Full Title	**REDS (REspiratory Drugs Survey) STUDY. Active surveillance of respiratory drugs, especially Inhaled Steroids (IS) in children**
Protocol Acronymus	REDS STUDY
Study Reference Number	On going
Ethic Committee Approval	ASREM Ethic Committee of December 22,2015
Responsible Parties	FP-MCRN Onlus. Family Pediatricians-Medicines for Children Research Network is a member of ENPR-EMA (European Network Paediatrc Research at the European Medicines Agency) and of ENCEPP (European Network of Centres of Pharmacoepidemiology and Pharamacovigilance) . The FP- MCRN is a non-profit organization in which its aims and resolutions are research, training and especially that of the protection of vulnerable groups such as children with disabilities and chronic diseases.
Name of lead investigator	Dr. Ettore Napoleone President of FP-MCRN Member of Coordinating Group of ENPREMA Member of Joint ENPREMA-ENCEPP Working Group on Paediatric Pharmacovigilance
ENCePP Study Seal	Under evaluation
Date of preparation	Draft Version n.1 of September 1,2015 Draft Versin n.2 of November 4,2015 Final Version n.3 of December 1,2015

Milestones	Start of Data Collection: April 10,2016 End of Data Collection: April 10,2018 Study Progress Report: April 10,2017 Interim Reports: November 10,2017 Final Report of Study Results: June 10,2018
Available funding	Pharmacovigilance AIFA (Italian Medicines Agency) Call 2010-2011
Partecipating Center	Participating in the research will be Family Pediatricians of their respective regions (Molise, Umbria and Emilia-Romagna) taking into account the Family Pediatrician's experience conducting clinical studies.
Research Quality	The FP-MCRN Onlus intends to pursue research projects based on scientific and ethical principles (Ethical Considerations - 2008 EMA), conducted according to the rules of GCP in clinical pediatric trials, according to the GVP – Guidelines on good pharmacovigilance pratice -Module VIII- PASS with the aim of improving the quality of primary care in pediatrics.
Duration of the Project	24 months

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ABSTRACT

Title

REDS (REspiratory Drugs Survey) STUDY.
Active surveillance of respiratory drugs, especially Inhaled Steroids (IS) in children

Date of Protocol

December 20,2015

Name and affiliation of main author

Dr. Ettore Napoleone President of FP-MCRN (Family Pediatricians-Medicines for Children Research Network) Onlus

Rationale and background,

Despite the prevalence of Asthma has settled down to between 9.5 and 10.5% in children aged 6 to 11 years, it has been particularly noted that IS (beclomethasone, budesonide, flunisolide, fluticasone, etc.), are used inappropriately in children with an "over prescription" for conditions that do not require their use. For example, beclomethasone is one of the most frequently prescribed medication in children. It is estimated that in Italy, it is used by about 2 million children and adolescents every year. Despite being an anti-asthmatic medicine, it is often prescribed for colds, coughs and sore throats. In the Enbe Study (Effectiveness of beclomethasone versus placebo in the treatment of preventing viral wheezing in the pre-school age group) beclomethasone reduced the risk of viral wheezing by 4% (from 11 to 7%) but the difference was not statistically significant. The results of Enbe confirms data already highlighted by some studies: that the IS has a modest effectiveness in preventing both recurrent wheezing viral and that of respiratory syncytial virus infections (bronchiolitis) in the child. In addition, no benefits were noted in reducing symptoms of infection to the respiratory tract. Therefore a more rational effort is needed regarding these pharmaceuticals both by doctors and above all by parents who frequently administer medicines to children for infections of the respiratory tract, without consulting their pediatrician.

Research question and objectives

Phase IV research project to be conducted by Family Pediatricians (FP) that can foresee on the one hand, training courses for Family Pediatricians and informational for families regarding the correct use of respiratory medication the ISs any iatrogenic illness caused by their improper use, on the other hand which may constitute a territorial survey on prescriptive appropriateness and safety of these pharmaceuticals in children aimed at evaluating the risk-benefit balance on usage.

The primary objective of the study is monitoring the use of respiratory medication and in particular the IS with careful analysis of the risk / benefit factor of the therapy (for possible ADRs) in the age group from 0 to 14 years, through: 1) Accuracy of diagnosis ,2) Therapeutic Appropriateness ,3) Safe use of medication ,4) Correct follow-up

Study design

Multicenter (Leading Region: MOLISE). The study is divided into two parts: an epidemiological / observational (case-control) and active surveillance (monitoring medications and follow-up)

Population

Children of both sexes, aged between 0 and 14 years suffering from illnesses (asthma, etc.) who are foreseen to be using respiratory medication and in particular the IS in compliance with the GL.

Variables

We have tried to reduce the selection bias through the insertion of a homogeneous population of children who are in need of CSI according to the GINA Guidelines (0-14 years). Children participating in the research are under the Family Pediatrician's care.In fact, the Italian FP take care of about 900 children from 0 up to 14 years of age. For this reason the case studies are absolutely homogeneous and the risk of drop out is really very low (<5%).

The information biases will be overcome through the collection of data taken directly from the FP database; the databases are always verifiable. This research will be verified by the Steering Committee (SC).Therefore there will be a careful analysis by the SC of the data to be included in the database according to the quality standards and without transcription biases.

