SCHOOL-SUPERVISED ASTHMA CONTROLLER STRATEGY

FINAL DEGREE PROJECT

Author: Pau Magester Carrasco

Clinical tutor: Dr. Andreu Peñas Aguilera
Methodological tutor: Dr. Abel López Bermejo

Department of Pediatrics
Hospital Universitari Dr. Josep Trueta
January 2020, Girona

First of all, I would like to thank Dr. Andreu Peñas for the huge involvement and dedication during these months, and all the help given to create this project.

I would also like to thank Dr. Abel López for solving all of my doubts and providing ideas to improve the project step by step.

Thanks to my family for being the power to carry on despite the difficulties. Especially I want to thank my mum for always being beside me.

Finally, but not less important, infinite thanks to all the people, classmates, and friends who have accompanied and helped me in the process during this trip.

INDEX

FIGURES INDEX:

1. ABSTRACT

Title: SCHOOL-SUPERVISED ASTHMA CONTROLLER STRATEGY: Association between a new asthma management strategy and the number of emergency department visits or hospital admissions due to asthma.

Background: Asthma is a very common chronic respiratory disease present worldwide and affecting all age groups. Prevalence among children in Spain is around 10% but its mortality levels are low. Adherence is defined as the ability of a patient to follow correctly the agreed treatment and change its daily habits. Education is a main factor to achieve good adherence levels in chronic diseases. The lack of adherence implies a sustained pro-inflammatory status, more symptomatology, increased risk of exacerbations, progressive loss of lung function and a subsequent huge amount of direct and indirect costs.

Aim: To analyze the effect of a new asthma treatment strategy based on school-supervision in which patients will have their controller medication during school time and under the supervision of their teachers. This strategy is expected to reduce the number of emergency department visits and admissions to hospital due to asthma worsening, since these features weigh greatly on asthma-related expenses and the use of sanitary resources.

Methods: A prospective multicenter clinical trial will be performed following 186 patients diagnosed with asthma and the need for inhaled corticosteroid at a low or moderate dosage as controller medication. All Hospitals in Girona Province will participate in this study. Patients will be collected in a combination of cluster and consecutive sampling methods and will be divided into two groups, the intervention and the control group. Intervention: Both groups will be informed equally of all non-pharmacological strategies for asthma management. The intervention group will follow the school-supervised treatment strategy. Outcomes: Asthma control level, ACT score, and the number of total exacerbations, emergency department visits and hospital admissions will be assessed during intervention time. At the end, statistical analysis of collected data will be performed, taking into account all covariables, using multiple regression models.

Key words: asthma, controller medication, stepwise strategy, inhaled corticosteroids, adherence, exacerbation, asthma control test, school-supervised strategy, sanitary resources, and asthma-related expenses.

2. ABBREVIATIONS

ACQ: Asthma Control Questionnaire.

ACT: Asthma Control test.

AE: Asthma Exacerbation.

AH: Admissions to Hospital.

ASM: Airway Smooth Muscle.

C-ACT: Childhood Asthma Control Test.

CEIC: Clinical Research Ethics Committee.

ECM: Extracellular Matrix.

ED: Emergency Department visits.

FeNO: Fractional Exhaled Nitric Oxide.

FEV_1: Forced Expiratory Volume in the first second.

FEV_1/FVC: the relation between Forced Expiratory Volume in the first second and Forced Vital Capacity.

FVC: Forced Vital Capacity.

GEMA: Guia Española para el Manejo del Asma.

GINA: Global Initiative for Asthma Management.

GRANMO: Sample Calculator.

ICS: Inhaled Corticosteroids.

LABA: Long-acting β_2-agonist.

LTRA: Leukotriene Receptor Antagonist.

NO_2: Nitrogen dioxide.

SABA: Song-acting β_2-agonist.

SO_2: Sulphur dioxide.

SPSS: Statistical Package for Social Science.

3. INTRODUCTION

Asthma is a heterogeneous disease, usually characterized by chronic airway **inflammation** and bronchial **hyperreactivity**. It is defined by the history of several respiratory symptoms such as wheezing and coughing that vary in intensity and over time. It is also described by variable expiratory **airflow limitation**, totally or partially reversible, that may later become persistent. (1,2)

3.1. PREVALENCE

Asthma is a major chronic respiratory illness that has a universal geographical distribution and affects all age groups but its prevalence varies markedly worldwide, ranging between 2% in Estonia and 11'9% in Australia (3,4).

The mean prevalence of childhood asthma in Spain is 10%, similar to the European Union mean prevalence, (5,6) but now the number of asthma patients is increasing over time (7). In our country, this heterogeneity in asthma distribution is also seen, as prevalence is higher in coastal areas, for example, in Barcelona it is three times higher than in Huelva (8). The total number of asthmatic patients is also increasing over time.

3.2. PATHOPHYSIOLOGY

The most important pathophysiological characteristics of asthma are the chronic inflammation of the whole airway system, associated with epithelium hyperresponsiveness to direct or indirect stimuli and the consequent bronchoconstriction that leads to an expiratory airflow limitation and respiratory symptoms appearance.

The chronic inflammation of the airway is the common pathological characteristic among all asthma phenotypes and is always present, but it is not necessarily well correlated with patient's symptomatology (9).

Both humoral and cellular immunity are involved in the immunopathophysiology of asthma and provoke chronic airway inflammation. A combination of immune response and an underlying genetic predisposition is needed for inflammation to produce the subsequent airway edema, mucus hypersecretion and airway remodeling (10).

The main immune cells involved in the inflammatory response are T helper lymphocytes (Th) type 1, 2 and 17, with a predominance of Th2. These cells lead the eosinophilic inflammation producing interleukin that stimulates B lymphocytes increasing IgE production (10).

Other immune cells play an important role in inflammation response as can be mast cells that induce bronchoconstriction and also produce proinflammatory factors such as histamine or D2 prostaglandin (11). Eosinophils are involved to by amplifying the inflammatory response (12).

Apart from inflammatory response, when the airway epithelium interacts with external agents such as allergens, viruses, pollutants or tobacco smoke; some changes occur throughout the epithelium, the airway smooth muscle (ASM) and the extracellular matrix (ECM). These changes include infiltration of immune cells, hypertrophy and hyperplasia of the ASM cell layer, a thicker and increased amount of mucus and a thickening of the epithelium with globet cell hyperplasia, and ECM remodeling and increased angiogenesis and fibrosis (13,14). These different structural changes are known as airway remodeling.

Bronchial Hyperresposive is another important factor in asthma pathophysiology and it is defined as an exaggerated response to some agents, innocuous to persons without asthma, that produces excessive constriction of ASM and changes in the nervous system (15). This hyperreactivity is related to airway remodeling, inflammation response, and asthma severity (16); and usually it is partially reversible with treatment.

All these pathophysiological factors described above produce structural changes that lead to an expiratory airflow limitation that can explain asthma symptoms. This airflow limitation can be resolved spontaneously or as drug response. However, clinical features may not be always present, and patients could have relatively long periods without symptoms.

3.3. RISK FACTORS

It is very important to distinguish between those risk factors related to asthma development and those other factor that can trigger asthma symptoms.

Several genetic factors are involved in asthma's pathophysiology (17) in different ways. For example, some genes are related to a higher production of total IgE levels and bronchial hyperreactivity (18). Also, other genes have a role in modulating other risk factor mechanisms or can be associated with individual treatment response (19).

There are several factors involved in asthma developing more related to the host and others more related to environmental agents. Some of them modulate the role of other risk factors. Genes are likely to interact with other genes and with environmental factors to determine asthma susceptibility (20,21).

The host's most important risk factors are genetics, sex, obesity, pre-term, atopy and more:

- Sex-related prevalence differences are greatly associated with age. In childhood, prevalence is greater in boys (22). And once patients grownup, women are more likely to have asthma. These differences are not very well known, one possibility is lung and airway size and growth differences between boys and girls (23,24).
- Obesity and especially women abdominal obesity is an important risk factor (25). Because of changes in airway function or the obesity's subsequent proinflammation status (26).

A lot of environmental factors seem to play a role in asthma development. Some can trigger asthma symptoms but other factors, depending on time exposure, can both be protective asthma developing factors or triggering factors. This phenomenon is seen with cats or dogs exposure (27–29). However, in this relationship between environmental factors and sensitization, a lot of other factors are involved such as allergens, the dose, the time of exposure, the child's age, and genetics. Most important environmental factors are:

- Allergens: several allergens are involved in both asthma development and precipitation of the symptomatology. Furthermore, most of them are very common in the house such are dust mites, mold and pet allergens.
    - Mold: For children at risk of asthma, dampness, visible mold and mold odor in the home environment are associated with an increased risk of asthma (30).
    - Dust Mites: in this case, the prevalence of sensitization has some evidence to be directly correlated with the exposure as a causal factor in the development of asthma (31–33).
    - Pets: some studies suggest an increased risk of allergic sensitization after pet exposure. But it is not really clear, as other studies have found no differences (34).

- Infections: a theory called "hygiene hypothesis" has been proposed in which early-life exposure to infections is related to a reduced asthma incidence and lower prevalence of other allergic diseases (35). Children with older siblings are more likely to have infections and also less likely to develop an allergic-related disease (36–38).
  Viruses are also important asthma triggering factors, especially rhinovirus.

- Tobacco smoke: another important factor is the exposure to tobacco smoke both prenatally and after birth. Mothers smoking during pregnancy have some effect on fetus' lung development, and as infants, they are more likely to have wheezing illnesses (39). Tobacco smoke exposure, known as passive smoking, increases the risk of asthma in childhood (40,41).

- Pollution: Exposure to a polluted environment, rich in NO_2, SO_2 or ozone (42); produces reduced lung growth and consequently low lung function (43) and higher asthma morbidity (44).

3.4. DIAGNOSIS

In order to diagnose a child with asthma, the physician need a combination of a history of symptoms explaining typical clinical features such as wheezing, and also, a lung function test that prove both expiratory airflow limitation and its reversibility.

As there are many differences between adults and child asthma diagnosis, from here below we will focus on child features.

3.4.1. CLINICAL FEATURES

There are some signs and symptoms known as alarm symptoms or guide symptoms that help the physician to create a pattern to evaluate the patient. These symptoms are: wheezing, shortness of breath, coughing and chest tightness Often these symptoms vary over time and in intensity, also can be worse at night or in the early morning. However, none of these symptoms are specific for asthma (45).

ANAMNESIS: During anamnesis, it is very important to ask about the commencement of respiratory symptoms, personal history of allergic rhinitis or eczema, and family history of asthma or allergy. These factors increase the probability of the aforementioned symptoms to be related to asthma.

In children younger than 5 years old, it is even more complicated to establish a diagnosis. That is why further anamnesis is needed to assess the probability of asthma in a child with wheezing (46).

Assessing the pattern of symptoms during and between respiratory viral infections is helpful in order to determine the probability of asthma (47).

These following factors are used to calculate the estimated probability of asthma diagnosis (48,49).

- Symptoms such as coughing, wheezing or heavy breathing for more than 10 days during upper respiratory tract infection.
- More than 3 episodes per year.
- Severe episodes and/or night symptoms worsening.
- Symptoms between episodes when doing exercise or laughing.
- Presence of risk factors (allergic sensitization, family history, ...).
- Therapeutic response to controller treatment.

PHYSICAL EXAMINATION: Often patients with asthma have a strictly normal physical exploration except for some wheezing or rhinitis. In children, wheezing is an important sign but difficult to assess in early childhood, since the lung function test is a challenging examination for patients younger than 6 years old (50).

3.4.2. LUNG FUNCTION TESTS

A patient with suspected asthma, who meets all clinical features, usually is not diagnosed until a lung function test demonstrates, objectively, an expiratory airflow limitation.

Assessing asthma diagnosis in children younger than 5 years old with lung function tests is very difficult, due to the inability of young patients to perform these tests and the need for adequate reference values (51,52).

In children, lung function tests are less useful than in adults because the majority of children with asthma, even those with moderate or severe asthma, have values of FEV_1 in a normal range. (53,54). These tests could help in asthma diagnosis in children but have little power discriminating according to severity. (55).

In children aged 6 or older, it's possible to start performing forced spirometries carried out by expert physicians and adequate equipment (56,57).

