadia, Pretoria
0083

E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413

- Trial participants and staff will be covered by clinical trial indemnity and insurance for the study.

How have patients and the public been involved in this study?

- We plan ongoing involvement of local patient and community advisory board and consultation groups through trial set-up, implementation, and dissemination phases. For example, during the trial set-up phase we have sought input into trial plans and wording of participant information and consent forms from the uMkhanyakude District Community Advisory Board and patient representatives. During trial implementation we will share progress reports, discuss, and troubleshoot problems that arise. When the study results are available these will be presented and pathways to impact discussed and planned.

Who is organizing and funding the study

- The National Institute of Health and Care Research (United Kingdom) via a Global Health Research Professorship Grant has awarded grant to Professor Refiloe Masekela
- Your doctor will not be paid for their role in the study (if contacted to verify information or follow up updates) and there will be no conflicts of interest.

Who has reviewed the study?

- We will request ethical review of the trial protocol and other documents by the University of KwaZulu Natal Biomedical Research Ethics Committee and the South African Health Products Regulating Authority (SAHPRA). The trial will not commence until we have ethical approval. The final approved version of the protocol will be registered with Current Controlled Trials Ltd and published in an open access format. Trial oversight committees will be established.

Further information and contact details:

- Please contact Professor Refiloe Masekela 031 260 4399, masekelar@ukzn.ac.za or in writing to:

  4th floor Dept of Paediatrics and Child Health
  Nelson R Mandela School of Medicine
  Durban
  4013

Thank you for considering taking part.

DECLARATION OF CONSENT

I …… have been informed about the study entitled 'Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial' by …….

I understand the purpose and procedures of the study is to compare different types of medicine in controlling asthma and preventing acute asthma episodes.

I have been given an opportunity to ask questions about the study and have had answers to my satisfaction.

I declare that the participation of my child in this study is entirely voluntary and that I may withdraw him/her at any time without affecting any treatment or care that he/she would usually be entitled to.

I have been informed about any available compensation or medical treatment if injury occurs to him/her as a result of study-related procedures.

If we have any further questions/concerns or queries related to the study we understand that we may contact the researcher at UKZN/AHRI.

If I have any questions or concerns about my child's rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2602486 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY:
The Chief Executive Officer
South African Health Products Regulatory Authority
Loftus Park
Building A
402 Kirkness Street
Arcadia, Pretoria
0083

E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413

PARTICIPANT NAME

_____

PARENT/GUARDIAN:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INFORM CONSENT ADMINISTRATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

WITNESS (If applicable)**:**

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

_____

Printed Name(s) and Surname

_____

Signature Date and Time

15.3 Appendix 4: Patient information and parents/guardian consent

PARENT/LEGAL GUARDIAN PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT

Each **participant** must receive, read and understand this document **before** any study-related procedure is performed

Study Number:	
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.0; 23 January 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Somkhele +27 (0)35 550 7500

To the potential participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

ICF administration starting time: _____ ICF administration finish time: _____

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*

I would like to invite you to consider taking part in a research study called "Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial. "

- Before you decide if you want to be part of this study, we would like to give you information to help you decide if you would like to be part of the study.
- Please take the time to think through the following information and discuss it with others if you wish. Knowing what is involved will help you decide if you want to take part.
- If you have any questions, do not hesitate to ask me.
- You should not agree to take part unless you are happy about all the procedures involved.
- Please be open with me regarding your health history since you may otherwise harm yourself by taking part in this study.
- If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will also be given a copy to keep and refer to.
- Should you agree to take part in the study we will do so without revealing your study identity.

What is the purpose of the study?

- The purpose of the study is to check whether using a newer asthma pump will lead to reduced asthma attacks compared to the normally used asthma pump in South African children and adolescents and to see if this will not cost a lot of money.

Why have I been invited?

- You have been selected to participate in this study because you have asthma symptoms and has been diagnosed with asthma. We got your details from Somkhele Campus of the African Health Research Institute (AHRI) database which includes all people living in your area. We are planning to include 1142 participants who will be divided into 2 age groups (6 -11 years) and (12 – 18 years). You will either be in the group that will be taking normal asthma medication dispensed at the clinic (standard medication) or you will receive the study asthma pump (new medicine called Vannair or Symbicort)

Do I have to take part?

- Taking part in this study is entirely voluntary. You do not have to take part if you would not like to. If you choose to take part and you change your mind later about participation in the study, you can

withdraw from the study at any point, without giving a reason. Withdrawal from the study will not affect your clinical care at the clinic or hospital and you will not incur any penalties

What will happen to me if I decides to take part?

- When you decide to take part, you will be asked to sign the consent form to confirm that you have received enough information about the what the study is about and that and you are willing to take part.
- You will be asked few questions so that we get to know your background better.
- You will be allocated one of the groups then be given asthma pump (standard one or new one) to use for your asthma management.
- Once allocated, you will stay in that group for the duration of the study.
- The number of participants in the standard asthma pump and the new asthma pump will be the same.
- You will be involved in this study for 12 months. During this period, you will have checkups every 3 months. The check-up will be either by one of the nurses/investigator at the clinic/hospital or will be done telephonically.
- The checkups are to check how you are feeling whether you had any asthma attacks or any undesired harmful effects from the medication or any concerns.
- You can go to the clinic at any point if you are unwell or you have any concerns, you don't have to wait for the scheduled appointments.

What should I consider?

- You cannot participate in the study if you do not have asthma or if you have active tuberculosis on medication. If you are taking any other medication, you will be expected to let us know what these are. If you are taking the medicine that can interact with any medicine in the new pump, you will not be expected to participate in the study. If you are involved in any other research studies, we will request that you let us know as this may not allow us to enroll you in this current study without discussion with the principal investigator of that study.

Are there any possible disadvantages or risks from taking part?

- The risks expected during the study are adverse events (side-effects) from the medicines being given, otherwise the project itself is not associated with any risks.

For the new medication that we will be giving for the study.

- The medicine is already recommended for use for the moderate to severe asthma treatment for children 6 to 11 years and for mild asthma treatment in adolescents over the age of 12 years.

- There may be side effects from the drugs. The most common side effects are minor and well-described and include headache, throat irritation, nausea, vomiting, diarrhoea, blocked nose, changes in voice, oral candidiasis, nasopharyngitis and upper respiratory tract infections. For the most common side effects, candida, throat irritation and voice changes these can be avoided by rinsing out the mouth after using the medicine.

What are the possible benefits of taking part?

- All trial participants will benefit from the asthma education and training provided at all health centres, from individualised advice about what action to take in the event of deteriorating asthma and an asthma attack. You will also be guaranteed availability of first-line asthma treatments during the study. If the study findings are positive, we will use the findings to recommend to the health policy makers to make the new medicine available for all children in South Africa.

Will my family doctor/ General Practitioner be informed of my participation?

- Your family doctor (should you have one) will be provided with the study information sheet and will be informed that you are taking part in the study. We will require him to fill out information for us should you experience an asthma attack and present to him/her for treatment.
- Your family doctor may be contacted if they are any other health concerns that may be picked up during the study.

Will my taking part in the study be kept confidential?

- Your participation to the study will be known by the relevant people such as clinical team at the clinic you will be attending.
- All trial staff will protect the rights of your information and privacy of your information will be maintained, including the informed consent or assent.
- Arrangements have been made to ensure that information is kept secure, in a locked cupboard accessible on the to the study team.
- Devices with participants details will be encrypted with the password. AHRI and UKZN will maintain all trial records and documents and retain these for at least 15 years.
- For the analysis of data, all direct identifiers to you will be removed, and participants will be identified only by numbers.