In addition a further quality control will be guaranteed mainly by a statistically correct interpretation.The confounding factors as age, sex, socio-economic and educational level are not relevant to this epidemiological investigation

Data sources

After visiting a child with specific symptoms, the Family Pediatrician follows clinical diagnosis according to the GL International Reference (GINA asthma - NICE for URTI etc.)

During the 12 months of observation each pediatrician can report in real time, via their database (Infantia, JUNIOR BIT) each case being added with its observations.

Each pediatrician will compile medical records in their database where all the data will be recorded related to the child during their check-up to highlight the effectiveness of therapy and possible ADRs linked to respiratory medications and especially the IS (evaluation of growing stages).

Data relating to the verification of the clinical efficacy of the therapy will be highlighted with the assessment, after treatment of the medication foreseen by GL, and follow-ups during the disappearance of symptoms. The data for the evaluation of risks associated with the treatment, i.e. ADRs related to the treatment in the acute phase, will be available (if highlighted) after the enrollment phase for children, immediately after treatment with the medication foreseen by the RG and the follow-up phase. All the data will be controlled by the Steering Committee that will guarantee the quality of collection and data analysis.

Study size

This observational study will involve about 30 Family Pediatricians who have in care about 900 children from 0 to 14 years of age . Considering the incidence of asthmatic disease being almost 10% in that age group, we plan to recruit about 3,000 children that will be under supervision in the follow up.

Data analysis

The data of prevalence of prescriptions of children (both sexes, aged between 0 and 14 years) with a medical condition (asthma etc) which require the use of IS in conformity with the requirements of the GL, will be compared with the historical data (regional data of pharmaceuticals, in question), prescribed in the previous year contained in the Family Pediatrician’s database.

Furthermore also the data of prevalence of the prescriptions of IS (not in conformity with the requirements of the GL) will be compared with the historical data (regional data of pharmaceuticals, in question), prescribed in the previous year contained in the Family Pediatrician’s database. All this in order to show an improvement in the prescriptive appropriateness after the training course on pediatricians and families. Finally any ADRs related to the use of IS will be highlighted during the year of follow up.

Variuos statistical methods have previously evaluated in this purpose and in this study a combinations of the best performing methods will be applied to data pooled from all database.

The univariate statistical analysis and description of the characteristics of the sample will produce frequencies, medians and interquartile range for variable nonparametric and medium ± standard deviation for parametric variables. The confidence intermissions at 95% will be calculated where possible. The bivariate analysis for variable categorical will be produced using the two-tailed $\chi 2$ test and when appropriate, the Fisher corrector will be used; for numeric variables, any differences in averages between groups will be assessed by the student's t-test. Statistical significance is defined by a value of $P < 0.05$ and will be calculated at 95% Confidence Intermissions. The calculations will be produced using the statistical software R version 2.13.0

Milestones
Start of Data Collection: April 10,2016
End of Data Collection: April 10,2018
Study Progress Report: April 10,2017
Interim Reports: November 10,2017
Final Report of Study Results: June 10,2018

FAMILY PEDIATRICIANS MEDICINES
FOR CHILDREN RESEARCH NETWORK

PAGE OF SIGNATURE

Responsible of the Study

Dr. Ettore Napoleone
President of FP-MCRN Onlus

FINAL VERSION n.3 of December 20,2015

FAMILY PEDIATRICIANS MEDICINES
FOR CHILDREN RESEARCH NETWORK

REDS (REspiratory Drugs Survey) STUDY.

Active surveillance of respiratory drugs, especially Inhaled Steroids (IS) in children

RATIONALE AND BACKGROUND

From the OSMED 2013 data of pharmaceutical prescription in which a frequent use of pharmaceuticals stratified by age, emerges in children, especially in the age group from 0 to 4 years, showing a prevalent use superior of that of the15 and 44 age group. Despite the growing campaigns undertaken by the AIFA (Italian Medicines Agency) , in fact, the consumption and unsuitable prescription for certain categories of medicines, antibiotics and respiratory medicines, especially inhaled corticosteroids (IS) in the age group from 0 to 14 years showing an increase in adverse reactions related to them [RFN-AIFA -BIF 1 2009] (1-4).

In particular, OSMED 2013 data reported that 28% of children aged 0 to 4 years received at least one medication to the respiratory system with the increase in consumption of 1.1% over the previous year, making it evident of a non-rational use of these medications are not always based on scientific evidence.

The reference Guidelines (GL) for the treatment of Asthma (GINA- Global Initiative for Asthma) have been well established for years, and, despite the prevalence of this illness, that has settled down to between 9.5 and 10.5% in children aged 6 to 11 years, it has been particularly noted that asthma medicines, such as IS (beclomethasone, budesonide, flunisolide, fluticasone, etc.), are used inappropriately in children with an "over prescription" for conditions that do not require their use.

For example, beclomethasone is one of the most frequently prescribed medication in children. It is estimated that in Italy, it is used by about 2 million children and adolescents every year. Despite being an anti-asthmatic medicine, it is often prescribed for colds, coughs and sore throats, meaning Italian children have a 3 times higher chance of receiving an anti-asthma medication than their peers living in other European countries. An independent clinical test has been conducted to evaluate the efficacy of beclomethasone in the prophylaxis of bronco spasm due to viral infections of the airways (the so-called viral wheezing).