Of all lung function tests available, most used in asthma children diagnosis are:

SPIROMETRY: This is the most used in asthma diagnosis, follow-up visits, and asthma control assessment. Spirometry gives information about airflow obstruction. The main parameters to determinate are both forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC), and also the ratio FEV_1/FVC.
A reduced score in FEV_1 demonstrates obstruction and helps to assess asthma severity and risk of exacerbation (24). But since FEV_1 can be found to be diminished in many other lung pathologies, the ratio FEV_1/FVC is widely used in diagnosis to define the obstruction when values obtained from spirometry are lesser than 0.90 (58) or 0.80-0.85 depending on reference study (2).

BRONCHODILATOR TEST: To complement information and achieve asthma diagnosis, it's very useful to carry out spirometries before and after bronchodilator administration, such can be salbutamol 200-400 mcg (24). This test evaluates the obstruction's reversibility defined as rapid improvement in spirometry parameters.
Values of reversibility that define a positive bronchodilator test are an increment of FEV_1 score greater than 12% and 200mL with respect to basal spirometry (24). But in children, just with the increment of FEV_1 being greater than 12%, it's possible to establish asthma diagnosis even if it's below 200mL (2).

PROVOCATION TEST: One option to assess airway hyperresponsiveness, when physicians have doubts when diagnosing children, is to refer patients for the provocation test (59).
Methacholine provocation test and post-exercise spirometry used in diagnosis, have moderate sensibility but limited specificity (59,60).

ALLERGY TESTS: The purpose of allergy evaluation consists of allergic asthma phenotype determination, as this can determine asthma evolution and risk of exacerbations. Both the prick tests and total and specific IgE determination can be done. But all allergy results must be well evaluated and related to symptoms in order to verify the clinical relevance of these results. (61).

OTHER TESTS: During asthma diagnosis, other tests can be performed to obtain more information about patients' status such as sputum analysis, fractional concentration of exhaled nitric oxide (FeNO) or peak flow variation, but have less weight in asthma diagnosis (62–64).

3.5. EXACERBATIONS

A great proportion of asthma patients occasionally have attacks known as exacerbations. Exacerbations are characterized by a progressive increase in symptoms and/or worsening of lung function, and usually need a change in the treatment (65,66) These episodes can occur both in patients with or without a previous diagnosis of asthma.

Asthma exacerbations (AE) are more often in patients with severe asthma but can appear in all asthmatic patients (67). These episodes are usually due to a combination of different factors: exposure to a trigger external agent, a poorly controlled asthma, low treatment adherence, ... but sometimes no triggering factor can be associated (68). Mainly factors related to AE, known as triggering factors, are:

- Viral respiratory infections.
- Allergen exposure.
- Food allergy.
- Outdoors air pollution.
- Seasonal changes and/or return to school.
- Poor adherence to medication.

3.5.1. DIAGNOSIS

An increased frequency of symptoms is a measure used in exacerbation diagnosis and it is more sensitive than other lung function tests and can be explored faster.

If we focus on establishment speed, most AE follow a pattern of a slow establishment. Usually, this process takes a few days or even weeks. But less frequently, these episodes are very acute with a status worsening in just 3 hours. And is very important to distinguish one from another, as the causing triggering factor and treatment will be different (69,70).

Severe AE could lead to a fatal ending. Therefore it's very important to know which factors are related to a greater risk of life-threatening asthma exacerbation in order to refer patients to the hospital faster for intensive care.

A sum-up of the most important factors is: hospital treatment required in the last year (71), bad treatment adherence or selection (71–73), and psychological or psychiatric related disease (73).

3.5.2. SEVERITY

Once all information about patient status is obtained, as can be clinical features, physical examination and monitoring; severity classification can be determined as it's important to assess the best treatment choice.

Three grades of severity can be distinguished according to Guía Española par el Manejo del Asma and are summarized in the following table:

Figure 1. Asthma exacerbation's severity classification

SEVERITY CLASSIFICATION	MILD EXACERBATION	MODERATE-SEVERE EXACERBATION	EXTREMELY SEVERE EXACERBATION
DYSPNEA	Mild	Moderate-severe	Extremely severe
SPEECH	Sentences	Words	
RESPIRATORY FREQUENCY	Increased	>20-30	
CARDIAC FREQUENCY	<100bpm	>100-120bpm	Bradycardia
CHEST TIGHTNESS	Absent	Present	Paradoxical movements
WHEEZING	Present	Present	Silent chest
CONSCIOUSNESS LEVEL	Normal	Normal	Diminished
PULSUS PARADOXUS	Absent	>10-25 mmHg	Absent (muscle fatigue)
FEV_1	>70%	<70%	
$SatO_2$	>95%	90-95%	<90%
PaO_2 (mmHg)	Normal	80-60 mmHg	<60 mmHg
$PaCO_2$ (mmHg)	<40 mmHg	>40 mmHg	>40 mmHg

All information has been extracted from GEMA guidelines (CITAR GEMA).

3.5.3. EXACERBATION TREATMENT

Once we have assessed the patient's exacerbation severity, immediate treatment must be administered to stop the evolution and prevent subsequent complications. Asthma patients should be provided with a written asthma plan that inform about self-management exacerbation assessment and treatment.

In mild exacerbations, the patients usually are able to recognize the symptoms worsening early and thus start the subsequent treatment immediately. The preferred strategy is based on increasing reliever medication dose and frequency. In the action plan, it is also important to inform about when and how OCS therapy should star, if needed, and when to access medical care.

Those patients with severe exacerbations will need multiple hospital treatment usually administered concurrently in order to achieve quick improvement. Most used therapies are O_2 administration, OCS, SABA and ipratropium bromide.

3.6. CHILDHOOD ASTHMA CLASSIFICATION

Asthma in adults has some characteristics that are not reproducible in children, that is why a different classification of asthma severity has been published by GEMA.

In children, often the asthmatic status is defined by sporadic attacks, more or less severe, and very little symptoms between exacerbations. The need for reliever medication, the symptoms pattern and lung function tests are the main parameters to determine the severity and are listed in the following table:

Figure 2. Classification of asthma severity in children. (Information extracted from GEMA guidelines)

ASTHMA SEVERITY	EPISODICAL & OCCASIONAL	EPISODICAL & FREQUENT	MODERATE & PERSISTENT	SEVERE & PERSISTENT
EPISODES CHARACTERISTICS	A few hours/days Max. 4-5/year and <1 each 4months	Max 6-8/year and <1 each 5-6weeks	More than 1 each month	Frequent
SYMPTOMS BETWEEN EPISODES	Asymptomatic	Asymptomatic	Mild	Frequent
WHEEZING	-	Only when intense effort	If moderate effort	Even when mild effort
NIGHT SYMPTOMS	-	-	≤ 2nights per week	> 2 nights per week
RELIEVER MEDICATION	-	-	≤ 3 days per week	> 3 days per week
LUNG FUNCTION TEST (FEV_1)	>80%	>80%	70-80%	<70%

3.7. ASTHMA MANAGEMENT & TREATMENT

The main goals of asthma management must be focused on current status control and worsening prevention. The optimal treatment should provide a good quality of life, where asthma symptoms don't keep patients from exercise, and no need for reliever medication. The aim must be also the assessment and prevention of future AE, and also help the patient's lung function to stay in a normality range.

Another very important aspect of asthma management is the patient and physician team-working. In asthma treatment strategy it has been seen that self-management education in asthmatic patients reduces morbidity in children and adults (74). A good communication between health care provider and the asthmatic patient environment is necessary (77) to achieve better outcomes, as can be a better patient treatment adherence (75) and reduce unnecessary use of health resources (76). Patients and parent's expectations have to be also taken into account during asthma assessment and treatment strategy selection.

3.7.1. NON-PHARMACOLOGICAL STRATEGIES

Before choosing between one or another drug to treat asthma symptoms and prevent exacerbations, there are a lot of habits and recommendations very useful to assist asthma management.

In general, these recommendations are focused on triggering factor avoidance.

1) EDUCATION: Educating patients about asthma management is an essential piece in treatment strategy (78), and has some benefits like lower risk of exacerbations or better quality of life (79).

If patients are well trained for using inhaler devices it can lead to better asthma control in children (80). Often, most patients don't know they are not doing the inhalation correctly, sometimes because the physician's demonstration is insufficient (81) and this implies inadequate asthma control (82).

2) TOBACCO AVOIDANCE: Passive smoking is a factor that increases the risk of asthma-related hospitalization and poor asthma control. But since the smoking-free area's legislation has been applied (44), we have enough evidence to support that tobacco smoke exposure cessation enhance asthma control and reduces hospitalization (83), and smoking cessation can improve bronchial inflammation status (84).

3) AVOIDANCE OF INDOOR ALLERGENS: It's very difficult sometimes to establish measures to avoid those substances that affect patient's asthma because multiple factors are involved and patient reactions can depend on other multiple factors. A great number of studies have been published discussing this topic, some of them have evidence on allergen levels reduction but only a few of them demonstrate the clinical relevance of these measures.

Most evidence recommendations are: encase bedding in impermeable covers (85), cockroach baits placed in the household (86), and rodent related integrated pest management strategies (87).

4) DIETARY-HYGIENICAL RECOMMENDATIONS: Other measures that can help the patient to feel better and have a good asthma control level are those related to diet and physical activity. They have no direct impact on asthma improvement but are very important in terms of general health as they can help the patient to feel better.

Physical activity is known to be an important triggering factor of exercise-induced bronchoconstriction. But progressive and continued moderate physical activity helps the patient improve cardiorespiratory fitness, and swimming more than any other sports seems to have a positive impact.

And as for diet, a high intake of fruit and vegetables is basic for healthy status. But it's important to remark that obesity is an important factor in asthma control (88), as it reduces the response to drugs (89) and lung function is improved by weight loss.

3.7.2. PHARMACOLOGICAL TREATMENTS

Asthma pharmacological treatment is the main pillar of asthma management but it's very essential to follow a consensual action plan between the patient and the physician to determine the main objectives to be achieved and the best way of doing it.

ROUTE OF ADMINISTRATION: In asthma management, drugs are wanted to act locally in the airway to give a faster response, a greater amount of drug in lung cells and lesser or null systemic effects. That's why the preferred route of administration is the inhaled therapy reporting better results than other routes but have some inconveniences associated, as could be the technical difficulty of inhalation (90,91) or oral and gastrointestinal side-effects.

Inhalation devices are used correctly for the majority of adult asthmatic patients. But in children, the coordination required during inhalation is difficult to achieve and drug intake is inaccurate, and all these factors prompt less gain from prescribed treatment (92,93).
Different kinds of inhalers exist but all of them have similar results when used correctly. (94).

To improve inhaler efficacy it must be accompanied by a spacer device that increases distribution and total drug amount in the lung, decrease oropharyngeal deposit and avoids coordination needs (95).

DRUG OPTIONS: Of all drug options, the most used are the following ones:

- INHALED CORTICOSTEROIDS: ICS are the most effective anti-inflammatory medications for the treatment of persistent asthma and decreasing airway hyperresponsiveness too, also in children (96). ICS reduce symptomatology, also the number and severity of exacerbations (97) and improves lung function and quality of life (98). Even at low-ICS dosage, these drugs obtain quick results in symptoms improvement (99) and are able to achieve a good level of asthma control in mild asthma (100). Some side-effects have been reported from ICS treatment especially in daily use and in moderate or high doses, such can be: growth retardation (101), oral candidiasis (reduced if spacer use) and, less frequently, neurological effects.

- INHALED β-ADRENERGIC AGONIST: Exist two main forms of β-adrenergic agonist those with quick response time and others with longer effectiveness time, known as short-acting inhaled β_2-agonists (SABA) and long-acting β_2-agonist (LABA) respectively.
  SABA are usually prescribed for bronchospasm treatment during exacerbations (102) and to prevent exercise-induced bronchospasm. Otherwise, LABAs are often used as ICS sparing treatment in ICS/LABA combination devices, achieving the same results in exacerbation decreasing ratio in front of ICS therapy but with just a quarter part of ICS needed (103).
  In younger children, SABA have as good results as in adults but LABA seems to have fewer benefits as add-on drug than in adults (104).