Will I be reimbursed for taking part?

- You will be reimbursed for travel expenses and inconvenience. Your involvement in the study should not cost you any amount.

What will happen to the data?

- The information received will be kept in a password crypted devices. Numbers will be used instead of personal identifiers during the data analysis and reporting. The information will be kept by the UKZN and AHRI for 15 years.
- We will be using information from AHRI to undertake this study. Research is a task that we perform in the public interest.
- We will use the minimum personally identifiable information.
- We will keep identifiable information about you for 15 years after the study has finished.
- We will store the anonymized research data and any research documents with personal information, such as consent forms, securely at UKZN and AHRI.

You can find out more about how we use your information by contacting UKZN 031 260 4399/ masekelar@ukzn.ac.za or AHRI 035 251 0650 .

What will happen if I don't want to carry on with the study?

- Participation is voluntary and you may change your minds at a later stage.
- Withdrawal will not affect the care you receive from any health service
- If you withdraw from the study, we will destroy all identifiable samples, but will use the data up to your withdrawal.

What happens at the end of the study?

- Your will not be identified from any report or publication placed in the public domain.
- We intend to publish the findings of the study, present it at conferences and give feedback to the community and policy makers.
- Some of the research being undertaken will also contribute to the fulfilment of an educational requirement (e.g. a doctoral thesis).

What if we find something unexpected?

- If there are unexpected clinical findings, you will be referred to the local clinic/ district hospital. We will need to report these findings, so please inform the study team should these happen.

What if there is a problem?

- In the event of any problems or concerns/questions you may contact Professor Masekela, at 031 260 4399/ masekelar@ukzn.ac.za or the UKZN Biomedical Research Ethics Committee and the South African Health Products Regulatory Authority on contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2602486 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY:
The Chief Executive Officer
South African Health Products Regulatory Authority
Loftus Park
Building A
402 Kirkness Street
Arcadia, Pretoria
0083

E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413

- Trial participants and staff will be covered by clinical trial indemnity and insurance for the study.

How have patients and the public been involved in this study?

- We plan ongoing involvement of local patient and community advisory board and consultation groups through trial set-up, implementation, and dissemination phases. For example, during the trial set-up phase we have sought input into trial plans and wording of participant information and consent forms from the uMkhanyakude District Community Advisory Board and patient representatives. During trial implementation we will share progress reports, discuss, and troubleshoot problems that arise. When the study results are available these will be presented and pathways to impact discussed and planned.

Who is organizing and funding the study

- The National Institute of Health and Care Research (United Kingdom) via a Global Health Research Professorship Grant has awarded grant to Professor Refiloe Masekela

- Your doctor will not be paid for their role in the study (if contacted to verify information or follow up updates) and there will be no conflicts of interest.

Who has reviewed the study?

- We will request ethical review of the trial protocol and other documents by the University of KwaZulu Natal Biomedical Research Ethics Committee and the South African Health Products Regulating Authority (SAHPRA). The trial will not commence until we have ethical approval. The final approved version of the protocol will be registered with Current Controlled Trials Ltd and published in an open access format. Trial oversight committees will be established.

Further information and contact details:

- Please contact Professor Refiloe Masekela 031 260 4399, masekelar@ukzn.ac.za or in writing to:

  4th floor Dept of Paediatrics and Child Health

  Nelson R Mandela School of Medicine

  Durban

  4013

Thank you for considering taking part.

DECLARATION OF CONSENT

I …… have been informed about the study entitled 'Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial' by …….

I understand the purpose and procedures of the study is to compare different types of medicine in controlling asthma and preventing acute asthma episodes.

I have been given an opportunity to ask questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

I have been informed about any available compensation or medical treatment if injury occurs to me as a result of study-related procedures.

If we have any further questions/concerns or queries related to the study we understand that we may contact the researcher at UKZN/AHRI.

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2602486 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY:
The Chief Executive Officer
South African Health Products Regulatory Authority
Loftus Park
Building A
402 Kirkness Street
Arcadia, Pretoria
0083

E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413

PARTICIPANT:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INFORM CONSENT ADMINISTRATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

WITNESS (If applicable)**:**

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

_____

Printed Name(s) and Surname

Signature Date and T

15.4 Appendix 5: Patient information and assent

PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT

Each **participant** must receive, be informed and/or read and understand this document **before** any study-related procedure is performed

Study Number:	
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1; 21 Aug 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

To the potential participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

ICF administration starting time: _____ ICF administration finish time: _____

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*

I would like to invite you to consider taking part in a research study called "Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial. "

- Before you decide if you want to be part of this study, we would like to give you information to help you decide if you would like to be part of the study.
- Please take the time to think through the following information and discuss it with others if you wish. Knowing what is involved will help you decide if you want to take part.
- If you have any questions, do not hesitate to ask me.
- You should not agree to take part unless you are happy about all the procedures involved.
- Please be open with me regarding your health history since you may otherwise harm yourself by taking part in this study.
- If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will also be given a copy to keep and refer to.
- Should you agree to take part in the study we will do so without telling anyone who you are or your study identity.

What is the study about?

- The reason for the study is about my asthma and to check whether using a newer asthma pump will may cause fewer asthma attacks compared to the normally used asthma pump and will cost less. You will either get the new pump or use the normal (regular) asthma medication from the clinic.

Why have I been invited?

- You have been invited because you have asthma. We are going to compare those who will be on medication the normally used at your clinic or hospital (standard) asthma pump and new asthma pump (Vannair or Symbicort).

Do I have to take part?

- No, you do not have to take part. If you agree to take part you are also free to quit the study at any time and this will not affect your care at the clinic or hospital.

What will happen to me if I decide to take part?

- When you decide to take part, you will be given the asthma medicine that you have been allocated to. You will take the medicine for a year in the group you are allocated to. You will have check-ups at the clinic twice and you will have two telephone visit with the study team.
- The nurses will ask you questions about your asthma, your medicines you used and any attacks you may have had.

Will I have bad effects from the medicine?

- The new medicine for asthma can make you feel slightly ill. You can feel feel unwell, want to vomit or have a blocked nose, sore head or change in your voice. If you are unwell let the study team know you are not well. Should you feel very bad from the medicine the doctor will check you and decide if the medicine should be stopped or not.

How will the study help?

- If we see that the new medicine works better that the normal medicine in the clinic, we will recommend that the new medicine should be given to children with asthma in South Africa.

Will my taking part in the study be kept confidential?

- No one but the study team will know what answers you have given and all the your name and information will not be available to anyone but the study team.

What if there is a problem or questions?

- In the event of any problems or concerns/questions you can speak to Professor Masekela, at 0312604399/ masekelar@ukzn.ac.za or the UKZN Biomedical Research Ethics Committee and the South African Health Regulatory authority on contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2602486 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY:

The Chief Executive Officer
South African Health Products Regulatory Authority

Loftus Park
Building A
402 Kirkness Street
Arcadia, Pretoria
0083

E-mail: Boitumelo.Semete@sahpra.org.za
Tel: 012 501 0413

PARTICIPANT ASSENT:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INFORM CONSENT ADMINISTRATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

WITNESS (If applicable)**:**

_____

Printed Name(s) and Surname

Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

Printed Name(s) and Surname

Signature Date and Time

15.5 Appendix 6: Asthma screening questionnaire

Study Number:	AIR-SA-001
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1 21 Aug 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela-uMkhanyakude sites
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

ASTHMA SCREENING QUESTIONNAIRE

Dear Potential participant,

You are kindly requested to answer to following 6 questions regarding your breathing. The parent/guardian is requested to assist in answering these questions.