In the Enbe Study (Effectiveness of beclomethasone versus placebo in the treatment of preventing viral wheezing in the pre-school age group) beclomethasone reduced the risk of viral wheezing by 4% (from 11 to 7%) but the difference was not statistically significant [Pediatrics, 2014 .133 (4) and 505-12].

The results of Enbe confirms data already highlighted by some studies: that the IS has a modest effectiveness in preventing both recurrent wheezing viral [BMJ 1997; 4.35 (7112) 858-62] and that of respiratory syncytial virus infections (bronchiolitis) [Cochrane Database Syst. Rev. 2013; 4.6] in the child. In addition, no benefits were noted in reducing symptoms of infection to the respiratory tract. Therefore a more rational effort is needed regarding these pharmaceuticals both by doctors and above all by parents who frequently administer medicines to children for infections of the respiratory tract, without consulting their pediatrician.

From these considerations, there is a necessity for a Phase IV research project to be conducted on individual regions by Family Pediatricians (FP) that can foresee on the one hand, training courses for Family Pediatricians and informational for families regarding the correct use of respiratory medication the CISs any iatrogenic illness caused by their improper use, on the other hand which may constitute a territorial survey on prescriptive appropriateness and safety of these pharmaceuticals in children aimed at evaluating the risk-benefit balance on usage.

This research wants to above all, overcome the limitations of the OSMED data in which there is an inability to track diagnosis behind prescriptions and of a proper assessment of prescriptions of the various pediatric age groups.

This research will be widely spread to Family Pediatricians Reference Guidelines (GL) and implement skills (training course for Family Pediatricians) for a correct diagnosis, a viable treatment and close follow up of pathologies that require the use of these pharmaceuticals in children from 0 to 14 years in relation to their clinical seriousness.

Therefore this research will provide and add to current knowledge:

a) improvements in the appropriateness of prescriptions;

b) the acquisition of epidemiological reference data with the fewest possible errors (<5%) ;

c) a reduction in bias enrollment and Protocol drop-outs;

d) a reduction in the number of respiratory prescriptions compared to historical data (data of prescriptions in previous years);

e) a reduction in public spending, through prescriptions and inappropriate hospital admittances;

f) a correct valuation, in question, of ADRs related to pharmaceuticals administered and in particular on the effects of growing children [Cochrane Database Syst. Rev. 2014,17,7] (through careful auxology monitoring in children receiving CIS especially when using high doses);

g) an increase in reports of ADRs after training of Family Pediatricians.

All in all ensuring the development of knowledge and facilitating the transfer of the best scientific evidence to the professional practice of the Family Pediatrician.

Finally, the study will encourage closer synergy between the Family Pediatrician and families through better and more accurate information given to families on the use of respiratory pharmaceuticals and in particular of IS [Pharmacoepidemiol. Drug Sat.

2014.23 (4), 406-10] that will lead to a reduction of the "do it yourself" and self prescription used for illnesses that are not foreseen in RG and certainly a reduction in lost working days for parents and also reducing inappropriate hospital admission.

All of this, together with an information campaign that will include, in addition to the Family Pediatrician’s direct contact with families through specific informative talks, an implementation of posters, brochures on display at Doctor’s Surgeries and possibly CDs (sent directly to the families) on the proper use of respiratory pharmaceuticals in pediatrics (and in particular ISs).

Therefore it becomes very important to conduct the research in specific environments like that of pediatric surgeries in which the Family Pediatrician of the area has a more adequate opportunity compared to hospital / university to carry out results of the research especially regarding some illnesses in some categories of medicines that do not require hospital admittance, also consideration of the progressive de-hospitalization of many illnesses, especially in children.

In addition, the large number of case studies, the relationship of close collaboration with the families and the ability to run a proper and careful follow-up, is an essential element for the realization of clinical studies scientifically valid by Family Pediatricians of the area.

Last but not least emphasizing the uniqueness of this multicenter research in which issues are dealt with regarding prescriptive appropriateness, training for Family Pediatricians, information for families, importance of assessments and reporting of ADRs linked to the medication in question which are the main foundations of a correct formula of active pharmacovigilance in pediatrics.

PROMOTOR

The promotor is the FP-MCRN Onlus.
The Family Pediatricians-Medicines for Children Research Network is a member of ENPR-EMA (European Network Paediatric Research at the European Medicines Agency) and of ENCEPP (European Network of Centres of Pharmacoepidemiology and Pharamacovigilance) .
The FP- MCRN is a non-profit organization in which its aims and resolutions are research, training and especially that of the protection of vulnerable groups such as children with disabilities and chronic diseases.
The FP-MCRN Onlus intends to pursue research projects based on scientific and ethical principles (Ethical Considerations - 2008 EMA), conducted according to the rules of GCP in clinical pediatric trials, according to the GVP – Guidelines on good pharmacovigilance pratice -Module VIII- PASS with the aim of improving the quality of primary care in pediatrics.

LEAD INVESTIGATOR

Dr. Ettore Napoleone
President of FP-MCRN
Member of Coordinating Group of ENPREMA
Member of Joint ENPREMA-ENCEPP Working Group on Paediatric Pharmacovigilance

AVAILABLE FUNDING

Pharmacovigilance AIFA (Italian Medicines Agency) Call 2010-2011

TYPE OF STUDY

Multicenter (Leading Region: MOLISE).