- LEUKOTRIENE RECEPTOR ANTAGONIST: Leukotriene modifiers are frequently used as add-on therapy together with ICS reducing corticosteroid dose requirements (105). This combination therapy reduces severe asthma exacerbations and improves asthma control levels but with worse results compared with LABA add-on therapy (106).

- ORAL CORTICOSTEROIDS: In some situations, the use of systemic corticosteroids is needed to stop the progression of severe exacerbation, and this helps reducing hospital admissions and morbidity. And when an exacerbation is resolved, symptoms have disappeared and lung function is normal, the OCS therapy must be stopped, even abruptly if this period has been shorter than 2 weeks.

3.7.3. ASTHMA MEDICATION CATEGORIES

In asthma treatment, there are a lot of drug options, even more than those explained above, and it's important to classify them to understand the purpose of each treatment. Most of them are classified in one of these three categories:

- **RELIEVER MEDICATION:** also called rescue medications, are usually used only as-needed when symptoms worsen or during exacerbations. But are also recommended for the pre-exercising time in order to prevent exercise-induced bronchospasm. This kind of medication is very useful for its very fast response time, but it's important to reduce the need for reliever medication as this would reflect a good asthma control level.

- **CONTROLLER MEDICATION:** These drugs are used to impact on asthma's pathophysiological pathways even though they don't cure asthma. Many drugs reduce inflammation of airways and also exacerbation risk, and help control symptomatology. Usually, they are prescribed often for daily use, especially in children, or as-needed in the case of ICS-formoterol therapy.

- **ADD-ON THERAPIES:** The combination of more than one drug is much used in asthma management most usually as ICS sparing treatment. They are often used when patients have persistent symptoms even at a high dosage of controller medication and modifiable risk factors have been treated.

3.7.4. CONTROL-BASED ASTHMA MANAGEMENT

Initial controller treatment based on ICS must be started just after asthma diagnosis, as soon as possible, because a quick improvement has been demonstrated in the patient's quality of life and also better future asthma control levels.

Both pharmacological and non-pharmacological treatments must be adjusted for each patient continuously with a cycle of assessment, adjustment and review. This means to individualize treatment strategy for each patient, and this conduces in better results in asthma outcomes (107) such as fewer exacerbations (108).
It's very important to take into account, in asthma assessment, both symptom control and risk of exacerbation to provide the best treatment possible.

3.7.5. STEPWISE TREATMENT STRATEGY

Once we have assessed and diagnosed our patient and we have chosen the first controller medication we must assure this cycle of assessment, medication adjustment and symptoms review.

The ideal goal must be to achieve a good level of symptom control, with the lower exacerbation risk possible and as little controller and reliever medication as possible. So controller medication can be adjusted to a higher or lower dose, add on more complementary medication, ...

GINA has published a stepwise personalized management protocol, with steps from number one to number five, with progressive increasing treatment power. There are two different infographics published depending on age group, first one for adolescents and adults (Figure 3), and the second one for children from 6 to 11 years old (Figure 4).
These following images summarize all information about reliever and controller medication in each step, with preferred options and other possible treatments.

Figure 3. Stepwise strategy for children +12yo and adults

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Preferred **CONTROLLER**	As needed low dose ICS-formoterol	Low dose ICS **or** as-needed low dose ICS-formoterol	Low dose ICS-LABA	Medium dose ICS-LABA + expert refer	High dose ICS-LABA + Refer to expert assessment + add-on therapies or OCS
Other options	Low dose ICS when SABA	LTRA **or** low dose ICS when SABA	Medium-dose ICS **or** Low dose ICS-LTRA	High dose ICS, add-on LTRA or others	
RELIEVER	*Preferred*	As-needed low dose ICS-formoterol			
	Alternative	As-needed SABA			

Information extracted from Global Initiative for Asthma 2019

Figure 4. Stepwise strategy for children from 6 to 11 years old

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Preferred **CONTROLLER**	-	Low dose ICS	Low dose ICS-LABA **or** medium-dose ICS	Medium dose ICS-LABA + expert refer	Refer to expert assessment + add-on therapies or OCS
Other options	Low dose ICS when SABA	LTRA	Low dose ICS-LTRA	High dose ICS-LABA, add-on LTRA or others	
RELIEVER	As-needed SABA				

Information extracted from Global Initiative for Asthma 2019

3.8. ASTHMA ASSESSMENT AND CONTROL

All asthma patients are different, and asthma affects each patient differently. So assessment of asthma patient, symptomatology and lung function test, and the subsequent treatment must be individualized.

Usually, the assessment of asthma includes asthma's symptoms control level and future exacerbation risk, the inhaler technique and treatment adherence. It's important to evaluate the patient's baseline status and how symptomatology is reduced or removed by treatment strategy. And most important factors involved in this process are genetics, disease evolution time, the treatment prescribed, environment and psychosocial factors (109). Lung function is important too to assess the future risk of exacerbations.

In order to assess the control level of the patients a lot of tools have been created and validated in multiple languages. Well-known numeric tools are the asthma control questionnaire (ACQ) (110) and the asthma control test (ACT) (110), and both ask for symptoms questions and reliever use, in addition ACQ-7 compares pre-bronchodilatation FEV_1 values and ACT includes a question about self-assessment of asthma control level.

In children, it is a little more complicated to assess the control level since they take longer to complain about asthma worsening. Some children avoid being exposed to those triggering factors as can be exercise and consequently they seem to be well controlled. In asthma control assessment, it is important to collect information from both parents and patients. The childhood asthma control test (c-ACT) (111) has been elaborated with divided sections for patients and parents to complete.

3.9. ASTHMA TREATMENT ADHERENCE

Adherence with medication is defined as the degree of taking the treatment, as agreed by physicians and the patient. At least, half of adults and children asthma patients forget to take medication some part of the time (112), and this can lead to a sustained inflammatory status and elevated risk of exacerbations. Some interventions are being developed to improve adherence levels (113).

To identify a patient with a low adherence level is very difficult and most of the times it's only possible to assess it with good communication skills and asking directly about it. Other ways to assess patient's adherence are pharmacist records or electronic inhaler monitoring (114).

The majority of patients initially have a good treatment adherence but they don't follow the treatment due to scheduling difficulties with clinicians or prescription continuity problems. And this is very common in ICS treatment (115,116).

Some studies have assessed treatment adherence in asthma controller medication in children and the main treatment adherence degree was 48% (117). And a low degree of adherence is a very important factor in asthma control evaluation. (118–120).

These patients, as a result of this poor adherence, have more risk of future exacerbations, and ED visits and admissions to a hospital (121). This means an increase in sanitary resources use, more expenses, and worse asthma status.

3.9.1. POOR-ADHERENCE FACTORS

Most important factors involved (122) are summarized in the following table:

Figure 5: Factors involved in poor treatment adherence

TREATMENT-RELATED	CLINICAL-RELATED	PATIENT-RELATED
Complex treatment schedule	Difficulties in scheduling appointments	Poor understanding of disease treatment
Inhaler use difficulty	Lack of empathy and interest from clinician	Lack of trust in healthcare professionals
Lack of an immediately discernible beneficial effect	Rotating physicians	Psychological or psychiatric problems
Adverse effects	Lack of feedback time	Social issues such as poverty
Cost, reimbursement problems	Lack of inhaler technique assessment	Illness perception and medication beliefs

4. JUSTIFICATION

Asthma is a very common chronic respiratory disease present worldwide and affecting all age groups. Asthma prevalence is increasing in many countries, especially among children, and in Spain, it has exceeded the 10% threshold. If this growth trend is followed, in 2025 it's estimated that the asthmatic population around the world will increase by 100 million, becoming the most prevalent chronic respiratory disease in childhood (123).

The impact of asthma is variable, affecting each patient differently, so individualized assessment and management must be required. All patients must be followed-up periodically by experts to achieve the best control with the least medication possible.

Once both the patient and the clinician have agreed on the treatment strategy, it's very important to ensure that the patient uses their controller medication with a correct intake technique and don't forget any dose. This ability to change daily-life routines and follow the treatment strategy prescribed is known as treatment adherence.

The lack of treatment adherence, a very common characteristic in chronic patients, is usually a complex and occulted problem. Poor adherence has a very important impact on patients' disease direct and indirectly. Poor adherence decreases the treatment's effectiveness, resulting in the persistence of symptoms and poor quality of life, and most importantly increasing the number of exacerbations and the severity of these.

An increase in emergency department visits and admissions to hospital due to low treatment adherence level has been reported, and an increase of those near-fatal episodes. This affects the patient's health directly and weighs greatly on asthma-related expenses and the use of sanitary resources.

One in every five asthma patients has exacerbations that need an emergency department visit or hospitalization in the past year (124), which represents more than 80% of the total direct expenses associated with asthma (125). In Spain, these expenses amount to 532 million Euros per year in children younger than 16yo (126).

There are no studies in our country studying this treatment strategy but in other countries similar interventions have achieves great results. Every strategy focused on improving adherence and consequently decreasing the risk of future exacerbations could help a lot in decreasing national health resource expenses.

5. HYPOTHESIS

5.1. MAIN HYPOTHESIS

The administration of asthma controller medications supervised by teachers or school tutors during school time could help to decrease the number of emergency department visits (ED) or admissions to hospital (AH) because of asthma exacerbations, as a result of better controller treatment adherence in school and high-school children from Girona.

5.2. SECONDARY HYPOTHESIS

- A new controller treatment strategy involving teachers or school-tutors that supervise the controller medications intake could decrease the total number of exacerbations by improving treatment adherence.
- School-supervised asthma treatment might improve children's asthma control levels, with better ACT scores.

6. OBJECTIVES

6.1. MAIN OBJECTIVE

Analyze if the administration of asthma controller medications supervised by teachers or school-tutors during school time reduces the number of ED visits and admissions to hospitals because of asthma exacerbations of children from 6 to 16 years old from Girona during one scholar year, by improving treatment adherence assessed with pharmacological reports

6.2. SECONDARY OBJECTIVES

- Determine if this school-supervised asthma control strategy could decrease the total number of exacerbations by improving children's treatment adherence, assessed with pharmacological reports.
- Study if the administration of asthma controller medications, supervised by teachers at school, improve subjective asthma control level, noticing fewer symptoms and limitations, measured with ACT.

7. METHODOLOGY

7.1. STUDY DESIGN

This study is designed as a prospective, multicenter, pragmatically randomized clinical trial with parallel groups.

Patients diagnosed with asthma that need inhaled corticosteroids at low or medium dosage as controller therapy will be randomly assigned in a 1:1 ratio to be either in the intervention or in the control group. The intervention group will follow the school-supervised asthma control therapy and the control group will follow the standard recommendations of the GINA and the GEMA.

The duration of the intervention will be one school year from September to June. Control appointments will be scheduled at the sixth month and at the end of the school year.

7.2. STUDY SUBJECTS

The target population of this study is children aged from 6 to 16 years old diagnosed with asthma and need of inhaled corticosteroids at low or medium dosage as controller medication. ICS must be prescribed for a once-daily use and by a physician from one of the hospitals in Girona Province: Blanes, Calella, Campdevànol, Figueres, Girona Olot, Palamós i Salt.

7.2.1. INCLUSION CRITERIA

- Patients aged from 6 years old to 16 years old, diagnosed with asthma defined as a positive history of respiratory symptoms and a variable expiratory airflow limitation confirmed with lung function tests.
- Patients with asthma diagnosis and classified as Step 2 or Step 3 of the stepwise treatment strategy published in GINA asthma guidelines.
- Patients must be treated with ICS at low or medium dosage as usual controller medication.
- Controller medication has to be prescribed for once-daily use.
- Controller medications must be prescribed by a physician from a hospital in Girona Province.

7.2.2. EXCLUSION CRITERIA

- Patients diagnosed with asthma but need no controller treatment or use a combination of ICS-formoterol as both controller and reliever medication
- Patients that need more than one dose of controller drug daily, high dose ICS or sparing corticosteroid treatment.
- Patients with concomitant severe morbidity or disease.
- Patients with allergy to inhaled corticosteroids.
- Patient with other pharmacological active treatment.
- Patients studying in a school not listed on the participating schools list.
- Patients without the informed consent sheet signed.