1. Have you **ever** had wheezing or whistling in the chest at any time in the past?
   Yes ☐ or No ☐
2. Have you had wheezing or whistling in the chest **in the past 12 months**?
   Yes ☐ or No ☐
3. Have you **ever** had asthma?
   Yes ☐ or No ☐
4. Was asthma confirmed by a doctor?
   Yes ☐ or No ☐
5. Have you used any inhaled medicines e.g. pumps or nebuliser to help your breathing problems at any time **in the past 12 months**? (when you didn't have a cold)

Yes ☐ or No ☐

6. How many attacks of wheezing have you had in the past 12 months?

   ☐ None

   ☐ 1 – 3

   ☐ 4 – 12

   ☐ More than 12

15.6 Appendix 7: Background information

BACKGROUND INFORMATION

Study Unique ID Number:	
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1; 21 Aug 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela: uMkhanyakude sites
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

To the potential participant: *This form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.*

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*
I would like you to help me understand your / your child's background information by answering these questions.

Background information

1. How old are you in years:_____
2. What is your date of birth: ____/___/_____
3. What is your sex:
   ☐ Male
   ☐ Female
4. Do you have a chronic condition/s? Yes☐ or No ☐
   State the name of the condition ……..
5. Are you taking any chronic medications? Yes☐ or No ☐
6. If yes to question 5, what is the name of the medication (s)?_____

   _____

Asthma diagnosis

7. Who diagnosed the asthma?
   ☐ Doctor
   ☐ Nurse
   ☐ Self
   ☐Other
8. Age at diagnosis
   ☐ Less than 4 years
   ☐ 4 – 11 years

☐ 12 years and above

Asthma medication

9. Are you taking any asthma medication currently? Yes ☐ or No ☐

10. Which medication? Tick appropriate medication below:
    - ☐ Budesonide
    - ☐ Beclomethasone
    - ☐ Fluticasone/salmeterol
    - ☐ Montelukast
    - ☐ Theophylline
    - ☐ Salbutamol
    - ☐ Symbicort
    - ☐ Vannair,
    - ☐ Other……..

11. How often do you use..? (NAEP poster to choose from)

    Anti-inflammatory
    - ☐ Only when needed
    - ☐ In short courses
    - ☐ Everyday
    - ☐ Never

    Salbutamol
    - ☐ Only when needed
    - ☐ In short courses
    - ☐ Everyday
    - ☐ Never

    Other (specify)…….
    - ☐ Only when needed
    - ☐ In short courses
    - ☐ Everyday

Asthma severity

12. How many attacks of asthma in the last year? (Required to go to clinic with wheezing, miss school, admission to hospital, nebulization at a doctor/clinic, medication (steroids)) indicate the number of times.

13. Peak expiratory flow rate

Blow 1		Blow 2		Blow 3		Best blow	

PARTICIPANT:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INFORM CONSENT ADMINISTRATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

WITNESS (If applicable)**:**

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint

15.7 Appendix 8: Childhood Asthma Control Test

CHILDHOOD ASTHMA CONTROL TEST

Study Number:	AIR-SA-001
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1 21 Aug 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela-uMkhanyakude sites
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

To the potential participant: *This form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.*

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*
I would like you to help me understand your / your child's asthma control by answering these questions.

How old is your child in years?_____

Parent/guardian is required to assist in completing this form.

c-ACT (ages 4-11)

1. How was your Asthma today?
   - ☐ 0 Very Bad
   - ☐ 1 Bad
   - ☐ 2 Good
   - ☐ 3 Very Good

2. How much of a problem is your asthma when you run, exercise or play sports?
   - ☐ 0 It's a big problem, I can't do what I want to do.
   - ☐ 1 It's a problem and I don't like it.
   - ☐ 2 It's a problem but it's okay.
   - ☐ 3 It's not a problem.

3. Do you cough because of your asthma?
   - ☐ 0 Yes, all the time.
   - ☐ 1 Yes, most of the time.
   - ☐ 2 Yes, some of the time.
   - ☐ 3 No, none of the time.

4. Do you wake up during the night because of your asthma?
   - ☐ 0 Yes, all of the time.
   - ☐ 1 Yes, most of the time.
   - ☐ 2 Yes, some of the time.
   - ☐ 3 No, none of the time.

The following questions are directed to the **caregiver or parent.**

5. During the last 4 weeks, on average, how many days per month did your child have any daytime asthma symptoms?
   - ☐ 5 Not at all
   - ☐ 4 1-3 days/month
   - ☐ 3 4-10days/month
   - ☐ 2 11-18 days/month
   - ☐ 1 19-24 days/month
   - ☐0 Everyday

6. During the last 4 weeks, on average, how many days per month did your child wheeze during the day because of asthma?
   - ☐ 5 Not at all
   - ☐ 4 1-3 days/mo
   - ☐ 3 4-10days/mo
   - ☐ 2 11-18 days/mo
   - ☐ 1 19-24 days/mo
   - ☐ 0 Everyday

7. During the last 4 weeks, on average, how many days per month did your child wake up during the night because of asthma?
   - ☐ 5 Not at all
   - ☐ 4 1-3 days/mo
   - ☐ 3 4-10days/mo
   - ☐ 2 11-18 days/mo
   - ☐ 1 19-24 days/mo
   - ☐ 0 Everyday

C-ACT Score:

_____

PARTICIPANT:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint

15.8 Appendix 9: Asthma Control Test

ASTHMA CONTROL TEST

Study Number:	AIR-SA-001
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1 21 Aug 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela-uMkhanyakude sites
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

To the potential participant: *This form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.*

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*

I would like you to help me understand your asthma control by answering these questions.

How old are you in years?_____

ACT (ages > 12 years)

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?
   - ☐ 1 All of the time
   - ☐ 2 Most of the time
   - ☐ 3 Some of the time
   - ☐ 4 A little of the time
   - ☐ 5 None of the time

2. During the past 4 weeks, how often have you had shortness of breath?
   - ☐ 5 Not at all
   - ☐ 4 Once or twice a week
   - ☐ 3 3- 6 times a week
   - ☐ 2 Once a day
   - ☐1 More than once a day

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night or earlier than usual in the morning?
   - ☐ 5 Not at all
   - ☐ 4 Once or twice
   - ☐ 3 Once a week
   - ☐ 2 2 or 3 nights a week
   - ☐ 1 4 or more nights a week

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as salbutamol)?

☐ 5 Not at all

☐ 4 Once a week or less

☐ 3 2 or 3 times per week

☐ 2 1 or 2 times per day

☐ 1 3 or more times per day

5. How would you rate your asthma control during the past 4 weeks?

☐ 5 Completely Controlled

☐ 4 Well Controlled

☐ 3 Somewhat Controlled

☐ 2 Poorly Controlled

☐ 1 Not Controlled at all

ACT Score:

_____

PARTICIPANT:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint

15.9 Appendix 10: Quality of life questionnaire

PAEDIATRIC ASTHMA QUALITY OF LIFE QUESTIONNAIRE

Study Number:	AIR-SA-001
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1 21 Aug 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela-uMkhanyakude sites
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

To the potential participant: *This form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.*

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*

I would like you to tell me about all the things you do in which you are bothered by your asthma.

Record identified activities.