The study is divided into two parts: an epidemiological / observational (case-control) and active surveillance (monitoring medications and follow-up)

THEMATIC AREAS

Emphasizing the originality of this multi-center research in which these issues are discussed

- prescriptive appropriateness,
- training (for Family Pediatricians)
- information (for families)
- the importance of evaluation and reporting of ADRs related to medications in question

MILESTONES

Start of Data Collection : April 10,2016
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RESEARCH QUESTION AND OBJECTIVES

Phase IV research project to be conducted by Family Pediatricians (FP) that can foresee on the one hand, training courses for Family Pediatricians and informational for families regarding the correct use of respiratory medication the ISs any iatrogenic illness caused by their improper use, on the other hand which may constitute a territorial survey on prescriptive appropriateness and safety of these pharmaceuticals in children aimed at evaluating the risk-benefit balance on usage.

In this study these questions will be discussed :

- prescriptive appropriateness,
- training (for Family Pediatricians)
- information (for families)
- the importance of evaluation and reporting of ADRs related to medications in question

The primary objective of the study

is monitoring the use of respiratory medication and in particular the IS with careful analysis of the risk / benefit factor of the therapy (for possible ADRs) in the age group from 0 to 14 years, through:

- Accuracy of diagnosis
- Therapeutic Appropriateness
- Safe use of medication
- Correct follow-up

Secondary objectives of the Study :

1) Evaluate the incidences / prevalence of illnesses that require the use of respiratory medication with particular reference to the IS of the region in children aged 0 to 14 years.

2)Widely disseminate the GL reference and implement skills (training for Family Pediatricians) for a correct diagnosis, for a viable therapy and follow-up of illnesses which require the use of these pharmaceuticals in children from 0 to 14 years in relation to their clinical severity.

3) Evaluate the effectiveness of the therapy in the acute phase according to the GL.

4) Reduce the number of pharmaceutical respiratory prescriptions (especially IS) compared to historical data (data of prescriptions by Family Pediatricians in previous years.)

5) Check and give a correct estimate of possible ADRs associated with this type of medication administered by Family Pediatricians (any effects on children’s growth through careful auxological monitoring in children receiving therapy especially when using high dosages of inhaled steroids.)

6) After training courses, increase the number of reported ADRs on behalf of Family Pediatricians.

7) Improve collaboration between the Family Pediatrician taking charge of the child up to 14 years and families for the management of this type of medication.

8) Decrease the "do it yourself" and auto prescriptions by parents after the information campaign.

9) Reduce lost working days on behalf of parents and hospital time.

10) Reduce government spending by reducing prescriptions and inappropriate admittances.

11) To disseminate results nationally and internationally, through scientific publications in peer review journals as an example of collaborative management between pediatrician and families.

12) Implement cooperation with the Family Pediatrician and Regional Pharmacovigilance Centers.

RESEARCH METHOD

STUDY DESIGN

Multicenter (Leading Region: MOLISE)
The study is divided into two parts: an epidemiological / observational (case-control) and active surveillance (monitoring medications and follow-up)

SETTING

Family Pediatrician Ambulatories

CENTERS INVOLVED

Participating in the research will be Family Pediatricians of their respective regions (Molise, Umbria and Emilia-Romagna) taking into account the Family Pediatrician's experience conducting clinical studies.

BASE OF THE STUDY

It is the population suffering from illnesses that are involved in the use of the medications in question recruited according to the criteria provided by the research i.e. the Family Pediatrician's patients in the (0-14 years) age group.

POPULATION

Children of both sexes, aged between 0 and 14 years suffering from illnesses (asthma, etc.) who are foreseen to be using respiratory medication and in particular the IS in compliance with the GL.

CASE DEFINITION

Children affected by(asthma etc) involving the use of the medication in question in compliance with the GL International (GINA)

CHILDREN TO BE ENROLLED

Inclusion criteria

- Children of both sexes, aged between 0 and 14 years suffering from illnesses (asthma, etc.) who are foreseen to be using respiratory medication and in particular the IS in compliance with the GL.
- Informed consent signed by parents or a legal representative
- Assent signed by children (aged 12 years)

Exclusion criteria

- Children of both sexes, aged between 0 and 14 years suffering from conditions that do not involve the use of respiratory medication and in particular the IS in compliance with the RG.
- Lack of informed consent signed by parents or a legal representative
- Lack of assent signed by children from 12 years of age

VARIABLES

We have tried to reduce the selection bias through the insertion of a homogeneous population of children who are in need of CSI according to the GINA Guidelines (0-14 years). Children participating in the research are under the Family Pediatrician's care.In fact, the Italian FP take care of about 900 children from 0 up to 14 years of age. For this reason the case studies are absolutely homogeneous and the risk of drop out is really very low (<5%).

The information biases will be overcome through the collection of data taken directly from the FP database; the databases are always verifiable. This research will be verified by the Steering Committee (SC).

Therefore there will be a careful analysis by the SC of the data to be included in the database according to the quality standards and without transcription biases.

In addition a further quality control will be guaranteed mainly by a statistically correct interpretation.

The confounding factors as age, sex, socio-economic and educational level are not relevant to this epidemiological investigation.

Method of controlling for confounders

The confounders shell be verified through:

1) Specific training courses allow FP to make an accurate diagnosis, even through the use of analysis and instrumental examinations, and the correct data entry in the database.