7.3. SAMPLING AND SAMPLE SIZE

7.3.1. SAMPLING

Our sampling will consist of a combination of a probabilistic cluster and a consecutive sampling. Of all hospitals in Girona province, six hospitals will be randomly selected and assigned to the control or the intervention group. Schools located in the same city of the intervention hospitals will be asked to confirm their participation. Afterwards, the consecutive sampling of study subjects will start. All asthmatic children from intervention hospitals, studying in a school of our participating school list, will be invited to participate in the study. We will assess if they meet all the inclusion criteria and none of the exclusion criteria.

7.3.2. SAMPLE SIZE

To calculate the sample size we used the GRANMO software. Our main dependent variable will be the number of either AH or ED visits during study time. The group ratio will be 1:1.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, we need 93 patients in the first group and 93 patients in the second group, with 186 patients in total; to detect a statistically significant difference in the proportion of patients that need ED or AH between the randomized groups, that we estimate as 0.2 in group B and 0.05 in group A. A follow-up loss rate of 25% has been estimated.

7.4. VARIABLES

7.4.1. INDEPENDENT VARIABLE

The intervention of our study will be the controller treatment strategy.

The first group will follow standard recommendations for controller medication, usually administrated by the patient's parents. This group will be identified as the control group.

The second group will follow the school-supervised controller treatment strategy where the patient's school tutor or teacher will administer or supervise the controller drug. This group will be identified as the intervention group.

This is considered a dichotomous qualitative variable.

7.4.2. DEPENDENT VARIABLE

The main dependent variable of this study is the proportion of patients with either admissions to hospital or ED visits due to asthma worsening.

Main dependent variable is a dichotomous qualitative variable.

7.4.3. SECONDARY DEPENDENT VARIABLES

Other secondary variables studied are:

- Patient's subjective evaluation of symptoms' control using a questionnaire called Asthma Control Test (ACT) for patients older than 11 years old and the Childhood Asthma Control Test (C-ACT) for those from 6 to 11 years old. These test results will be classified into two different ranges assessing the probability of a well or poorly controlled asthma.
  - ACT or c-ACT score of 19 or less: asthma may not be well controlled.
  - ACT or c-ACT score of 20 or more: good asthma control levels. (111)

  This will be treated as a dichotomous qualitative variable.

- The number of exacerbations, defined as an acute or sub-acute worsening of asthma symptoms. This is a discrete quantitative variable.

7.4.4. COVARIABLES

Since the sample will be randomized, there will be no confounders.

But as the randomization will be done in each hospital, there can be a difference between hospitals so the possible residual confusions will be controlled.

We will collect the baselines characteristics of patients to obtain epidemiological and clinical data at the beginning of the study, such as:

- Age: (years, quantitative discrete).
- Sex: (male/female, qualitative dichotomous).
- Age of diagnosis: (years, quantitative discrete).
- Baseline FEV_1: (%, quantitative continuous).
- The number of total exacerbations in the past year: (nº, quantitative discrete).
- Admissions to the hospital in the past year: (nº, quantitative discrete).
- ED in the last year: (nº, quantitative discrete).
- ACT score at baseline: (<20 or ≥ 20, qualitative dichotomous).
- Asthma controller and reliever treatment used: (qualitative).

7.5. STUDY INTERVENTIONS

7.5.1. PATIENTS SELECTION AND RANDOMIZATION

The participant hospitals of the study will be randomly divided into two groups, in a 1:1 ratio, performed according to a randomization list generated by nQuert Advisor 7.0 (Statiscal Solutions Ltd., Cork, Ireland), to have 3 hospitals in each group. After that, schools in the same city of the hospitals that are in the intervention group will enter the study. Afterwards, a consecutive sampling will be performed to recruit study subjects.

- Group A: this group will follow the school-supervised asthma controller treatment strategy.
- Group B: this group will follow the standard recommendations about controller treatment.

7.5.2. STUDY INTERVENTIONS

After the recruitment of patients who meet all the inclusion criteria and none of the exclusion ones, they will be informed about which strategy they must follow:

- Group A: this group will continue their usual controller treatment once-daily but it will be administered in their school and supervised by their school-tutor or teacher during school time each day at the same hour. Teachers will be well trained by an inhaler devices expert, and informed about how to act in different scenarios. Those non-school days, treatment will be administered and/or supervised by patients parents or caregivers.
- Group B: this group will continue their usual controller treatment once-daily and following standard recommendations of GINA guidelines. The medication will be administered and/or supervised by patients parents or caregivers.

The aim of this intervention is to demonstrate the importance of treatment adherence in order to achieve good asthma control levels. With that, we want to achieve less number of future exacerbations, especially, those that need to be admitted to hospital for intensive care.

It is important to highlight that all the participants cannot change his/her basal treatment or start immunotherapy and that the use of reliever medication is always allowed.

7.6. DATA COLLECTION AND STUDY CIRCUIT

For data collection we will work together with the physicians, in charge of children asthma managing, working in the Pediatrics Department of each Hospital in the Girona Province. After a first coordination meeting, before the beginning of the recruitment, main investigators and the team collaborators will keep in touch through the mail.

All the patients with a previous asthma diagnosis, that come to a Pediatrics Department will be evaluated to see if they meet all the inclusion criteria and none of the exclusion.

In the next step, the patients included will receive the information sheet for this clinical trial, and physicians must ensure they answer all the questions and that patients and parents understands all the information given.

Once we assure they understand the research project and if they agree with our study, they will sign the informed consent document. And in the same visit we will assess the patient baseline characteristics:

Figure 5: Baseline characteristics assessment:	
Age	Nº AH over the past year
Sex	Nº ED visits over the past year
Age of diagnosis	ACT score
Baseline FEV_1	Asthma medication
Nº Exacerbation over the last year	

All participants will be given the information about asthma control and the importance of asthma's treatment adherence and also non-pharmacological strategies. They will also be informed about how they use their inhaler device and the spacer device. They will be provided with information on when and how the must go for advanced medical care, in case of exacerbation or symptoms worsening.

Follow-up visits will be scheduled for the sixth and the ninth month from the beginning of the study. In all visits, the patient will be asked about their asthma status and will answer the ACT or c-ACT, depending on their age. Afterwards, a forced spirometry will be performed.

If patients requires an increasing in their controller medication due to bad control levels, and add-on medication or high doses of ICS are prescribed, they will be excluded of the study and will be considered a follow-up loss.

8. STATISTICAL ANALYSIS

The statistical analysis will be performed using the Statistical Package for Social Science (SPSS) version 25 for Windows®. A statistical expert will help our research team in data analysis. It will be considered statistically significant differences between both groups when p-value <0.05, with a confidence interval of 95%.

8.1. DESCRIPTIVE ANALYSIS

The descriptive analysis of the variables will be performed to ensure both intervention and control groups are comparable.

Our main dependent variable and the secondary variable (proportion of patients with the need for ED or AH during intervention time, and proportion of patients with ACT score >20) are qualitative and dichotomous. These variables will be summarized as proportions (%), stratifying by intervention and control group.

The other dependent variable (total nº of exacerbations during intervention time) is a quantitative variable, and will be summarized as mean +/- standard deviation (SD), stratifying by intervention and control group.

8.2. BIVARIATE INFERENCE

For the main outcome of the study, the difference of proportion of patients with the need for ED or AH during intervention time, between the intervention and the control group, will be analyzed by the Chi-square test ($\chi 2$).

For the secondary outcome, the difference of proportion of patients with ACT score >20, between intervention and control group, will be analyzed by Chi-square test ($\chi 2$).

For the secondary outcome, the total number of exacerbations during intervention time, the comparison of means, between the intervention and the control group, will be analyzed by the Student's T-test.

8.3. MULTIVARIATE ANALYSIS

In order to assess the association between the intervention variable and the main dependent variable, the difference of proportion of patients that need ED or AH, several logistic regressions will be carried out, adjusted by the covariates (age, sex, ...)

For secondary dependent variable nº of exacerbations, as it is a quantitative variable we will use multiple lineal regression, adjusted for the same covariables.

For secondary variable, proportion of patients with ACT score >20, as it is qualitative we will use multiple logistic regressions, adjusted for the same covariables.

9. ETHICAL CONSIDERATIONS

This clinical trial will be conduced according to the medical ethics requirements expressed by the World Health Association in the Declaration of Helsinki (1964), lasted revised in 2013, about the Ethical Principles for Medical Research Involving Human Subjects.

When the protocol would be finished, this clinical trial will be presented for approval to the "Clinical Research Ethics Committee" (CEIC) of one of the hospitals within the study. As this study is multicenter, with the validation of a single CEIC is enough valid for the rest of the centers. Approval of the informed consent form and the information sheet of the trial for the patient will be assessed.
The management of the centers that enter in the study will have to approve it as well.

All patients will be properly informed and will have time to contemplate participation. No patient will enter the study until freely given his/her consent by reading and signing the informed consent (see ANNEX 8). Patient autonomy will be respected, not only before entering the trial but always. All patients in this study will receive treatment and follow-up according to the most recent clinical guidelines of asthma.

All the information obtained about patients will be confidential and anonymous following “Ley orgánica 3/2018, de 5 diciembre, de Protección de datos personales y garantía de los derechos digitales” to ensure the principle of confidentiality.

10. DRUGS AND SAFETY

The drug used in this study is inhaled corticosteroids and can be prescribed in low or medium dose. The doses depend of the drug and the patient age. Low dose for children younger than 6, in most used drugs, are below 200 μg/day and for medium dose is usually below 400 μg/day. And in adolescents the doses are doubled.

Most frequent adverse effects are local effects including oropharyngeal candidiasis, dysphonia, and coughing, but if a spacer device is used these effects could be reduced. Also mouth washing after drug intake helps reducing oropharyngeal candidiasis.

Systemic side effects during long-term treatment with ICS are much less frequent compared in OCS. At high doses, ICS could increase the risk of adrenal suppression, decreased bone mineral density, and especially in children ICS can interfere in children growth. And also an increased risk of tuberculosis has been seen in long therapy with ICS.

These effects are seen in a minority of asthmatic patients and especially in these patients with need for high doses of ICS and for a long time. And the risk is increased if OCS are used too.

It is also important to take into account the possibility of a paradoxical bronchospasm with wheezing increase. This happens very rarely and in front of these cases it is important to stop the inhalation. Often, the immediate administration of a SABA treatment is enough to improve breathing difficulties. A new option for controller drug must be considered.
If teachers notice a worsening during supervised therapy, they must stop controller medication inhalation and then if necessary administer reliever medication as could be SABA.

11. STRENGH AND LIMITATIONS

An inherent feature of clinical trials is the lack of reproducibility understood as the possibility of the results to be extrapolated to the general population. Therefore, more studies will have to be done in order to confirm the results, and thus be able to support our hypothesis.

In our study, much teachers and schools have showed the predisposition to participate in our study. However, the lack of certainty that the school centers agree to participate could be a possible limitation for future studies. But if our study shows good results, this could open a door to changes in the current legislation or the possibility to reward teachers who want to participate.

School teachers are expected to be very responsible and organized professionals. We must ensure that teachers understand the importance of controller medication, treatment adherence, the high degree of security of the treatment and all benefits of this treatment strategy. Well-trained and properly informed teachers will be perfectly able to supervise or administer asthma treatment.

Researchers involved in this study have already shown results in several papers and publications about this topic. They have enough experience in this study area to help ensure the viability of the study.

The main strength of this study is the possibility of assess a new strategy to ensure treatment adherence and consequently a better asthma control and treatment efficacy. Sometimes parents or the patients itself forget or refuse treatment because they feel well and have the perception of no need of controller medication. But in a long term, uncontrolled asthma implies more severe exacerbation, less lung function and increased morbidity.

12. WORK PLAN

For this study we need 186 patients to be recruited from the hospitals of Girona Province, so we estimate a recruitment time of a half-year. Main investigators will be Andreu Peñas (Ph) and Pau Magester (student), and one pediatrician of each participating hospital will collaborate. But also, we need nursing staff and school supervisors as coinvestigators.

To ensure the data collected is well analyzed we will hire a statistical expert. Also it is important to hire an external expert in inhaler technique to train school teachers so they know how to properly administer or supervise the drug inhalation.

12.1. PROTOCOL DESING AND APPROVAL

In this first stage, study protocol will be developed by main investigators and just after send to the CEIC of the Hospital Trueta for revision and approval.

- Duration: 4 months, from November 2019 to February 2020.