Together, we are going to look at a list of things that you may have done during the last week. Because of your asthma, you may have found some of these activities difficult to do or not so much fun. Let's look at the list and you tell me in which activities you've been bothered by your asthma during the past week. If you haven't done something on the list or if it hasn't bothered you, just say 'no'.

Read activities, omitting those which the patient has identified spontaneously. Pause after each activity to give the patient a chance to reply.

Activities		
1.Ball hockey	13. Sleeping	25. Shouting
2. Baseball	14. Soccer	26. Gymnastics
3. Basketball	15. Swimming	27. Rollerblading
4. Dancing	16. Volleyball	28. Skateboarding
5. Football	17. Walking	29. Track and field
6. Playing at recess	18. Walking uphill	30. Tobogganing
7. Playing with pets	19. Walking upstairs	31. Skiing
8. Playing with friends	20. Laughing	32. Ice skating
9. Riding a bicycle	21. Studying	33. Climbing
10. Running	22. Doing Household chores	34. Getting up in the morning
11. Skipping rope	23. Singing	35. Talking
12.Shopping	24. Doing Crafts or hobbies	

Of the activities you have listed, I would like you to tell me which three bother you the most.

Read together the list of identified activities. Write the three activities in Questions 1–3 of the Questionnaire.

I now would like you to tell me how much you were bothered by your asthma while doing these activities. I will tell you which card to use. Pick the number which best describes how much you were bothered by your asthma in doing each activity during the past week.

1. How much have you been bothered by your asthma in (Activity 1:
. . .) during the past week? ☐ (BLUE CARD)
2. How much have you been bothered by your asthma in (Activity 2:
. . .) during the past week? ☐ (BLUE CARD)

3. How much have you been bothered by your asthma in (Activity 3:
. . .) during the past week? ☐ (BLUE CARD).

4. How much did COUGHING bother you in the past week? ☐ (BLUE CARD)
5. How much did ASTHMA ATTACKS bother you during the past week? ☐ (BLUE CARD)
6. How much did WHEEZING bother you during the past week? ☐ (BLUECARD)
7. How much did TIGHTNESS IN YOUR CHEST bother you during the past week? ☐ (BLUE CARD)
8. How often did you feel DIFFERENT or LEFT OUT because of your asthma during the past week? ☐ (BLUE CARD)
9. How much did SHORTNESS OF BREATH bother you during the past week? ☐ (BLUE CARD)
10. Think about all the activities that you did during the past week. How much were you bothered by your asthma doing these activities? ☐ (BLUE CARD)
11. How often did your asthma make you feel FRUSTRATED during the past week? ☐ (GREEN CARD)
12. How often did your asthma make you feel TIRED during the past week? ☐ (GREEN CARD)
13. How often did you feel WORRIED, CONCERNED OR TROUBLED because of your asthma during the past week? ☐ (GREEN CARD)
14. How often did your asthma make you feel ANGRY during the past week? ☐ (GREEN CARD)
15. How often did you feel IRRITABLE (cranky) during the past week? ☐ (GREEN CARD)
16. How often did you feel FRUSTRATED BECAUSE YOU COULDN'T KEEP UP WITH OTHERS during the past week? ☐ (GREEN CARD)
17. How often did your asthma WAKE YOU UP DURING THE NIGHT during the past week? ☐ (GREEN CARD)
18. How Often did you feel UNCOMFORTABLE because of your asthma during the past week? ☐ (GREEN CARD)
19. How often did you feel OUT OF BREATH during the past week? ☐ (GREEN CARD)
20. How often did you feel YOU COULDN'T KEEP UP WITH OTHERS because of your asthma during the past week? ☐ (GREEN CARD)
21. How often did you have trouble SLEEPING AT NIGHT because of your asthma during the past week? ☐ (GREEN CARD)
22. How often did you feel FRIGHTENED BY AN ASTHMA ATTACK during the past week? ☐ (GREEN CARD)
23. How often did you have difficulty taking a DEEP BREATH during the past week? ☐ (GREEN CARD).

Response options

Domain Questions

Symptoms

Activities

Emotions

BLUE CARD

1. Extremely bothered
2. Very bothered
3. Quite bothered
4. Somewhat bothered
5. Bothered a bit
6. Hardly bothered at all
7. Not bothered

GREEN CARD

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

Four scores, including 3 main topics and 1 total, are obtained from the scale. Each question on the scale is evaluated over 7 points. While 1 indicates excessive discomfort or constant complaining, 7 indicates absence of complaints in relation to scoring. A high score shows a higher quality of life.

PARTICIPANT:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INFORM CONSENT ADMINISTRATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

WITNESS (If applicable)**:**

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

_____

Printed Name(s) and Surname

_____

Signature / Mark or Thumbprint Date and Time

15.10 Appendix 11: Scheduled telephonic follow-up

SCHEDULED VISIT 2 and VISIT 4

Study Number:	AIR-SA-001
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1 21 Aug 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela-uMkhanyakude sites
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

To the potential participant: *This form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.*

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*

I would like you to help me understand your / your child's asthma control by answering these questions.

Telephonic / clinic visits

1. How many times in the past three months have you had: cough, wheeze, difficulty in breathing
   - ☐ zero
   - ☐ less than 2 per month
   - ☐ 2- 4 per month
   - ☐ more than 4 per month
2. Have you gone to a doctor or a clinic to receive nebulizer for your asthma?

   Yes ☐ or No ☐
3. Did you receive a syrup or tablet for the asthma attack?

   Yes ☐ or No ☐
4. If yes how many days did you take the syrup or tablet for?
   - ☐ less than 3
   - ☐ 3 – 7
   - ☐ more than 7
5. Have you changed any of your asthma medications in the last three months

   Yes ☐ or No ☐
6. Did you miss any days of school because of your asthma

   Yes ☐ or No ☐
7. Did your parent or guardian miss days of work because of your asthma

   Yes ☐ or No ☐
8. Did you have any side effects from the medication?

   Yes ☐ or No ☐
9. If yes state what you experienced

……

……

10. How long was this side-effect for?

☐ less than 3 days

☐ 3 – 7 days

☐ more than 7 days

11. Did you use any treatment for this side-effect

Yes ☐ or No ☐

STUDY STAFF:

_____

Printed Name(s) and Surname

_____

Signature Date

15.11 Appendix 12: Schedule follow-up visit

SCHEDULE VISIT 3 AND VISIT 5

Study Number:	AIR-SA-001
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1 21 Aug 2023
Sponsor:	Africa Health Research Institute.
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Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

To the potential participant: *This form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.*

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*

I would like you to help me understand your / your child's asthma control by answering these questions.

Follow up 6 months and 12 months

Asthma medication

1. Are you taking any asthma medication currently? Yes ☐ or No ☐

2. Which medication? Tick appropriate medication below:
   - ☐ Budesonide
   - ☐ Beclomethasone
   - ☐ Fluticasone/salmeterol
   - ☐ Montelukast
   - ☐ Theophylline
   - ☐ Salbutamol
   - ☐ Symbicort
   - ☐ Vannair,
   - ☐ Other……..

3. How often do you use..? (NAEP poster to choose from)

   Anti-inflammatory (Symbicort/Vannair OR Inhaled corticosteroid)
   - ☐ only when needed
   - ☐ In short courses
   - ☐ Everyday
   - ☐ Never

   Salbutamol
   - ☐ only when needed
   - ☐ In short courses
   - ☐ Everyday
   - ☐ Never

Other (specify)…….