2) the FP database will ensure homogeneity and validation of the data also through the help of the Steering Committee that will control them. So we will have very few erroneous information.

3) The appropriate information given to families will avoid IS in clinical situations or conditions not foreseen by the GL.

4) the correct information on pediatric drugs will reinforce the concept to families to consult their pediatrician before administering any medication to

their children.

5)Regarding ADRs related to the administration of IS, taken into account is the fact that although there is a considerable amount of research, there is not enough information especially on the medium-long term follow-up.

6) The fact that Family Pediatrician have children up to 14 years of age under their care is a guarantee of a careful valuation in follow-ups regarding ADRs verified by the Steering Committee.

7) in addition, we will have to take into account the auxology evaluation of those children who use high concentrations of IS that are potentially most at risk for negative effects on their growth.

DATA SOURCES

DESCRIPTION OF THE STUDY

After visiting a child with specific symptoms, the Family Pediatrician follows clinical diagnosis according to the GL International Reference (GINA asthma - NICE for URTI etc.) also through the use of any laboratory tests (ESR, TAS, PCR, Prick tests, rapid tests for GABHS, urine stick etc) and (spirometry etc) that can be performed at the ambulatory (SELF-HELP) after a specific training course.

Setting out a follow-up medicinal and clinical collaboration with the families previously prepared on the correct use of respiratory medication and in particular the ISs as an ad hoc information campaign.

The Family Pediatrician who is in charge of the child suffering from a medical condition that requires the proper use of the IS, monitors vital signs and clinical observation for possible ADRs related to treatment and pursues the follow-up (auxology evaluation.)

For proper implementation of the project a close cooperation with the Family Pediatrician is required with the Regional Pharmacovigilance Centres who will give their logistical support and the necessary experience.

During the 12 months of observation each pediatrician can report in real time, via their database (Infantia, JUNIOR BIT) each case being added with its observations, which will comply with a baseline check-up, with an evaluation of the EO, body weight, will diagnose the illness and decide the treatment to be adopted in compliance with the international guidelines.

Each pediatrician will compile medical records in their database where all the data will be recorded related to the child during their check-up which will indicate all relevant symptom changes, any laboratory tests and other tests performed by the Family Pediatrician (SELF-HELP) or of other specialists and the type of therapy concerning the diagnosed pathology.

Despite the enrollment phase being 12 months, the Family Pediatrician’s database will be a very effective means for verifying the accuracy of the diagnosis, prescriptive appropriateness through the GL and constant epidemiological evaluation; It will also be important to highlight the effectiveness of therapy and possible ADRs linked to respiratory medications and especially the IS (evaluation of growing stages with careful auxological monitoring in children receiving therapy especially when using high dosages of inhaled steroids.)

Family Pediatricians taking care of children from (0-14 years) affected by illnesses is a guarantee of the applicability of the temporal database and follow-up without any suspension caused by a failure of communication by the families (a few drop-out.)

Assuming that the data contained in the Family Pediatrician’s database will be available through time, specific data research will be available soon after the statistical processing.

Data relating to the verification of the clinical efficacy of the therapy will be highlighted with the assessment, after treatment of the medication foreseen by GL, and follow-ups during the disappearance of symptoms.

The data for the evaluation of risks associated with the treatment, i.e. ADRs related to the treatment in the acute phase, will be available (if highlighted) after the enrollment phase for children, immediately after treatment with the medication foreseen by the GL and the follow-up phase.

All the Phasis of the study will be controlled by the Steering Committee that will guarantee the quality of collection and data analysis.

TIMETABLE AND PHASIS – workpackages :

The project will last 24 months.

After the preparation and approval phase of the project by the reference Ethics Committees, the project will consist of the five work packages:

1) In the **Start-up phase**:

a) **Recruitment of Family Pediatricians**: Family Pediatricians of the region will be involved in deciding to join together multi-regional project coordinated by the Molise region, recruited into the network of Pediatrician Experimenters (FP-MCRN);

b) **Constitution of the Steering Committe**

c) **Training for Family Pediatrics**: An investigator's Meeting will be organized by the Scientific Coordinator of the project on the plan of the research concerning the proper use of respiratory medication and in particular the CIS in childhood, the correct use of the Guidelines, prescriptive appropriateness, on possible iatrogenic illnesses caused by their improper use and on the general importance of reporting ADRs.

d) **Information for Families**: Posters, brochures and possibly CDs (directly to families) will be prepared and displayed in Family Pediatrician's surgeries or delivered directly to parents on the proper use of medicines in children, in particular the IS, in order to avoid the "do it yourself "and self-prescription for clinical situations not foreseen by the GL.

2) **Phase of Enrollment**:

a) Children will be examined in clinics (or at home) by the Family Pediatrician;

b) Laboratory tests and other medical tests will be carried out for a correct diagnosis (SELF-HELP) for the correct therapy and for possible monitoring;

c) The Family Pediatrician will conduct specific informational interviews with parents at the time of children's enrollment on the correct use of medications;

d) Therapies will be administered and will be included in the research of all cases of children aged between 0 and 14 years added with the Family Pediatrician's observations within the time limit of 12 months, effected with pathologies that require the correct use according to the GL;

3**) Follow-up Phases** of 12 months in which examinations of follow-up will be carried out (checkups which are part of the Family Pediatrician's normal routine - growth assessment with careful auxological monitoring in children receiving therapy especially when using high dosages of IS) for an attentive clinical evaluation, for result and safety measures and monitoring for possible ADRs.