12.2. COORDINATION

Once the study protocol is approved, and right after the first step of cluster randomized sampling, we will start the coordination phase. It's important to first know which hospitals will be participating in our study as intervention hospitals, in order to start asking schools for joining the study.

As soon as hospital selection is done we'll carry on a face-to-face meeting with all pediatricians and nursing staff of each hospital in Girona to coordinate and have a consensus about chronogram, sample selection, and other features.

- Duration: 1 month, March 2020.

12.3. PATIENTS SELECTION

A second step of sampling will be done with a consecutive sampling of those patients who attend to follow-up visits in the participating hospital. All patients must be properly informed about this study and assessed to know if they meet all the inclusion and exclusion criteria. If they accept, the informed consent must be signed.

In the same visit we will check baseline characteristics, of the enrolled patients, previously explained. All information about non-pharmacological treatment, inhaler technique and asthma control will be explained to all participants.

- Duration: 5 months, from April to August 2020.

12.4. SCHOOL SUPERVISORS TRAINING

The two first weeks of September, we will carry out the inhaled devices training with all the teachers or school-workers in the study. An inhaled devices expert will lead these training sessions. The training will be done for 2 hours in each city of the intervention-group hospitals.

We've decided to train teachers during these weeks because, in Spain, teachers go to school to work but children are still on vacation.

In addition, as a correct inhaler technique is a main pillar of controller treatment, a second training will be scheduled for March 2021, the same month of the patients' first follow-up visit.

- Duration: 2 weeks, September 1st to September 10th. Also 1 week in March 2021.

12.5. INTERVENTION, FOLLOW-UP VISITS AND DATA COLLECTION

The intervention time will be one school year, and follow-up visits will be scheduled for March 2021 and, once finished the school year, in June or July 2021. In these visits, data will be collected and recorded in the database for each pediatrician participating.

In the first follow-up visit, the pediatrician must assess asthma status and explain again all non-pharmacological strategies.

- Duration: 10 months, from September 2020 to July 2021.

12.6. STATISTICAL ANALYSIS

In this stage, the main investigators and the hired statistical expert will perform the analysis of collected data.

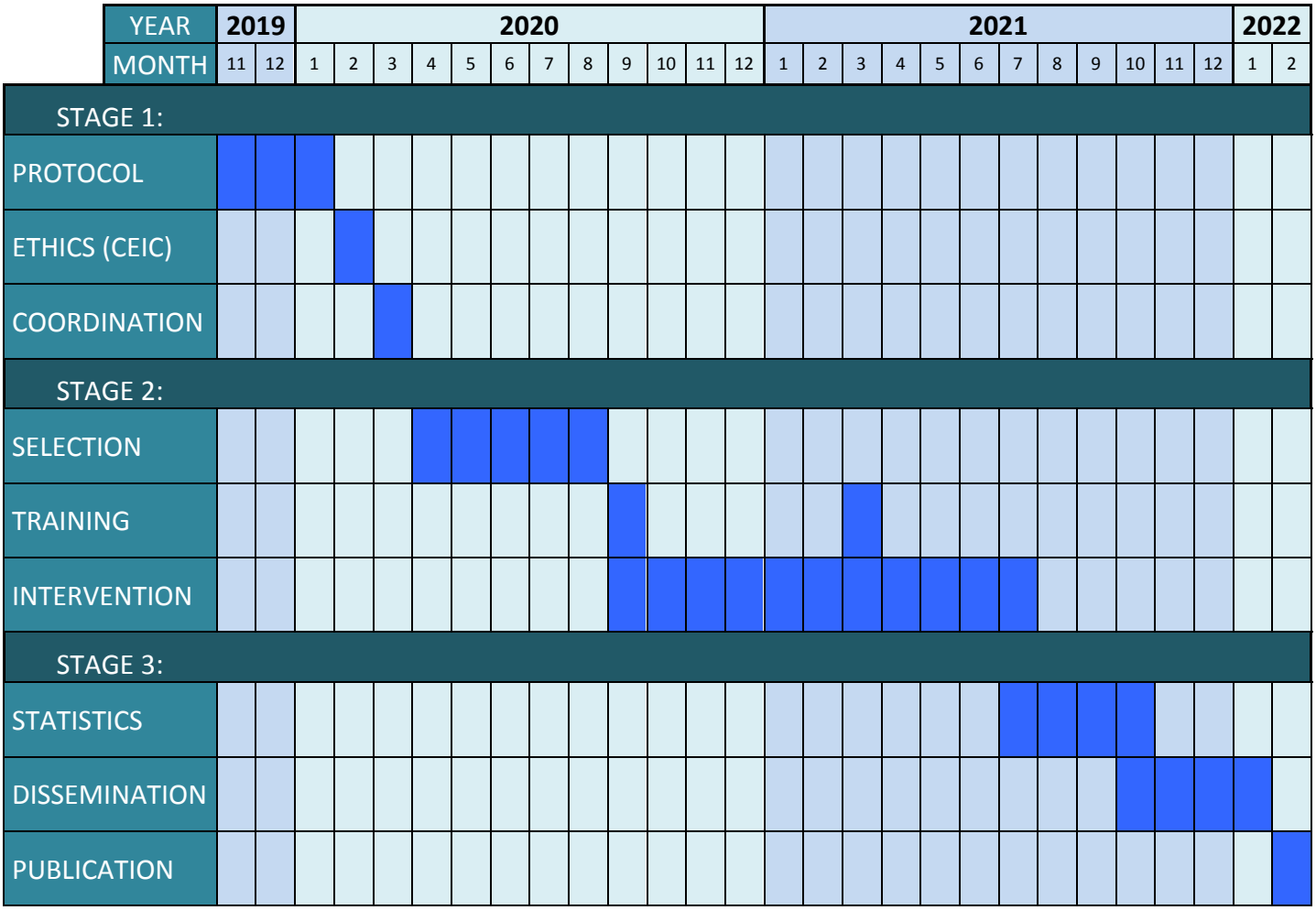
- Duration: 4 months, from July 2021 to October 2021.

12.7. INTERPRETATION, DISSEMINATION AND PUBLICATION

After all data processing and statistical analysis, results will be interpreted and conclusions will be drawn. The final study will be written with all this information and then will be send to different national and international journals for its publication, and also defended in congresses and conferences.

- Duration: 4-5 months, from October 2021 to approx. February 2022.

13. CRHONOGRAM



14. BUDGET

For this study, the help of a statistical expert and an inhaler devices expert will be required. During statistical analysis, our research team and the expert will work together to summarize the collected data. The inhaler devices expert will train school-teachers to administer and supervise correctly the inhaled treatment.

All pediatricians and nurses of the participating hospitals will meet in Girona for a coordination meeting before study begins. Diet and trip expenses will be contemplated in the study budget. Future conversations or follow-up meeting will be done using mail or Skype.

To assess lung function, spirometries will be performed at baseline and later on in the sixth and the ninth months from the beginning of the intervention (September 2020). Asthmatic patients often visit the physician twice a year in follow-up visits. For our study, the spirometries performed at baseline and at the sixth months won't be contemplated in the budget, as they are a piece of routine control tests.

	AMOUNT	COST	SUBTOTAL
PERSONAL EXPENSES			
STATISTICAL EXPERT	40h	30€/h	1.200 €
INHALER DEVICES EXPERT	12h	30€/h	360 €
EXECUTIVE EXPENSES			
COORDINATION MEETING (diets +trip)	12 person	30€/person	360 €
Spirometries (1 spirometries/patient)	186	14 €	7.812,00 €
Printing	186 patients	(10 copies) = 0,30 €	55,80 €
PUBLICATION EXPENSES			
SCIENTIFIC PUBLICATION	2	1.500 €	3.000 €
CONGRES ATTENDANCE	X	1.000 €	1.000 €
		TOTAL	**13.788 €**

15. IMPACT ON HEALTHCARE

This study paves the way for future studies to improve treatment adherence of those chronic diseases that are well tolerated by patients but like asthma, need controller or continued treatment. There is a lot of evidence that controller medication is effective when used properly, and could help to achieve a good level of asthma control.

Therefore, it is very important to work on adherence especially in those patients that really need controlled medication, to avoid exacerbations, but feel well between episodes and don't see the relevance of controller medication's strategy in their asthma management. A patient with a well-controlled asthma is able to perform daily activities with hardly any barrier and can exercise and work normally.

Related consequences of a poor treatment adherence in asthma management influence directly the patients well-being, risk of future exacerbations, progressive loss of pulmonary functions, loss of school-days, higher morbidity and risk of related diseases. But also this affects indirectly caregivers' loss of workdays and the use of huge sanitary resources.

These expenses derived from the use of sanitary resources represents more than 2/3 parts of asthma-related costs and in the majority of the cases would have been avoided just by improving treatment adherence and/or good control of asthma. Investing in treatment adherence could helps decrease greatly the sanitary costs of ED and hospital treatments. Thus mean that this money could be used for other purposes.

This study puts forward a new strategy to ensure patient's adherence. Moreover it demonstrates adherence importance since we will be assessing this asthma management strategy for 9 months.

16. BIBLIOGRAPHY

1. Boulet L-P, Reddel HK, Bateman ED, Bacharier LB. GINA Global Initiative for Asthma: GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION. 2019;
2. Barranco Sanz P, del Cuvillo Bernal A, Mullol i Miret J, Navarro Pulido AM. GEMA4.3. Guía española para el manejo del asma. 2018.
3. Burney P, Chinn S, Jarvis D, Luczynska C, Lai E. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur Respir J. 1996;9(4):687–95.
4. Jarvis D, Knox J. The European Community Respiratory Health Survey II. Eur Respir J. 2002;20:1071–9.
5. Carvajal-Urueña I, García-Marcos L, Busquets-Monge R, Morales Suárez-Varela M, García De Andoin N, Batlles-Garrido J, et al. Variaciones geográficas en la prevalencia de síntomas de asma en los niños y adolescentes españoles. International Study of Asthma and Allergies in Childhood (ISAAC) fase III España [Internet]. Vol. 41, Arch Bronconeumol. 2005 [cited 2020 Jan 20]. Available from: http://isaac.auckland.ac.nz
6. Garcia-Marcos L, Quiros AB, Hernandez GG, Guillen-Grima F, Diaz CG, Urena IC, et al. Stabilization of asthma prevalence among adolescents and increase among schoolchildren (ISAAC phases I and III) in Spain*. Allergy [Internet]. 2004 Dec [cited 2020 Jan 20];59(12):1301–7. Available from: http://doi.wiley.com/10.1111/j.1398-9995.2004.00562.x
7. Urrutia I, Aguirre U, Sunyer J. Cambios en la prevalencia de asma en la población española del Estudio de Salud Respiratoria de la Comunidad Europea (ECRHS-II). Arch Bronconeumol. 2007;43:425–30.
8. Asma GE del EE en. Estudio europeo del asma Prevalencia de hiperreactividad bronquial y asma en jóvenes en 5 regiones de España. Med Clin. 1996;761–7.
9. Levine SJ, Wenzel SE. Narrative review: The role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes. Ann Intern Med. 2010;152(4):232–7.
10. Gans MD, Gavrilova T. Understanding the immunology of asthma: Pathophysiology, biomarkers, and treatments for asthma endotypes. Paediatr Respir Rev [Internet]. 2019 Oct [cited 2020 Jan 20]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S1526054219300818
11. Galli S, Tsai M. IgE and mast cells in allergic disease. Nat Med. 2012;18:683–704.