☐ only when needed

☐ In short courses

☐ Everyday

4. Have you gone to a doctor or a clinic to receive nebulizer for your asthma?

   Yes ☐ or No ☐

5. Did you receive a syrup or tablet for the asthma attack?

   Yes ☐ or No ☐

6. If yes how many days did you take the syrup or tablet for?

   ☐ less than 3

   ☐ 3 – 7

   ☐ more than 7

7. Have you changed any of your asthma medications in the last three months

   Yes ☐ or No ☐

8. Did you miss any days of school because of your asthma

   Yes ☐ or No ☐

9. Did your parent or guardian miss days of work because of your asthma

   Yes ☐ or No ☐

10. Did you have any side effects from the medication?

    Yes ☐ or No ☐

11. If yes state what you experienced

    ……

    ……

12. How long was this side-effect for?

    ☐ less than 3 days

    ☐ 3 – 7 days

    ☐ more than 7 days

13. Did you use any treatment for this side-effect

    Yes ☐ or No ☐

Asthma severity

14. How many attacks of asthma in the 3 months? (Required to go to clinic/hospital with wheezing, miss school, admission to hospital, nebulization at a doctor/clinic) indicatethe number of times.

    ☐

15. Peak expiratory flow rate

Blow 1 ☐ Blow 2 ☐ Blow 3 ☐ Best blow ☐

INVESTIGATOR:

_____

Printed Name(s) and Surname

_____

Signature Date

15.12 Appendix 13: Asthma Diary National Asthma Education Programme (NAEP)

Study Unique ID Number:	
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.0; 21 August 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela, uMkhanyakude sites
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Somkhele +27 (0)35 550 7500

Month																															
SYMPTOMS		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Cough – Day																																
Cough – Night																																
Wheeze *I* tight chest																																
Used reliever																																
Clinic/ Hospital visit for nebulizer																																
Controller	Day																															
	Night																															
Other	Day																															
	Night																															

Month																															
SYMPTOMS		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Cough – Day																																
Cough – Night																																
Wheeze/ tight chest																																
Used reliever																																
Clinic/ Hospital visit for nebulizer																																
Controller	Day																															
	Night																															
Other	Day																															
	Night																															

Month																															
SYMPTOMS		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Cough – Day																																
Cough – Night																																
Wheeze / tight chest																																
Used reliever																																
Clinic/ Hospital visit for nebulizer																																
Controller	Day																															
	Night																															
Other	Day																															
	Night																															

15.13 Appendix 14: The economic impact of Asthma tool

(Youth Proxy version)

Study Unique ID Number:	AIR-SA-001
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1; 21 Aug 2023
Sponsor:	Africa Health Research Institute.
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Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

This questionnaire aims to determine Asthma's economic impact/burden (child patient perspective). Asthma is a chronic disease, but the economic impact data will be collected over a short time period (from a month up to 6 months).

The tool includes:

Part 1: Child Socioeconomic and demographic information

Part 2: Direct costs for asthma services

2.1 Outpatient services

2.2 Inpatient services

Part 3: Indirect costs for asthma services

3.1 Outpatient services

3.2 Inpatient services

3.3 Productivity loss by Child and Caregivers

PART 1: CHILD SOCIOECONOMIC AND DEMOGRAPHIC INFORMATION

1.1 Individual child

Please fill in the following information about yourself as a parent/guardian and the child you represent

1) Please indicate whom you are answering these questions on behalf of

☐ I am answering these questions on behalf of a child with asthma aged between 6-11 years old

☐ I am answering these questions on behalf of a child with asthma aged between 12-18 years old

2) What is your relationship with the child? Choose one from the list

☐ Parent

☐ Legal Guardian

☐ Relative

1.2 Household of the child

Note: The questions must be answered by someone who knows about the child patient's household income. This must be the sum of all people in the household who are working and contribute to the household's spending.

3) Does someone in the household work for pay/income?

☐ Yes

☐ No

[If yes, continue with Question 4; If no, skip to Questions 5 and 6]

4) How much is your household income a month? _____

5) Who supports the household with income (tick all that apply)?

☐ Family (not living in the child's household)

☐ Government/social grant

☐ No one

☐ Others, specify _____

6) How much does the household get monthly from the supporter/s in question 5? _____

7) How much does your household spend monthly on essential items, excluding medicines for asthma? (Essential items are items you cannot live without, like food, cooking, energy, etc.)

Food: _____
Clothing:_____
Accommodation: _____
Transportation: _____
Education:_____
The household energy source (e.g. fuel, electricity):_____
Other: specify
Item1 (name item_____), state the amount _____
Item2 (name item_____), state the amount, _____

8) Where do you buy/get the child's medicine for asthma?

☐ Local Pharmacy
☐ Hospital/Clinic
☐ I don't use medicine for the child's treatment of asthma
Others (specify) _____

[If selected 'I don't use medicine for the child's treatment', skip to Question 10]

9) How much do you spend monthly on the child's medication for asthma? _____

10) If the child does not use medicine, why not?

☐ I don't have money to buy it
☐ The pharmacy/clinic/hospital is too far
☐ I choose not to use medicine for the child
Others (specify)_____

11) Is the child covered by any kind of private or government health/medical insurance scheme?

☐ Yes
☐ No

[If yes, continue with Question 12; If no, skip to Question 16]

12) What type?

☐ Private medical insurance

☐ National health insurance

☐ Other (specify)

13) If the child is covered by private medical insurance, how much do you or the main insurance member pay monthly for cover? _____

14) Does the insurance cover all the child's treatment costs (tests, consultation fees) for their asthma?

☐ Yes

☐ No

15) Does the insurance cover all the child's medicines for their asthma?

☐ Yes

☐ No

16) In the past 6 months, did you borrow any money to cover costs due to the child's asthma?

☐ Yes

☐ No

[If yes, continue with Question 17; If no, skip to Question 20]

17) In the past 6 months, how much did you borrow?

Amount borrowed_____

18) From whom did you borrow?

☐ Family

☐ Neighbors/friends

☐ Bank

☐ Local social club, e.g. cooperative society or Stokvel

☐ Other (specify)_____

19) What is the interest rate on the loan (in %)?

☐ less than 5%

☐ 5% to 10%

☐ more than 10%

☐ I don't know

☐ I do not need to pay back the money

20) In the past 6 months, have you sold any of your property to pay for the child's treatment costs for asthma?

☐ Yes

☐ No

[If yes, continue with Question 21; If no, skip to Question 23]

21) Did you have to sell the asset in a hurry (rush)?

☐ Yes

☐ No

22) What did you sell?

☐ Land

☐ Livestock/farm products

☐ Car/Vehicle

☐ Household item

☐ Personal electronics

☐ Other (specify): _____

PART 2: DIRECT COSTS OF ASTHMA SERVICES FOR CHILD AND THEIR CAREGIVERS

Please fill in the following information about yourself as a parent/guardian and the child you represent.

2.1 Outpatient services

23) For how long has the child been receiving treatment for asthma?

_____Years

24) Where does the child get health care when there is an asthma attack or cough/breathing emergency problem?