4) **Phase of statistical analysis** of the data obtained.

5) **Phase of publication and dissemination of results**.

STUDY SIZE

This observational study will involve about 30 Family Pediatricians who have in care about 900 children from 0 to 14 years of age . Considering the incidence of asthmatic disease being almost 10% in that age group, we plan to recruit about 3,000 children that will be under supervision in the follow up.

DATA MANAGEMENT AND DATA ANALYSIS

Data Control

The data of prevalence of prescriptions of children (both sexes, aged between 0 and 14 years) with a medical condition (asthma etc) which require the use of IS in conformity with the requirements of the GL, will be compared with the historical data (regional data of pharmaceuticals, in question), prescribed in the previous year contained in the Family Pediatrician’s database.

Furthermore also the data of prevalence of the prescriptions of IS (not in conformity with the requirements of the GL) will be compared with the historical data (regional data of pharmaceuticals, in question), prescribed in the previous year contained in the Family Pediatrician’s database. All this in order to show any improvement in the prescriptive appropriateness after the training course on pediatricians and families.

Finally any ADRs related to the use of IS will be highlighted during the year of follow up. Calculating the impact of ADRs in the population at risk taking part in the research, until the risk assessment of some ADRs are compared and associated with specific pharmaceuticals within groups.

Various statistical methods have previously evaluated in this purpose and in this study a combinations of the best performing methods will be applied to data pooled from all database.

The univariate statistical analysis and description of the characteristics of the sample will produce frequencies, medians and interquartile range for variable nonparametric and medium ± standard deviation for parametric variables. The confidence intermissions at 95% will be calculated where possible. The bivariate analysis for variable categorical will be produced using the two-tailed $\chi 2$ test and when appropriate, the Fisher corrector will be used; for numeric variables, any differences in averages between groups will be assessed by the student's t-test. Statistical significance is defined by a value of $P < 0.05$ and will be calculated at 95% Confidence Intermissions. The calculations will be produced using the statistical software R version 2.13.0

QUALITY ASSURANCE AND QUALITY CONTROL

The responsibilities that the Steering Committee (SC) within the FP are:

- Ensure the leadership that pediatricians involved in the study have operated at their best, respecting the policy quality;

- Ensure the preparation, review, storage, distribution, training and compliance with Standard Operating Procedures (SOP);

- Carry out, with predifined frequency, the audit of the various activities of a clinical study and the results obtained, ensuring correspondence with protocol, ICH-GCP compliance, of SOPs and local regulations;

- Review documents created by FP such as protocols, CRFs, Informed Consents and Information Sheets for the patient and contracts with companies; Diary of the subject

- Verify the completeness of the Trial Master File (documentation filed with the trial sponsor);, as defined by ICH-GCP.

- The final report of the study (including date listing and Statistical Report).

The audits are of two types and are conducted according to ENGAGE (European Network of GCP Auditors and other GCP Experts)

1) - specific study, are subjected to audit the activities of a specific study to assess
The quality; the FP-MCRN gives priority to studies on the basis of:

- Importance of the study; - Type and complexity of the study; - number of subjects enrolled; - risk level of the subjects;

2) -The System is audited in a single process, applied to all clinical tests, conducted
within the FP; which serves to ensure the completeness of operational steps
and disclosure of the entire process, through the application of SOP and compliance with GCP and with GPV;

The processes that primarily are verified by SC are the Communication and recording adverse events during clinical tests, the preparation of the Investigator's Brochure (documentation containing all clinical and non-clinical testing of the product), the management of the SOP and training of pediatricians involved in clinical tests.

To ensure that the data produced by a clinical study, were collected and recorded in accordance with the Protocol, the SOP, the GCP ,the GPV and the applicable regulatory requirements, the FP-MCRN conducts audits at the FP Experimenters' Offices.

The audit at the experimenters' is also useful to ensure that the monitoring is conducted in a qualitative way. The SC check that the documentation of the study (information sheet, informed consent, CRF, medical records or other original documents)is to collect all the documents required by GCP and that those documents be coherent and to conformity; verifying adherence to the protocol: if in compliance with the criteria of inclusion / exclusion and to follow the correct procedures for the evaluation of subjects, ensure the accuracy and completeness of recording the data. The data reported in CRF(or in FP database) must correspond with what has been written in the medical record and in CRF, information should not be omitted for the study purposes. The SC ascertains the presence of informed consent of all patients enrolled in the study, verifying that it has been signed and dated by the person and shall record the signature and the date of the investigator who conducted the discussion with the patient's informed consent. It also ensures that the PdF-investigator has successfully managed the experimental drug, accounting it and storing it in a cabinet in the pharmacy.

At the end of the audit at the center, the SC assesses the investigator who recorded the observations and offers helpful suggestions to improve the quality of the study.

After each audit the SC must draw up a report which shows their comments highlighting any deficiencies and possibly suggesting corrective actions.

TECHNICAL ISSUES

Preface

The system, implemented with the collaboration o with technology engineers at the forefront in the design and implementation of IT systems, has enabled the creation of a network between the different pediatricians involved. Through this network process monitoring and exchange of data can be carried out with centralized management as required by the regulations.