12. Rosenberg HF, Dyer KD, Foster PS. Eosinophils: changing perspectives in health and disease HHS Public Access. Nat Rev Immunol. 2013;13(1):9–22.
13. Prakash YS. Airway smooth muscle in airway reactivity and remodeling: what have we learned? Am J Physiol Lung Cell Mol Physiol [Internet]. 2013 [cited 2020 Jan 20];305:912–33. Available from: www.ajplung.org
14. Koziol-White CJ, Panettieri Jr RA. Airway smooth muscle and immunomodulation in acute exacerbations of airway disease. Immunol Rev [Internet]. 2011 Jul [cited 2020 Jan 20];242(1):178–85. Available from: http://doi.wiley.com/10.1111/j.1600-065X.2011.01022.x
15. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA).
16. O'Byrne P, Inman M. Airway Hyperresponsiveness. chest J. 2003;123(3):411–6.
17. Ober C, Yao T-C. The Genetics of Asthma and Allergic Disease: A 21 st Century Perspective.
18. Irkje D, Ostma SP, Leecker URB, Amela P, Melung JA, Olroyd EJH, et al. GENETIC SUSCEPTIBILITY TO ASTHMA-BRONCHIAL HYPERRESPONSIVENESS COINHERITED WITH A MAJOR GENE FOR ATOPY. 1995.
19. Israel E, Chinchilli V, Ford J. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet. 2004;364(9444):1505–12.
20. Ober C, Vercelli D. Gene-Environment Interactions in Human Disease: Nuisance or Opportunity? The Problem: Accounting for the Heritability of Common Human Diseases. 2010;
21. Holgate S. Genetic and environmental interaction in allergy and asthma. J Allergy Clin Immunol. 1999;104:1139–46.
22. Horwood LJ, Fergusson DM, Shannon FT. Social and Familial Factors in the Development of Early Childhood Asthma. Pediatrics. 1985;75:859–68.
23. Martinez F, Wright A, Taussig L. ASTHMA AND WHEEZING IN THE FIRST SIX YEARS OF LIFE. Vol. 332. 1995.
24. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests.
25. Beuther DA, Sutherland ER. Overweight, Obesity, and Incident Asthma A Meta-analysis of Prospective Epidemiologic Studies. [cited 2020 Jan 20]; Available from: www.atsjournals.org

26. Boulet L-P. Asthma and obesity. Clin Exp Allergy [Internet]. 2013 Jan [cited 2020 Jan 20];43(1):8–21. Available from: http://doi.wiley.com/10.1111/j.1365-2222.2012.04040.x
27. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: A population-based cross-sectional study. Lancet. 2001 Mar 10;357(9258):752–6.
28. Gern JE, Reardon CL, Hoffjan S, Nicolae D, Li Z, Roberg KA, et al. Effects of dog ownership and genotype on immune development and atopy in infancy. J Allergy Clin Immunol. 2004;113(2):307–14.
29. Melen E, Wickman M, Nordvall S, van Hage-Hamsten M, Lindfors A. Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. Allergy [Internet]. 2001 Jul [cited 2020 Jan 20];56(7):646–52. Available from: http://doi.wiley.com/10.1034/j.1398-9995.2001.00387.x
30. Quansah R, Jaakkola MS, Hugg TT, Heikkinen SAM, Jaakkola JS. Residential Dampness and Molds and the Risk of Developing Asthma: A Systematic Review and Meta-Analysis. PLoS One [Internet]. 2012 [cited 2020 Jan 20];7(11):47526. Available from: www.plosone.org
31. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. J Allergy Clin Immunol. 1997;99(6 I SUPPL.):763–9.
32. Huss K, Adkinson NF, Eggleston PA, Dawson C, Van Natta ML, Hamilton RG. House dust mite and cockroach exposure are strong risk factors for positive allergy skin test responses in the Childhood Asthma Management Program. J Allergy Clin Immunol. 2001;107(1):48–54.
33. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A Longitudinal, Population-Based, Cohort Study of Childhood Asthma Followed to Adulthood. N Engl J Med [Internet]. 2003 Oct 9 [cited 2020 Jan 20];349(15):1414–22. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa022363
34. Carlsen KCL, Roll S, Carlsen K-H, Mowinckel P, Wijga AH, Brunekreef B, et al. Does Pet Ownership in Infancy Lead to Asthma or Allergy at School Age? Pooled Analysis of Individual Participant Data from 11 European Birth Cohorts. [cited 2020 Jan 20]; Available from: www.plosone.org
35. Brooks C, Pearce N, Douwes J. The hygiene hypothesis in allergy and asthma: An update. Vol. 13, Current Opinion in Allergy and Clinical Immunology. 2013. p. 70–7.
36. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL.

Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N Engl J Med. 2000 Aug 24;343(8):538–43.

37. De Meer G, Janssen NAH, Brunekreef B. Early childhood environment related to microbial exposure and the occurrence of atopic disease at school age. Vol. 60, Allergy: European Journal of Allergy and Clinical Immunology. 2005. p. 619–25.
38. Illi S, von Mutius E, Lau S, Bergmann R, Niggemann B, Sommerfeld C, et al. Early childhood infectious diseases and the development of asthma up to school age: A birth cohort study. Br Med J. 2001 Feb 17;322(7283):390–5.
39. Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: The influence of maternal smoking and a genetic predisposition to asthma. Am J Respir Crit Care Med. 1999;159(2):403–10.
40. Nafstad P, Kongerud J, Botten G, Hagen JA, Jaakkola JJK. The Role of Passive Smoking in the Development of Bronchial Obstruction during the First 2 Years of Life [Internet]. Vol. 8, Epidemiology. Lippincott Williams & Wilkins; [cited 2020 Jan 20]. p. 293–7. Available from: https://www.jstor.org/stable/pdf/3702256.pdf
41. PEDIATRICS AAO. Environmental Tobacco Smoke: A Hazard to Children [Internet]. 1997 [cited 2020 Jan 20]. Available from: www.aappublications.org/news
42. Hehua Z, Qing C, Shanyan G, Qijun W, Yuhong Z. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: A systematic review. Vol. 159, Environmental Research. Academic Press Inc.; 2017. p. 519–30.
43. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, et al. The Effect of Air Pollution on Lung Development from 10 to 18 Years of Age. N Engl J Med [Internet]. 2004 Sep 9 [cited 2020 Jan 20];351(11):1057–67. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa040610
44. Zheng XY, Ding H, Jiang LN, Chen SW, Zheng JP, Qiu M, et al. Association between Air pollutants and asthma emergency room visits and hospital admissions in time series studies: A systematic review and meta-Analysis. PLoS One. 2015 Sep 18;10(9).
45. Bel EH. Clinical phenotypes of asthma. Vol. 10, Current Opinion in Pulmonary Medicine. Lippincott Williams and Wilkins; 2004. p. 44–50.
46. Doherty G, Bush A. Diagnosing respiratory problems in young children. Practitioner [Internet]. 2007 Aug [cited 2020 Jan 20];251(1697):20, 22–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17882893
47. Brand PLP, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, et al. Classification and pharmacological treatment of preschool wheezing: Changes since 2008.

In: European Respiratory Journal. European Respiratory Society; 2014. p. 1172–7.

48. Price DB, Tinkelman DG, Halbert RJ, Nordyke RJ, Isonaka S, Nonikov D, et al. Symptom-Based Questionnaire for Identifying COPD in Smokers. Respiration [Internet]. 2006 [cited 2020 Jan 20];73(3):285–95. Available from: https://www.karger.com/Article/FullText/90142
49. Halbert RJ, Isonaka S. International Primary Care Respiratory Group (IPCRG) Guidelines: Integrating diagnostic guidelines for managing chronic respiratory diseases in primary care. Prim Care Respir J. 2006;15(1):13–9.
50. Brand PLP, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: An evidence-based approach. Eur Respir J. 2008 Oct;32(4):1096–110.
51. Pérez-Yarza EG, Villa JR, Cobos N, Navarro M, Salcedo A, Martín C, et al. Espirometría forzada en preescolares sanos bajo las recomendaciones de la ATS/ERS: estudio CANDELA. An Pediatr. 2009 Jan;70(1):3–11.
52. Stanojevic S, Wade A, Lum S, Stocks J. Reference equations for pulmonary function tests in preschool children: A review. Vol. 42, Pediatric Pulmonology. 2007. p. 962–72.
53. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Sorkness CA. Classifying Asthma Severity in Children. Am J Respir Crit Care Med [Internet]. 2004 Aug 15 [cited 2020 Jan 20];170(4):426–32. Available from: http://www.atsjournals.org/doi/abs/10.1164/rccm.200308-1178OC
54. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: Confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol. 2011;127(2).
55. Lang A, Konradsen J, Carlsen KH, Sachs-Olsen C, Mowinckel P, Hedlin G, et al. Identifying problematic severe asthma in the individual child - Does lung function matter? Acta Paediatr Int J Paediatr. 2010 Mar;99(3):404–10.
56. Levy ML, Quanjer PH, Booker R, Cooper BG, Holmes S, Small IR. Diagnostic spirometry in primary care: Proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations. Vol. 18, Primary Care Respiratory Journal. 2009. p. 130–47.
57. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Vol. 26, European Respiratory Journal. 2005. p. 319–38.
58. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic

reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. Eur Respir J. 2012 Dec 1;40(6):1324–43.

59. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for Methacholine and Exercise Challenge Testing - 1999. Vol. 161, American Journal of Respiratory and Critical Care Medicine. American Lung Association; 2000. p. 309–29.
60. Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahlén B, et al. Indirect airway challenges. Vol. 21, European Respiratory Journal. European Respiratory Society; 2003. p. 1050–68.
61. Burbach GJ, Heinzerling LM, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S, et al. GA2LEN skin test study II: Clinical relevance of inhalant allergen sensitizations in Europe. Allergy Eur J Allergy Clin Immunol. 2009 Sep;64(10):1507–15.
62. Caudri D, Wijga AH, Hoekstra MO, Kerkhof M, Koppelman GH, Brunekreef B, et al. Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. Thorax. 2010;65(9):801–7.
63. Taylor DR, Pijnenburg MW, Smith AD, De Jongste JC. Exhaled nitric oxide measurements: Clinical application and interpretation. Vol. 61, Thorax. 2006. p. 817–27.
64. Djukanovic´* RD, Sterk PJ, Fahy J V, Hargreave FE. Standardised methodology of sputum induction and processing.
65. Honkoop PJ, Taylor DR, Smith AD, Snoeck-Stroband JB, Sont JK. Early detection of asthma exacerbations by using action points in self-management plans. Eur Respir J. 2013 Jan 1;41(1):53–9.
66. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol. 2008;121(5).
67. Mcfadden ER, Kiser R, DeGroot WJ. Acute Bronchial Asthma: Relations between Clinical and Physiologic Manifestations. N Engl J Med. 1973 Feb 1;288(5):221–5.
68. Ramnath VR, Clark S, Camargo CA. Multicenter study of clinical features of sudden-onset versus slower-onset asthma exacerbations requiring hospitalization. Respir Care. 2007 Aug;52(8):1013–20.
69. Woodruff PG, Emond SD, Singh AK, Jr. CAC. Sudden-onset Severe Acute Asthma: Clinical Features and Response to Therapy. Acad Emerg Med [Internet]. 1998 Jul [cited 2020 Jan 20];5(7):695–701. Available from: http://doi.wiley.com/10.1111/j.1553-2712.1998.tb02488.x
70. Plaza V, Serrano J, Picado C, Sanchis J, Abal J, Ancochea J, et al. Frequency and clinical

characteristics of rapid-onset fatal and near-fatal asthma. Eur Respir J. 2002;19(5):846–52.

71. Alvarez GG, Schulzer M, Jung D, FitzGerald JM. A systematic review of risk factors associated with near-fatal and fatal asthma. Vol. 12, Canadian Respiratory Journal. Hindawi Limited; 2005. p. 265–70.
72. Suissa S, Blais L, Ernst P. Patterns of increasing β-agonist use and the risk of fatal or near-fatal asthma. Eur Respir J. 1994;7(9):1602–9.
73. Sturdy PM, Victor CR, Anderson HR, Bland JM, Butland BK, Harrison BDW, et al. Psychological, social and health behaviour risk factors for deaths certified as asthma: A national case-control study. Thorax. 2002 Dec 1;57(12):1034–9.
74. Guevara JP. Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. BMJ. 2003 Jun 12;326(7402):1308–1308.
75. Clark NM, Cabana MD, Nan B, Gong ZM, Slish KK, Birk NA, et al. The clinician-patient partnership paradigm: Outcomes associated with physician communication behavior. Clin Pediatr (Phila). 2008 Jan;47(1):49–57.
76. Partridge MR, Hill SR, Barnes GR, Bauman A, Beasley R, Clark NM, et al. Enhancing care for people with asthma: The role of communication, education, training and self-management. Eur Respir J. 2000;16(2):333–48.
77. Wilson SR, Strub P, Buist AS, Knowles SB, Lavori PW, Lapidus J, et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. Am J Respir Crit Care Med. 2010 Mar 15;181(6):566–77.
78. Gibson PG, Powell H, Coughlan J, Wilson AJ, Abramson M, Haywood P, et al. Self-management education and regular practitioner review for adults with asthma. Cochrane database Syst Rev [Internet]. 2003 [cited 2020 Jan 20];(1):CD001117. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12535399
79. Jansen J, McCaffery KJ, Hayen A, Ma D, Reddel HK. Impact of graphic format on perception of change in biological data: Implications for health monitoring in conditions such as asthma. Prim Care Respir J. 2012 Mar;21(1):94–100.
80. Klijn SL, Hiligsmann M, Evers SMAA, Román-Rodríguez M, Van Der Molen T, Van Boven JFM. Effectiveness and success factors of educational inhaler technique interventions in asthma & COPD patients: A systematic review. npj Prim Care Respir Med. 2017 Dec 1;27(1).
81. Fink JB, Rubin BK. Problems with inhaler use: A call for improved clinician and patient education. In: Respiratory Care. 2005. p. 1360–74.