☐ Clinic/local health centre

☐ Hospital

☐ Alternative providers

☐ They don't go anywhere

Others (specify) _____

[If selected 'clinic/local health centre' or 'hospital', continue with Question 25 through to question 28; If selected 'They don't go anywhere, skip to Question 29]

25) How much do you pay per visit for
Consultation? _____
Medicine? ___
Transportation? ____
Food whilst seeking health care?___
Other medical services?_____

26) How many visits does the child make to the healthcare facility per month for treatment of asthma? _____

27)How far is that facility
_____minutes/_____hours walking,
_____ minutes/_____hours with public transportation

28)List the latest visits (in the last six months) the child made to that facility for asthma and the cost related to these visits

Visit	Purpose of visits	Time spent (hours at the facility, including travelling time)	Waiting time (where visited)	Administration cost (e.g. card fees)	Cost of medical services
1					
2					
3					

29) If the answer to Question 24 is "They don't go anywhere", what is the reason for not seeking health care (tick all that apply)
☐ We self-treat at home
☐ Distance to the health facility is too far
☐ Too expensive

☐ Waiting time at the facility

☐ Lack of facilities

☐ Other reasons (specify) _____

2.2 Inpatient services

30) In the past 6 months, was the child hospitalized as part of treatment for asthma?

☐ Yes

☐ No

[If yes, continue with Questions 31 and 32; If no, skip to Question 33]

31) How many days did the child spend in the hospital during the last hospital stay? ___ _____days

32) How much money did you spend during the child's last stay in the hospital on:

Hospital admin fees _____

Food (not provided by the hospital)____

Medicine_____

Tests ____

Others_____

PART 3: INDIRECT COSTS FOR CHILD OR CAREGIVERS OF A CHILD

Please fill in the following information about yourself as a parent/guardian and the child you represent

3.1 Outpatient care

33) Do you or someone else in the household go with the child to the healthcare facility when they receive treatment for asthma?

☐ Yes

☐ No

[If yes, continue with Question 34; If no, skip to Question 35]

34) Please indicate how much you or the caregiver (the person who went to the facility with the child) spent on the last visit

Cost per visit on transport ____

Cost per visit on food _____

3.2 Inpatient care

35) Did you or the child's caregiver spend time in the hospital with the child during the child's last hospitalisation?

☐ Yes

☐ No

[If yes, continue with Questions 36; If no, skip to Question 37]

36) While in the hospital, how much did you/they spend on

Food_____

Accommodation____

Transport____

Other_____

3.3 Productivity Loss by Child and Caregivers

School/Work Days Lost

37) How many days per week does the child go to school? ____ days

38) Did the child miss school during the past 6 months due to their asthma?

☐ Yes

☐ No

[If yes, continue with Question 39; If no, skip to Question 40]

39) During the past 6 months, how many days was the child unable to go to school due to their asthma? _____days

40) During the past 6 months, did you or someone else (caregiver) stay home from work or school to care for the child due to their asthma or go with them to receive treatment?

☐ Yes

☐ No

[If yes, continue with Question 41; If no, skip to Question 44]

41) How many days in a month did you or the caregiver miss work or school to care for the child? _____days

42) In the past 6 months, did you or the caregiver lose any income on the days you/they stayed home to care for the child?

☐ Yes

☐ No

[If yes, continue with Question 43; If no, skip to Question 44]

43)How much income did you/they lose per day? _____

Non-School Activities Missed

44) During the past 6 months, did the child's asthma prevent them from participating in one or more non-school activities (such as playing, visiting friends/relatives, or other activities)?

☐ Yes

☐ No

[If yes, continue with Question 45]

45) During the past 6 months, how many total days did they not participate in non-school activities due to their asthma? ____days

15.14 Appendix 15: CHILD-FRIENDLY EQ-5D-Y

Study Number:	AIR-SA-001
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1 21 Aug 2023
Sponsor:	Africa Health Research Institute.
Investigator (Principal & Site):	Prof Refiloe Masekela-uMkhanyakude sites
Institution:	Africa Health Research Institute
Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

To the potential participant: *This form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.*

ICF administration starting time: _____ ICF administration finish time: _____

INTRODUCTION

Good day, my name is _____ *(INSERT NAME OF STUDY STAFF)*, I am a _____ *(INSERT DESIGNATION)* at _____ (*INSERT SITE).*

I would like you to describe your health TODAY

Under each heading, mark ONE box that best describes your health TODAY

Mobility (walking about)

☐ I have no problems walking about because of my asthma

☐ I have some problems walking about because of my asthma

☐ I have a lot of problems walking about because of my asthma

Looking after myself

☐ I have no problems washing or dressing myself because of my asthma

☐ I have some problems washing or dressing myself because of my asthma

☐ I have a lot of problems washing or dressing myself because of my asthma

Doing usual activities (*for example, going to school, hobbies, sports, playing, doing things with family or friends)*

☐ I have no problems doing my usual activities because of my asthma

☐ I have some problems doing my usual activities because of my asthma

☐ I have a lot of problems doing my usual activities because of my asthma

Having pain or discomfort

☐ I have no pain or discomfort because of my asthma

☐ I have some pain or discomfort because of my asthma

☐ I have a lot of pain or discomfort because of my asthma

Feeling worried, sad or unhappy

☐ I am not worried, sad or unhappy because of my asthma

☐ I am a bit worried, sad or unhappy because of my asthma

☐ I am very worried, sad or unhappy because of my asthma

How good is your health TODAY

We would like to know how good or bad your health is TODAY

The line is numbered from 0 to 100

100 means the best health you can imagine

0 means the worst health you can imagine

Please mark X on the line that shows how good or bad your health is TODAY

The worst health you can imagine	0……..25……50……75……100	The best health you can imagine

PARTICIPANT/GUARDIAN:

_____

_____

Printed Name(s) and Surname

_____

_____

Signature / Mark or Thumbprint Date and Time

INFORM CONSENT ADMINISTRATOR:

_____

_____

Printed Name(s) and Surname

_____

_____

Signature / Mark or Thumbprint Date and Time

WITNESS (If applicable)**:**

_____

_____
Printed Name(s) and Surname

_____

_____
Signature / Mark or Thumbprint Date and Time

INVESTIGATOR:

_____

_____
Printed Name(s) and Surname

_____

_____
Signature / Mark or Thumbprint

15.15 Appendix 16: Health facility costing tool for asthma

HEALTH FACILITY COSTING TOOL FOR ASTHMA

Study Unique ID Number:	AIR-SA-001
Study Title:	Anti-Inflammatory Reliever therapy for asthma using inhaled budesonide/formoterol as-needed with or without maintenance in South African children: A Pragmatic Open Label Phase 3 Randomised Controlled Trial.
Protocol Version and Approval Date:	Version 1.1; 21 Aug 2023
Sponsor:	Africa Health Research Institute.
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Daytime and After-Hours Telephone Number(s):	Daytime:+27 (0)35 550 7500 After-Hours 079 056 4232

This questionnaire is filled by the Health facility manager who has overall information. The data collector would leave the questionnaire and ask for an appointment to collect it.

A. GENERAL FACILITY INFORMATION

Question1: Describe your facility:

A1	Name of the facility	
A2	City	
A3	District	
A4	Type/level of facility	
A5	Operating Hours	

Question 2: List the number of staff (medical and non-medical) working with asthma services. Include staff who might be working there part time or a few hours. The cost centre referred here can be the mainstream department providing asthma services or support department like the admin/finance department staff providing support to asthma medical personnel or patients.

Number of staff	Position	Time dedicated to asthma services a week	Department or cost centre where staff is located

Question 3: What is the average number of asthma patients served per day?

_____ patients

B. HEALTH PROFESSIONAL TIME

Please provide the following information for the staff that work at your facility in providing asthma services.

Staff title	Number of staff with this title	Staff monthly salary	Average training costs for staff per month	Housing allowance per month	Value of Other benefits per month	Total days worked per month	Time used daily to serve asthma	Time used daily to serve non-asthma

							patients	patients

C. SUPPLIES TYPICALLY USED IN ASTHMA TREATMENT

Please provide the following information for supplies such as masks, syringes and other supplies used to treat asthma patients.