The system

The system, accessible from any computer connected to the Internet through the use of user name and password, is aimed at users also not experts in computer science and does not foresee the need for training, as the computerized process accurately reproduces the paper flow .The entry procedures and data management are standardized .The registration form involves the insertion of personal identifiers (name, e-mail)

After filling out the form the system will send an e-mail to the e-mail address registered indicating the details for the connection, according to the guidelines required by the safety and the privacy legislation. For security reasons, the system prompts the user to change their password on the first connection..

User profiles and activities

The data recorded in the system belong to the individual operating units (pediatricians). Each user can enter and view data on their patients and will analyze them through navigable reports available online.

At the central database, the information is available in a combined structure without details individual patients. Access to data and functionality is made in relation to the profile assigned to each user who logs in using their access codes.

Subjects with "active" profile

Pediatrician: provides the insertion of data, updated and consultation data on patients treated at their clinic. The pediatrician registers the patient, inserts the record diagnosis card, provides data on the state of health of the patient. Registers the therapy required (for whatever reason) and concludes the record card.

Subjects with "consultative" profile

Computer engineer: access for centralized monitoring, both in consultation and in updating information related to the entire registry. Pediatrician: see the reports with aggregated view of data.

Access to information

The standardization of quality procedures and centralized control guarantee the immediate availability of the data entered. Therefore, descriptive reports and monitoring have been made, updated daily and accessible directly via the web at different levels of aggregation.

The quality of the data

Many quality controls have been implemented, which are activated during data entry. At the registration of a patient, the system performs a check on homonyms and notes if the same patient is registered in the database for the same drug, by notifying the information to the clinician and tracing the course of treatment of patients treated with major pharmacies. The system also checks the parameters of eligibility to the treatment of the patient: in the case where the appropriateness of use is not met, the system will stop recording, indicating the data that makes the request non appropriate. To help clinicians to meet the expected timing of the completion of the ballot patient, the system recalls the completion of the data using an automatic summary of situations apparently remained pending, entitled "Reminder". The reminder is updated daily with the findings from the completeness checks performed by automatic procedures in the night. An e-mail is sent fortnightly to interested users in order to evoke the consultation of the Reminder.

Changing data: e-Query

The data entered by clinicians cannot be changed by the user. To ensure the integrity and consistency of information data can only be changed by technology engineers.

If the pediatrician has a necessity to correct the data previously entered, a request must be sent to the computer engineer using the form e-Query. The computer engineer receives an e-mail notification, evaluates the change requested and makes the correction in the database. The exchange of requests, responses, and the changes are automatically tracked and stored in a historical database.

Security and confidentiality of data

The computer engineer applies the rules and regulations laid down under national legislation on privacy (Legislative Decree 30 June 2003, n. 196); in particular, guaranteed are the rules concerning the mechanisms of data protection.

Below some salient aspects of the system are enucleated.

It is the faculty of the medic to show, for example, only the patient’s initials in the appropriate place of the tabs. It stresses that, in this situation, it is a natural aspect of the data telematics that promotes respect for the privacy of the patient finally overcoming, for example, the previous general practice of sending paper ballots completed by hand and faxed with the patient’s data in clear visibility. The National Insurance No. is requested when there are cases of obliged discounts approved by the pharmaceutical companies in agreement with named pharmacies. As a consequence, in these cases, there is a necessity to individualise potential homonyms of multiple registrations of the same patient in other clinical centers.

The technology partner entrusted with the management of the information is the computer engineer who has a special System Certification of information security management (ISO 27001: 2005), issued by the International Certification on data security . The certification regards the following areas of activity: "Analysis, design, development, maintenance and supplying services of the Decision Support System and infrastructure information systems for conducting, monitoring and analysis of clinical tests and epidemiological registries, aimed at organizations working in the health sector.”The domain system domain thus appears well circumscribed to the activities of the department" information systems and services for health ", who takes data processing to elevate sensibility and criticality. This standard provides security not only as a set of technological countermeasures, but also organizational and behavioral measures, defined within documented operating procedures.

User support

To provide guidance to users on the use of the computer system a "Guide to using the system" has been prepared and constantly updated, printable or can be searched online to consult the Register. In addition, the section "Information and updates" provides general information on the computer system and has the latest features implemented. To support users in their data entry tasks and to provide information or clarification a centralized help desk has been prepared. In case you need assistance you can send an email using the link provided on the homepage. Information about the requests received and answers are stored in a dedicated system that, in addition to offering the user a continuity of care, allows the verification of the fulfillment of requests, monitoring response times.

LIMITATION OF THE RESEARCH METHOD

From what is described in the preceding paragraphs, we do not think there are many limitations of the research method in this observational study.