82. Melani AS, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. Respir Med. 2011 Jun;105(6):930–8.
83. Rayens MK, Burkhart P V., Zhang M, Lee S, Moser DK, Mannino D, et al. Reduction in asthma-related emergency department visits after implementation of a smoke-free law. J Allergy Clin Immunol. 2008;122(3).
84. Chaudhuri R, Livingston E, McMahon AD, Lafferty J, Fraser I, Spears M, et al. Effects of Smoking Cessation on Lung Function and Airway Inflammation in Smokers with Asthma. Am J Respir Crit Care Med [Internet]. 2006 Jul 15 [cited 2020 Jan 20];174(2):127–33. Available from: http://www.atsjournals.org/doi/abs/10.1164/rccm.200510-1589OC
85. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing severe asthma exacerbations in children a randomized trial of mite-impermeable bedcovers. Am J Respir Crit Care Med. 2017 Jul 15;196(2):150–8.
86. Eggleston PA, Wood RA, Rand C, Nixon WJ, Chen PH, Lukk P. Removal of cockroach allergen from inner-city homes. J Allergy Clin Immunol [Internet]. 1999 Oct [cited 2020 Jan 20];104(4 Pt 1):842–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10518830
87. Matsui EC, Perzanowski M, Peng RD, Wise RA, Balcer-Whaley S, Newman M, et al. Effect of an integrated pest management intervention on asthma symptoms among mouse-sensitized children and adolescents with asthma a randomized clinical trial. JAMA - J Am Med Assoc. 2017 Mar 14;317(10):1027–36.
88. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respir Med. 2006 Apr;100(4):648–57.
89. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DYM. Body mass and glucocorticoid response in asthma. Am J Respir Crit Care Med. 2008 Oct 1;178(7):682–7.
90. Price D, Bosnic-Anticevich S, Briggs A, Chrystyn H, Rand C, Scheuch G, et al. Inhaler competence in asthma: Common errors, barriers to use and recommended solutions. Respir Med. 2013 Jan;107(1):37–46.
91. Consenso SEPAR-ALAT sobre terapia inhalada Consenso SEPAR-ALAT sobre terapia inhalada SEPAR-ALAT Consensus for Inhaled Therapies. 2013 [cited 2020 Jan 20]; Available from: www.archbronconeumol.orgwww.archbronconeumol.org
92. Lavorini F, Magnan A, Christophe Dubus J, Voshaar T, Corbetta L, Broeders M, et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and

COPD. Respir Med. 2008;102(4):593–604.

93. Kamps AWA, Van Ewijk B, Roorda RJ, Brand PLP. Poor inhalation technique, even after inhalation instructions, in children with asthma. Pediatr Pulmonol. 2000 Jan;29(1):39–42.
94. Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: A systematic review of the literature. Vol. 5, Health Technology Assessment. NIHR Journals Library; 2001.
95. Crompton GK. Problems patients have using pressurized aerosol inhalers. Eur J Respir Dis. 1982;63(Suppl. 119):101–4.
96. Castro-Rodriguez JA, Rodrigo GJ. The role of inhaled corticosteroids and montelukast in children with mild-moderate asthma: Results of a systematic review with meta-analysis. Arch Dis Child. 2010 May;95(5):365–70.
97. Pauwels RA, Löfdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med. 1997 Nov 13;337(20):1405–11.
98. Juniper EF, Svensson K, O'Byrne PM, Barnes PJ, Bauer CA, Löfdahl CGA, et al. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. Eur Respir J. 1999;14(5):1038–43.
99. Powell H, Gibson PG. High dose versus low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. Cochrane database Syst Rev [Internet]. 2004 [cited 2020 Jan 20];(2):CD004109. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15106238
100. Rodrigo GJ, Neffen H. Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: A systematic review. Pediatr Allergy Immunol. 2017 Sep 1;28(6):573–8.
101. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, et al. Effect of Inhaled Glucocorticoids in Childhood on Adult Height. N Engl J Med [Internet]. 2012 Sep 6 [cited 2020 Jan 20];367(10):904–12. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1203229
102. Using β2-stimulants in asthma. Vol. 35, Drug and Therapeutics Bulletin. BMJ Publishing Group; 1997. p. 1–4.
103. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma. N Engl J Med [Internet]. 2018 May 17 [cited 2020 Jan 20];378(20):1877–87. Available from:

http://www.nejm.org/doi/10.1056/NEJMoa1715275

104. Stempel DA, Szefler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, et al. Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma. N Engl J Med [Internet]. 2016 Sep [cited 2020 Jan 20];375(9):840–9. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1606356

105. Löfdahl CG, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, et al. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. Br Med J. 1999 Jul 10;318(7202):87–90.

106. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Vol. 2014, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2014.

107. Aït-Khaled N, Enarson DA, Bencharif N, Boulahdib F, Camara LM, Dagli E, et al. Implementation of asthma guidelines in health centres of several developing countries [Internet]. Vol. 10, INT J TUBERC LUNG DIS. 2006 [cited 2020 Jan 20]. Available from: www.iuatld.org]

108. Haldar P, Pavord ID, Shaw DE, Berry M a, Thomas M, Brightling CE, et al. Europe PMC Funders Group Cluster Analysis and Clinical Asthma Phenotypes. Am J Respir Crit Care Med. 2014;178(3):218–24.

109. Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. Vol. 32, European Respiratory Journal. 2008. p. 545–54.

110. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902–7.

111. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol. 2007 Apr;119(4):817–25.

112. Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence. The Goal to Control Asthma. Vol. 33, Clinics in Chest Medicine. 2012. p. 405–17.

113. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RCM, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: A systematic review. Vol. 157, Annals of Internal Medicine. American College of Physicians; 2012. p. 785–95.

114. Chan AHY, Harrison J, Black PN, Mitchell EA, Foster JM. Using Electronic

Monitoring Devices to Measure Inhaler Adherence: A Practical Guide for Clinicians. J Allergy Clin Immunol Pract. 2015;3(3):335-349.e5.

115. Stevenson FA, Cox K, Britten N, Dundar Y. A systematic review of the research on communication between patients and health care professionals about medicines: The consequences for concordance. Vol. 7, Health Expectations. 2004. p. 235–45.

116. Kuethe MC, Vaessen-Verberne AA, Bindels PJ, Van Aalderen WM. Children with asthma on inhaled corticosteroids managed in general practice or by hospital paediatricians: Is there a difference? Prim Care Respir J. 2010 Mar;19(1):62–7.

117. Bender B, Milgrom H, Rand C. Nonadherence in asthmatic patients: is there a solution to the problem? Ann Allergy Asthma Immunol [Internet]. 1997 Sep [cited 2020 Jan 20];79(3):177–85; quiz 185–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9305223

118. Friedman HS, Navaratnam P, McLaughlin J. Treatment and outcomes - Adherence and asthma control with mometasone furoate versus fluticasone propionate in adolescents and young adults with mild asthma. J Asthma. 2010 Nov;47(9):994–1000.

119. Navaratnam P, Friedman HS, Urdaneta E. Treatment with inhaled mometasone furoate reduces short-acting β2 agonist claims and increases adherence compared to fluticasone propionate in asthma patients. Value Heal. 2011;14(2):339–46.

120. Jentzsch NS, Camargos P, Sarinho ESC, Bousquet J. Adherence rate to beclomethasone dipropionate and the level of asthma control. Respir Med. 2012 Mar;106(3):338–43.

121. Metlina LS, Rachlin S, Rottenbucher T. Mathematics in preschool : an aid for the preschool educator. Soviet studies in mathematics education. Reston, Va.: National Council of Teachers of Mathematics; 1991. xiii, 371 p.

122. Bender BG. Overcoming barriers to nonadherence in asthma treatment. 2002;

123. Molina París J, Mascarós Balaguer E. Recursos asistenciales en atención primaria para manejo del asma: proyecto Asmabarómetro. 2018 [cited 2020 Jan 22]; Available from: https://doi.org/10.1016/j.aprim.2018.09.009

124. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2007 Feb;119(2):405–13.

125. Altzibar JM, Tamayo-Uria I, De Castro V, Aginagalde X, Albizu M V., Lertxundi A, et al. Epidemiology of asthma exacerbations and their relation with environmental factors in the Basque Country. Clin Exp Allergy [Internet]. 2015 Jun [cited 2020 Jan

22];45(6):1099–108. Available from: http://doi.wiley.com/10.1111/cea.12419

126. Úbeda-Sansano MI, Cano-Garcinuño A, Rueda-Esteban S, Praena-Crespo M. Resources to handle childhood asthma in Spain: The role of plans and guides and the participation of nurses. Allergol Immunopathol (Madr). 2018 Jul 1;46(4):361–9.

17. ANNEXES

17.1. ASTHMA CONTROL TEST

Nombre del paciente: Fecha: ID# de paciente: Su doctor de cuidado primario:

Asthma Control Test™ –ACT (La prueba de Control del Asma) es:

- Una prueba rápida que produce un resultado numérico para evaluar el control del asma.
- Reconocida por los Institutos Nacionales de la Salud (National Institutes of Health - NIH) en sus directrices sobre el asma de 2007.[1]
- Convalidada clínicamente por espirometría y evaluaciones de especialistas.[2]

PACIENTES:

1. Contesten cada pregunta y escriban el número de la respuesta en el cuadro que aparece a la derecha de la pregunta.
2. Sumen sus respuestas y escriban la puntuación total en el cuadro del TOTAL que se muestra abajo.
3. Hablen con su doctor sobre sus resultados.

						PUNTUACIÓN
1. En las últimas **4 semanas**, ¿cuánto tiempo le ha impedido su **asma** hacer todo lo que quería en el trabajo, en la escuela o en la casa?	Siempre 1	La mayoría del tiempo 2	Algo del tiempo 3	Un poco del tiempo 4	Nunca 5	
2. Durante las últimas **4 semanas**, ¿con qué frecuencia le ha faltado el aire?	Más de una vez al día 1	Una vez al día 2	De 3 a 6 veces por semana 3	Una o dos veces por semana 4	Nunca 5	
3. Durante las últimas **4 semanas**, ¿con qué frecuencia sus síntomas del **asma** (respiración sibilante o un silbido en el pecho, tos, falta de aire, opresión en el pecho o dolor) lo/la despertaron durante la noche o más temprano de lo usual en la mañana?	4 o más noches por semana 1	De 2 a 3 noches por semana 2	Una vez por semana 3	Una o dos veces 4	Nunca 5	
4. Durante las últimas **4 semanas**, ¿con qué frecuencia ha usado su inhalador de rescate o medicamento en nebulizador (como albuterol)?	3 o más veces al día 1	1 ó 2 veces al día 2	2 ó 3 veces por semana 3	Una vez por semana o menos 4	Nunca 5	
5. ¿Cómo evaluaría el control de su **asma** durante las **últimas 4 semanas**?	No controlada en absoluto 1	Mal controlada 2	Algo controlada 3	Bien controlada 4	Completamente controlada 5	
						TOTAL

Si obtuvo 19 puntos o menos, es probable que su asma no esté bajo control. Asegúrese de hablar con su doctor sobre sus resultados.