Please list the supplies used in a typical visit during asthma service	Unit for measurement	Year purchased	Number of items used per visit	How long the item is used for asthma service

D. Medicines, drugs, laboratory tests for user of asthma services

Medicines, tests and other services rendered to asthma patients in the month of _____ 202__

Serial number	Type of medicine/ lab test or other service	Quantities per month	Average number of asthma patients served per day

E. Equipment used for the provision of asthma services

Please provide the following information for medical equipment used such as x-ray machines etc.

Serial number	Type of equipment	Year, month and date of purchase	Total initial expense	Repair/Maintenance expense per year	Number of asthma patients served a day	Number of non-asthma patients served by equipment a day

F. Transportation costs

Please provide the following information on vehicles and ambulances used in transporting patients from a place to another.

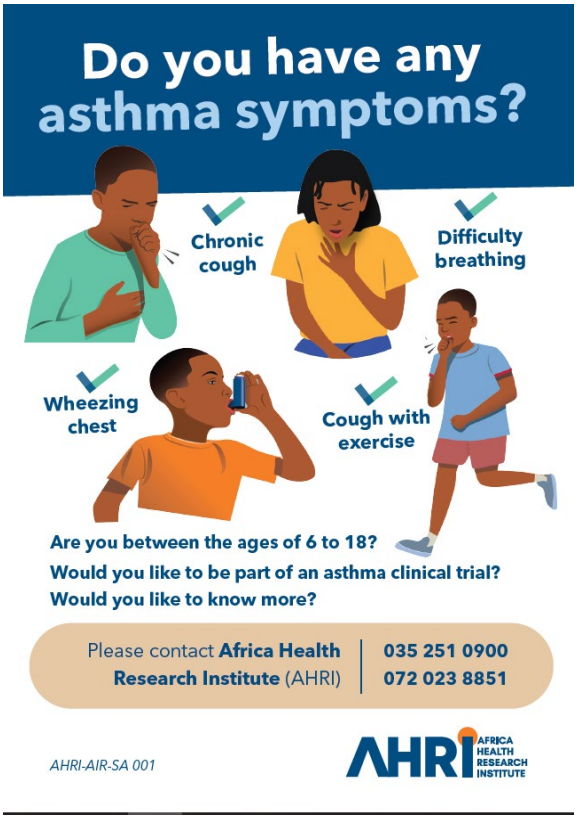
Registration number	Type of vehicle	Year, month and date of purchase	Total initial expense	Repair/Maintenance expense per year	Number of asthma patients served by vehicle a month	Number of non-asthma patients served by vehicle a month

G. Costs for building facilities used

Please provide information regarding the number of rooms serving asthma patients, the area of these rooms and whether or not the rooms serve other non-asthma patients

Serial number	Room name	Medical department where room/hall is located	Area of the room, hall (m^2)	Area of building where room is located (m^2)	Cost (or rental) of the building where room is located	Number of asthma patients served in a room per day	Number of non-asthma patients served in a room per day

15.16 Appendix 17: Asthma Advert



15.17 Appendix: 18 SMART ACTION Plan

For participants on budesonide/formoterol

(Example of action plan template for budesonide/formoterol. A similar action plan could be constructed for other ICS/formoterol formulations, e.g., mometasone/formoterol)

My Asthma Action Plan

For Single Inhaler Maintenance and Reliever Therapy (SMART)
with budesonide/formoterol

Name: _____

Action plan provided by: _____

Date: _____

Doctor: _____

Normal mode

My SMART Asthma Treatment is:

☐ budesonide/formoterol 160/4.5 (12 years or older)

☐ budesonide/formoterol 80/4.5 (6-11 years)

My Regular Treatment Every Day:

(Write in or circle the number of doses prescribed for this patient)

Take [1, 2] inhalation(s) in the morning

and [0, 1, 2] inhalation(s) in the evening, every day

Reliever

Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms

I should always carry my budesonide/formoterol inhaler

Asthma Flare-up

If over a Period of 2-3 Days:

- My asthma symptoms are getting worse **OR NOT** improving

OR

- I am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years or older) or more than 4 inhalations a day (if aged 6-11 years)

I should:

☒ Continue to use my regular everyday treatment **PLUS** 1 inhalation budesonide/formoterol whenever needed to relieve symptoms

☐ Start a course of prednisolone

☐ Contact my doctor

Course of Prednisolone Tablets:

Take _____mg prednisolone

tablets per day for _____days **OR**

_____

_____

Asthma Emergency

Signs of an Asthma Emergency:

- Symptoms getting worse quickly
- Extreme difficulty breathing or speaking
- Little or no improvement from my budesonide/formoterol reliever inhalations

If I have any of the above danger

While I am waiting for the ambulance start my asthma first aid plan:

- Sit upright and stay calm.
- Take 1 inhalation of budesonide/formoterol. Wait 1-3 minutes. If there is no improvement, take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion).

My asthma is stable if:

- I can take part in normal physical activity without asthma symptoms

AND

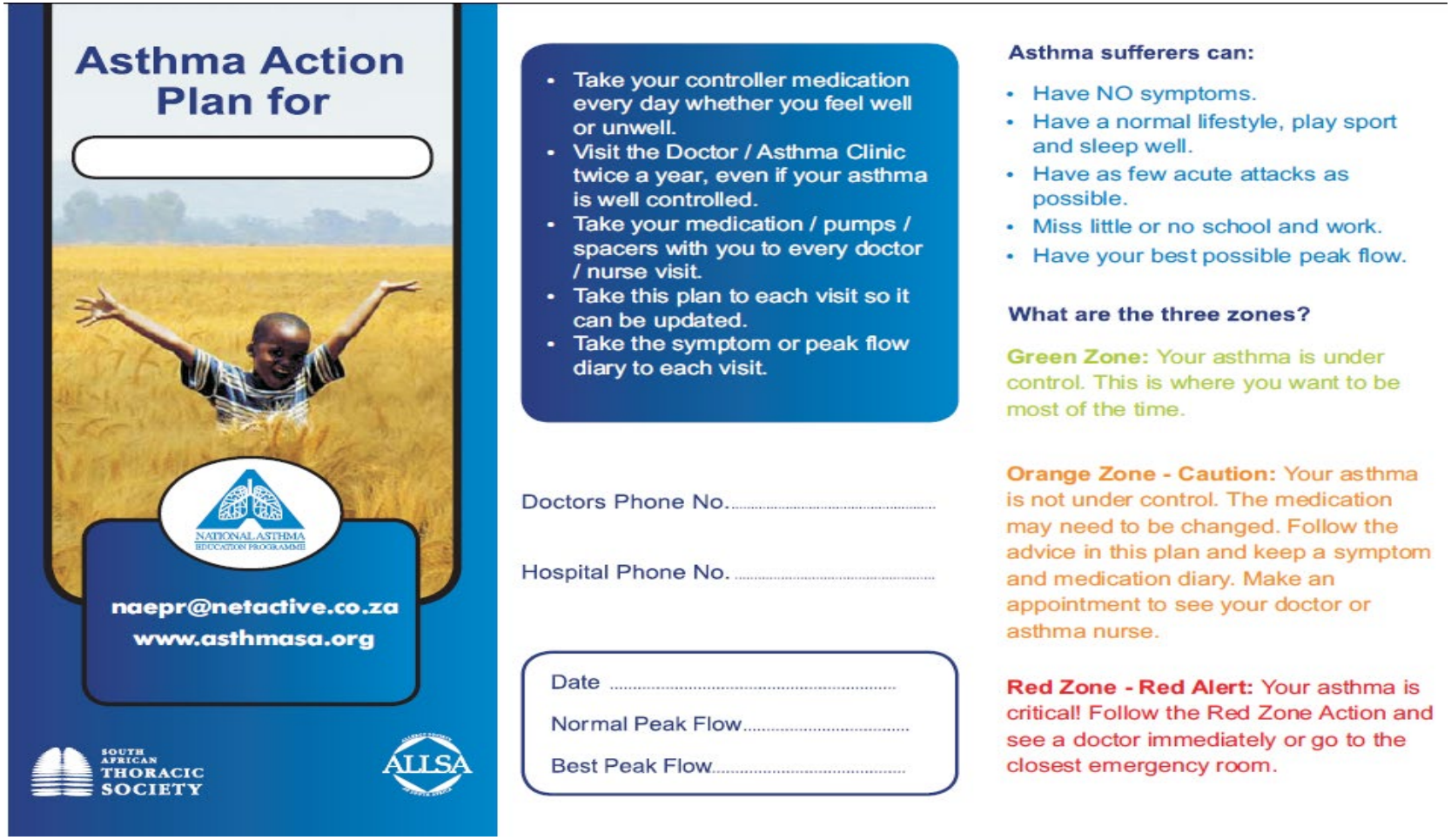
- I do not wake up at night or in the morning because of asthma