EXPECTED RESULTS

1) Improving the appropriateness of prescription after specific training courses for Family Pediatricians according to the RG requirements (GINA - NICE etc.) for a correct diagnosis.
2) Acquire epidemiological data reference with the fewest possible errors (<5%)
3) To conduct clinical research to ensure the development of knowledge and facilitate the transfer of the best scientific evidence by the Family Pediatrician.
4) Provide better and more accurate information to families on the use of respiratory medications and in particular of the ISs
5) Make a reduction of the "do it yourself", self prescription of IS for illnesses that are not foreseen in RG requirements
6) Reduce the number of prescriptions for respiratory (IS) compared to historical (prescription data of the FP in previous years)
7) Reduce government spending by decreasing prescriptions and inappropriate hospital admittances

8) Highlight the smallest possible number of ADRs associated with the administration of the medication in question

9) Make an increase in reports of ADRs after training and after proper information to families

10) Improve synergy between Family Pediatricians and Families

11) Reduce lost working days by parents and of any inappropriate hospital admittances

12) Know and reproduce this type of experience as a fact on regional, national and international levels

13) Implement collaboration with Family Pediatricians and the Regional Centres of Pharmacovigilance (PV)

INDICATORS (structure, process, outcome)

Number of children involved in the study; number of FP involved in the study; incidence of asthma in children from 0 to 14 years ; number and prevalence of the prescriptions of the IS in children with medical conditions requiring treatment with IS (asthma etc); number and prevalence of the prescriptions of the IS in children with medical conditions that not require treatment with IS (viral infections, viral wheezing, bronchiolitis, etc.); number of ADRs related to IS.

VALUATION OF THE RESULTS

Accuracy of diagnosis: diagnostic evaluation on the basis of available data (spirometry, FEV, etc.) by a Steering Committee (SC)

- Number of children with medical conditions requiring treatment with IS (asthma etc), number of children suffering from illnesses that do not require treatment with IS (viral infections, viral wheezing, bronchiolitis, etc.).
- Appropriate treatment - Verification by the SC:

1) if the prescribed pharmaceuticals are those identified and suggested by GL (also depending on the stage of the illness);

2) if the children take the prescribed medications appropriately; then verification of adherence to treatment through the MPR (medication possession ratio) or PDC (proportion of days covered) from the DDD.

- Pharmaceutical expenditure - Number of prescriptions (FARMASTAT, Social Security Card, Family Pediatrician Database), number of packs sold
- Public expenditure – Number of inappropriate hospital admittances
- Safety usage- calculating the impact of ADRs in the population at risk taking part in the research, until the risk assessment of some ADRs are compared and associated with specific pharmaceuticals within groups.
- Number of ADRs. Number of reports of ADRs by Family Pediatricians

INSURANCE

Being an observational study (all is within norm as part of the clinical routine of the Family Pediatrician) therefore insurance cover is not foreseen.

PROTECTION OF HUMAN SUBJECTS

Commencing from the principles of the Helsinki Declaration, the study will be conducted according to GCP and GVP (Guidelines on good Pharmacovigilance practice – Module VIII-PASS) standards, respecting European Directives, in accordance with the guidelines for the conduct of clinical trials in children and in accordance with the Ethical Considerations for clinical trials on medicinal products conducted with the pediatric population - EMEA 2008.

This study will be subject to very specific rules regarding the protection of personal data in accordance with the Guidelines for the processing of personal data in the context of clinical trials of drugs (Official Gazette no. 190 of 14.08.08), refering to applicable regulations, nature of the data, notification, ownership of treatments aimed at testing, other parties involved in the testing of drugs, information for patients, consent to data processing, exercise rights, data transfer abroad, retention period of biological data and samples for further research purposes, custody and security of medical data. This Protocol will be evaluated by Ethic Committee of ASREM Molise.

All parents (or legal guardian) of the children participating in the research will be given an informative document regarding the project objectives and organisation, highlighting security as its aim.

There will be a great deal of information to families providing necessary facts, giving them the possibility of signing a willing and informed consent, according to ICH GCP and in compliance with the Helsinki Declaration and Ethical Considerations for clinical experiments on medical products for the pediatric age group - EMEA 2008.

A written consent will then be required regarding the processing of personal data according to law 196/2003.

A copy of the informed consent and assent, signed for acceptance, will be retained by the FP; a second copy will be given to parents (or legal guardian) of the patient and directly to the children.

Possible risks for Patients

There are no particularly important maneuvers and invasiveness for enrolled children. Expert FP will also be recruited to ensure all the safety standards required for proper implementation of the Protocol. There will be a great deal of infomation and explanatons given to families giving them the possibility of signing a willing consent.

Reasonable possibilities benefits

Through the REDS Study we hope a improvement of: 1) prescriptive appropriateness and the educational of FP; 2) the correct families information to avoid self-prescription and "do it yourself" 3) the reduction of ADRs associated with the improper use of IS.

MANAGMENT AND REPORTING OF ADRs

An adverse event (AE) is any undesirable medical event occurring in a subject to which study product was administered, regardless of causality assessment. An adverse event can therefore be a negative sign, and not intentional (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study product, whether or not considered related to the product itself. All adverse events, including reported or encountered problems, complaints, or symptoms should be recorded in the form. Any adverse event must be evaluated for the duration, intensity, and the causal relationship with the investigational product or other factors.

Patients should be instructed to report any EA that arise to the FP-investigator.

FP-Investigators are required to assess the presence of any EA for each visit. Any EA occurring during clinical trial, including the follow-up period, must be registered in the form of adverse events.

In Follow-up Phases of 12 months in which examinations of follow-up will be carried out (checkups which are part of the Family Pediatrician’s normal routine) FP will check and give a correct estimate of possible ADRs associated with this type of medication administered (any effects on children’s growth through careful auxological monitoring in children receiving therapy especially when using high dosages of inhaled steroids.)

AMENDMENTS AND UPDATES

No one amendment and update had be done

PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

To disseminate results nationally and internationally, through scientific publications in peer review journals

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