Referencias: 1. Departamento de Salud y Servicios Humanos de EE.UU, Institutos Nacionales de la Salud, Instituto Nacional del Corazón, los Pulmones y la Sangre. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3 2007)*. Ítem de NIH No. 08-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Consultado el 10 de septiembre de 2007. **2.** Nathan RA y otros. *J Allergy Clin Immunol*. 2004;113:59-65.

17.2. CHILDHOOD ASTHMA CONTROL TEST

1. ¿Cómo está tu asma hoy?

				PUNTAJE
 0 Muy mala	 1 Mala	 2 Buena	 3 Muy buena	

2. ¿Qué tan problemática es tu asma cuando corres, haces ejercicio o practicas algún deporte?

 0 Es un problema grande, no puedo hacer lo que quiero hacer.	 1 Es un problema y no me siento bien.	 2 Es un problema pequeño pero está bien.	 3 No es un problema.	

3. ¿Tienes tos debido a tu asma?

 0 Sí, siempre.	 1 Sí, la mayoría del tiempo.	 2 Sí, algo del tiempo.	 3 No, nunca.	

4. ¿Te despiertas durante la noche debido a tu asma?

 0 Sí, siempre.	 1 Sí, la mayoría del tiempo.	 2 Sí, algo del tiempo.	 3 No, nunca.	

Por favor conteste usted las siguientes preguntas.

5. Durante las últimas 4 semanas, ¿cuántos días tuvo su niño/a síntomas de asma durante el día?

5 Nunca	4 De 1 a 3 días	3 De 4 a 10 días	2 De 11 a 18 días	1 De 19 a 24 días	0 Todos los días

6. Durante las últimas 4 semanas, ¿cuántos días tuvo su niño/a respiración sibilante (un silbido en el pecho) durante el día debido al asma?

5 Nunca	4 De 1 a 3 días	3 De 4 a 10 días	2 De 11 a 18 días	1 De 19 a 24 días	0 Todos los días

7. Durante las últimas 4 semanas, ¿cuántos días se despertó su niño/a durante la noche debido al asma?

5 Nunca	4 De 1 a 3 días	3 De 4 a 10 días	2 De 11 a 18 días	1 De 19 a 24 días	0 Todos los días

TOTAL

17.3. TRIAL INFORMATION SHEET

FULL INFORMACIÓ DE L'ASSAIG CLÍNIC:

Títol de l'estudi: School-supervised asthma controller therapy. El tractament de manteniment de l'asma i l'escola: una nova estratègia.

Investigadors: _____

Hospital: _____

Apreciat/da:

Ens dirigim a vostès per informar-los sobre la realització d'un estudi d'investigació en el que es convida al seu fill o a la seva filla a participar. Aquest assaig clínic ha estat aprovat pel Comitè d'Ètica i Investigació Clínica de l'Hospital Universitari doctor Josep Trueta.

El seu fill o la seva filla pateix d'asma i per això se li ha prescrit tractament diari a base de corticoides inhalats a baixes o mitjanes dosis per poder millor el seu estat a mitjà-llarg termini.
És possible però, que l'estratègia del tractament no obtingui els resultats òptims per culpa d'una baixa adherència al tractament, és a dir el compliment. En aquest estudi es vol estudiar els resultats de l'aplicació d'una nova estratègia que involucri les escoles i els mestres. Els professors i professores seran els encarregats de supervisar i/o administrat el tractament diari de manteniment al seu fill o filla.

La nostra intenció es que vostè rebi tota la informació necessària de forma correcta i que sigui suficient per a que vostè pugui decidir si participar o no en aquest estudi. És per això que li agrairíem que llegís atentament aquest full d'informació i posteriorment els investigadors li aclariran tots els dubtes que pugui tenir.

Primer de tot, vostè ha de saber que la participació en quest estudi és totalment VOLUNTÀRIA. Si decideix que el seu fill o filla participi de l'estudi ha de saber que podrà abandonar en qualsevol moment sense que això suposo una alteració de la relació amb el seu metge o metgessa habitual ni que es produeixi ningun perjudici en el seu tractament.

Si accepten participar en l'estudi, li garantim la confidencialitat de les seves dades personals ('Ley Orgánica de Protección de Datos de Caràcter personal 3/2018') i així com els resultats de l'estudi.
A continuació li expliquem com es durà a terme tot l'estudi.

FINALITAT: El nostre objectiu és conèixer si una nova estratègia de tractament de l'asma, en la qual la medicació de manteniment s'administri i supervisi a l'escola per part dels professors, resulta en un millor control de la malaltia dels nens i nenes. Volem estudiar si aplicant aquesta nova estratègia es poden disminuir el número de visites a urgències hospitalàries i els ingressos hospitalaris deguts a exacerbacions greus.

DESCRIPCIÓ DE L'ESTUDI: Abans de la seva participació a l'estudi, informarem dels objectius del protocol i resoldrem tots els dubtes que li puguin sorgir a les famílies dels infants participants.
Al igual que al seu fill o filla, a tots els pacients asmàtics d'entre 6 i 16 anys que preguin corticosteroides inhalats a dosis baixes o mitjanes com a tractament de manteniment de l'asma se'ls convidarà a participar en aquest estudi.

En aquesta visita de control rutinària, se li realitzaran un seguit de preguntes per tal de poder avaluar si el seu fill o filla es candidat a participar en aquest estudi de forma voluntària. En cas que sigui un/a candidat/da idoni/a i que vostès com a tutors legals del menor accedeixin a participar hauran de firmar el full de consentiment informat. Seguidament se li realitzaran més preguntes o proves per avaluar l'estat actual de l'asma dels seu fill o filla.
En aquesta visita se li realitzarà: una espirometria forçada i se li passarà el test de control de l'asma (ACT) o la versió per infants de 6 a 11 anys c-ACT. A més se li preguntarà pel número d'exacerbacions durant l'any anterior, les visites a urgències, etc.

Seguidament se li donaran un seguit d'instruccions i recomanacions per al maneig de l'asma del seu fill/a. I se li comunicarà si el seu fill/a formarà part del grup control o el grup intervenció, aquest darrer grup seguirà el tractament segons la nova estratègia que es basa en l'administració i supervisió de la medicació de control de l'asma per parts dels professors durant les hores lectives.
Independentment del grup que se li assigni, se li explicaran detalladament totes les estratègies no farmacològiques que haurà de seguir per tal que el seu fill/a pugui assolir el millor control de l'asma possible amb la menor dosi de tractament necessària. També se'ls proporcionarà informació sobre com utilitzar els inhaladors, la càmera volumàtica, etc.

CONTROLS: Els controls hospitalaris es programaran pel sisè i el novè mes des de l'inici del curs escolar. El primer control formarà part del planning de controls rutinaris, mentre que el control del novè mes és addicional i servirà per avaluar els resultats durant el temps d'intervenció que correspon a un any escolar. Durant aquests controls se li repetirà tot la informació sobre estratègies no farmacològiques i l'educació sobre els dispositius d'inhalació.

BENEFICIOS Y RIESGOS: Si el seu fill/a forma part del grup intervenció, és possible que es beneficiï d'un millor control de l'asma amb la conseqüent disminució del risc de futures exacerbacions, si els resultats de l'aplicació del tractament durant les hores lectives són positius.

Si el seu fill participa en el grup control, rebrà la mateixa informació i el mateix tractament que si no participés en el estudi. També es possible que el seu fill/a no contempli cap benefici o millor de forma directa però si que pot contribuir en una millor comprensió de l'asma i el seu tractament i que això serveixi com a fonaments per a futurs estudis.

No es preveu en cap cas que el seu fill/a tingui cap risc ni inconvenient si forma part de l'estudi.

Els participants no rebran cap compensació econòmica per participar en l'estudi, ja que això podria suposar un biaix i pèrdua de pes científic de l'estudi.

CONFIDENCIALITAT: Tota la informació recopilada durant l'estudi serà codificada i arxivada confidencialment d'acord amb la " Ley Orgánica 15/1999 sobre la Protección Personal de Datos y el correspondiente RD 1720/2007" i no es podrà fer pública.

L'accés a aquestes dades romandrà restringit al personal de l'estudi, autoritats sanitàries corresponents i al CEIC si es que en requereix informació i es respecti la legislació vigent.

REVOCACIÓ i PARTICIPACIÓ: És important que entengui que la participació en aquest estudi és voluntària. És per això que vostè pot demanar en qualsevol moment de l'estudi sortir de l'estudi i que totes les dades relacionades amb la seva participació siguin eliminades sense necessitat de donar explicacions. Aquest fet no repercutirà en cap cas amb l'assistència mèdica que vostè rebi en endavant.

MÉS INFORMACIÓ: Si en qualsevol moment de l'estudi li sorgeixen nous dubtes o vol més informació, no dubti en posar-se en contacte amb l'equip d'investigadors a través del mail schoolstrategy@udg.edu o al mòbil 67543156710 (Sr. Magester).

Gràcies per llegir aquest full.

Si us plau, guardi aquest full informatiu.

Si accepta participar en l'estudi, haurà de firmar el consentiment informat que li proporcionarà el metge.

Al firmar, es compromet a complir amb els procediments de l'estudi que se li han explicar amb anterioritat.

Gràcies.

17.4. INFORMED CONSENT

CONSENTIMENT INFORMAT:

TÍTOL DE L'ESTUDI: School-supervised asthma controller strategy. El tractament de manteniment de l'asma i l'escola: una nova estratègia.

Jo, _____(nom i cognoms del tutor legal) amb DNI _____, accepto que el/la meu/va fill/a _____ amb DNI _____, participi en l'assaig clínic sobre la nova estratègia del tractament de manteniment, i confirmo que:

· He llegit tota la informació que se m'ha entregat sobre el projecte.
· He tingut l'oportunitat de preguntar els dubtes sobre l'estudi.
· He rebut respostes satisfactòries a les meves preguntes.
· He rebut suficient informació sobre aquest projecte.
· He entès els possibles riscos associats a la participació en aquest projecte.

He parlat amb_____ (nom i cognoms de l'investigador).
Comprenc que la participació es voluntària
Comprenc que puc retirar-me de l'estudi:
· Quan vulgui.
· Sense haver de donar explicacions.
· Sense alteracions amb les meues assistències sanitàries posteriors.

Estic informat/da de:
· La existència d'un fitxer automatitzat de dades de caràcter personal.
· La informació podrà ser utilitzada exclusivament per a finalitats científiques amb confidencialitat.
· El fitxer estarà en mans de l'investigador principal i tinc dret a l'accés, rectificació, cancel·lació i oposició.
Accepto lliurement participar en aquest estudi.
Signatura del pacient
Signatura de l'investigador

Lloc i data: _____, _____ de _____ del 20__.

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Jo, _____, revoco el consentiment prèviament signat per la participació en l'assaig clínic especificat a dalt.

Signatura del pacient

Signatura de l'investigador

Lloc i data: _____, ____ de _____ del 20__.

17.5. DATA COLLECTION SHEET

FULL DE RECOLLIDA DE DADES	**HOSPITAL:**
TITOL: School-supervised asthma controller strategy.	**PACIENT (inicials):**
INSTRUCCIONS: - S'han de contestar tots els apartats - Si no coneixen la resposta a la pregunta escriguin **NS** (No se Sap) - Si el pacient no ha respost la pregunta escriguin **NC** (No Contestada) - Marqui les caselles de resposta amb una **X**	
El pacient ha llegit el Full d'Informació ☐ ☐ **El pacient ha llegit el Full d'Informació**	
INFORMACIÓ DEL PARTICIPANT:	**EDAT:** **SEXE:** **M** ☐ **F** ☐
EDAT AL DIAGNÒSTIC: **FEV_1/FVC:** **ACT SCORE:**	
NÚMERO TOTAL D'EXACERBACIONS DURANT L'ANY ANTERIOR: **NÚMERO DE VISITES A URGÈNCIES PER ASMA L'ANY ANTERIOR:** **NÚMERO D'INGRESSOS HOSPITALARIS PER ASMA L'ANY ANTERIOR:**	
NÚMERO TOTAL D'EXACERBACIONS DURANT L'ESTUDI: **NÚMERO DE VISITES A URGÈNCIES PER ASMA DURANT L'ESTUDI:** **NÚMERO D'INGRESSOS HOSPITALARIS PER ASMA DURANT L'ESTUDI:**	