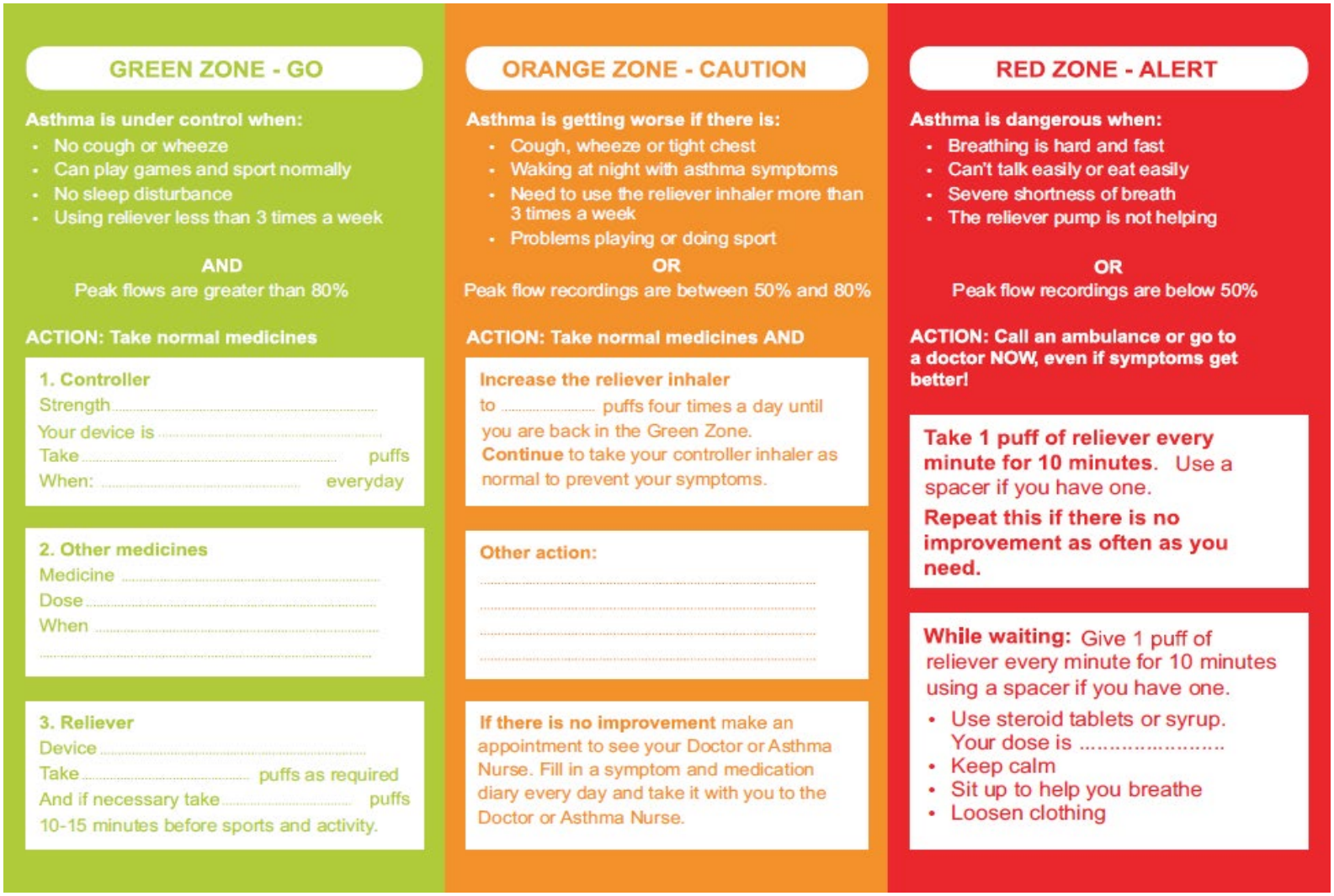
If I need more than **12 budesonide/formoterol inhalations (total)** in any day (or more than 8 inhalations for children 6-11 years), I **MUST** see my doctor or go to the hospital the same day.

Other Instructions

_____

15.18 Appendix 19: NAEP Asthma Action Plan





GREEN ZONE - GO

Asthma is under control when:

- No cough or wheeze
- Can play games and sport normally
- No sleep disturbance
- Using reliever less than 3 times a week

AND

Peak flows are greater than 80%

ACTION: Take normal medicines

1. Controller
Strength.....
Your device is.....
Take..... puffs
When: ..... everyday

2. Other medicines
Medicine .....
Dose.....
When .....
.....

3. Reliever
Device.....
Take..... puffs as required
And if necessary take..... puffs
10-15 minutes before sports and activity.

ORANGE ZONE - CAUTION

Asthma is getting worse if there is:

- Cough, wheeze or tight chest
- Waking at night with asthma symptoms
- Need to use the reliever inhaler more than 3 times a week
- Problems playing or doing sport

OR

Peak flow recordings are between 50% and 80%

ACTION: Take normal medicines AND

Increase the reliever inhaler
to ..... puffs four times a day until you are back in the Green Zone.
Continue to take your controller inhaler as normal to prevent your symptoms.

Other action:
.....
.....
.....
.....

If there is no improvement make an appointment to see your Doctor or Asthma Nurse. Fill in a symptom and medication diary every day and take it with you to the Doctor or Asthma Nurse.

RED ZONE - ALERT

Asthma is dangerous when:

- Breathing is hard and fast
- Can't talk easily or eat easily
- Severe shortness of breath
- The reliever pump is not helping

OR

Peak flow recordings are below 50%

ACTION: Call an ambulance or go to a doctor NOW, even if symptoms get better!

Take 1 puff of reliever every minute for 10 minutes. Use a spacer if you have one.
Repeat this if there is no improvement as often as you need.

While waiting: Give 1 puff of reliever every minute for 10 minutes using a spacer if you have one.

- Use steroid tablets or syrup. Your dose is .....
- Keep calm
- Sit up to help you breathe
- Loosen clothing

15.19 Appendix 20: NAEP Medicine poster