PROTOCOL

STUDY ON MEDICINES ACCEPTABILITY IN CHILDREN

ClinSearch
110, Avenue Pierre Brossolette
92240 Malakoff
France
Phone: +33 1 47 35 17 17

June 29th, 2016

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1 INTRODUCTION

Medicines are designed to address unmet therapeutic needs while ensuring the safety of patients. Preclinical and clinical trials allow medicines' designers to support the efficacy and safety of their medicinal product under normal conditions of use and thus get a marketing authorisation from competent authorities.

Safety and efficacy of medicines depend on patient's compliance. It is the extent to which patient follow physicians' instructions. Poor compliance could cause poor health outcomes as treatment failure or complications. Ensuring patient's compliance require to prevent under or over consumption of medicines. So, a medicine must be designed to be accepted by patients but not to be their preferred product. Medicine's designers have to prevent barriers to acceptability but there is no requirement to maximise users' pleasure [1].

Consideration of patient acceptability becomes of utmost importance in paediatric or geriatric populations to prevent poor compliance and unlicensed used. Effectively, unauthorized tablet crushing or capsule opening for child and elderly patients is frequently reported in literature whereas it may cause dosing inaccuracies and impair bioavalabitilty [2, 3]. It is due to no accessibility of well-accepted age-appropriate formulations.

The European Medicine Agency (EMA), in its guideline on pharmaceutical development of medicines for paediatric use [4], underlines the importance of acceptability and its critical effect on compliance. Acceptability is defined as "the overall ability and willingness of the patient to use and its care giver to administer the medicine as intended". It is determined by patients and medicines characteristics. Patient's characteristics that are mainly prone to affect acceptability are the patient's age, its health status, behaviour, disabilities and socio-cultural background. Regarding medicines, such characteristics could be its palatability, swallowability, appearance, required dose, required dosing frequency, duration of treatment, complexity of the preparation, mode of administration, selected administration device or container closure system [4]. The main elements impacting on acceptability which have to be considered in testing may depending on medicines and patients population [5]. For instance, taste could be important for oral medicines but not for ear preparations. It could be more important for children than for elderly because taste sensitivity is decreased in this population [6].

According to this guideline, coming into effect the 15 February 2014, "evaluation of the patient acceptability of a paediatric preparation should be an integral part of the pharmaceutical and clinical development" [4]. However, the EMA underlines that knowledge on acceptability testing remains limited and there is no internationally-agreed method to evaluate it. Medicine's designers have to select cautiously among methods that could produce different outcomes when testing a same medicine in a particular patient population. The relevance of the choice will need to be addressed when submitting the application for marketing authorisation.

Preliminary results of an observational, multicentre, transversal and national study in the French paediatric population showed that a model using mapping and clustering processes, based on objective measures on medicines use, allows to assess the acceptability of medicines for paediatric use [7, 8]. The model allows to position any medicine on the acceptability map and to define an acceptability profile ("well-accepted",

"accepted", "poorly accepted" and "not accepted") whichever the medicines' and the patients' characteristics. Thus it allows standardized comparison among medicines and patient populations.

In order to increase the knowledge on acceptability of medicines in a wide paediatric population we propose to involve doctors or pharmacists in community or hospital dispensaries in France and abroad as recruiting centres. In addition, longitudinal data would be collected to study the acceptability of medicines over time and the impact of the required dosing frequency and duration of treatment on it. Therefore, this observational, multicentre, longitudinal and international study will be carried out.

2 OBJECTIVES

Develop the knowledge on medicines acceptability in the paediatric population with a standardized assessment.

3 STUDY DESIGN

An observational, multicentre, longitudinal and international study.

4 METHODOLOGY

4.1 Investigational centres

Investigational centres will be doctors or pharmacists into community or hospital dispensaries. They will be recruited in different countries by phone, on a voluntary basis.

Written information about the study shall be provided to each recruited centre and will specify inclusion criteria, arrangements for participation, content of the questionnaire, a login test code allowing for exploration of the online questionnaire without recording any data, as well as contact details of the researcher responsible for the study.

Concomitantly, investigating centres will receive written information to be handed over to patient's guardian and patient specifying study context, arrangements for participation, the contact details of the healthcare professional responsible for the recruitment, confidentiality and regulatory considerations.

Investigating centres will also receive participation leaflets specifying the observational measures that need to be performed during the medicine use, the web address of the online questionnaire and a personal access code, which will allow the participants to connect to the questionnaire. The access codes sent to each investigating centre will be recorded by the research team.

Investigating centres will be encouraged to propose the study to eligible participants.

4.2 Inclusion criteria

- Patient's age < 18 years
- Receiving any medicine
- Oral participation agreement of the patient's parent/guardian and oral agreement of the patient if its age and its all-over health status allows him to do that
- Patient and/or patient's parent/guardian ability to understand and complete a written web-questionnaire

4.3 Study participation

Volunteers will be invited to complete a web-questionnaire.

The web-questionnaire could be completed by a parent or a relative hereafter referred to as *assistant* and/or by the patient if its age and its all-over health status allows him to do so, and/or by a professional healthcare.

To fill in the questionnaire, the participants need to access the study website at the address written on the participation leaflet and to login with the personal access code, which they will also find on the leaflet. A unique access code for each patient. The access codes are unique. They have 3 different levels: 2 letters corresponding to the country, 3 randomly selected digits and 3 randomly selected letters.

The questionnaire focuses on the first medicine taken by the child following study inclusion.

Participants are asked to complete the questionnaire at 3 time-points:

- After the first medicine administration;
- After the medicine administration occurring 24 hours after the first one (if the required dosing frequency allows it);
- After the medicine administration occurring 15 days after the first one or after the last medicine administration if the duration of treatment is prior to 15 days (if the required dosing frequency allows it).

At inclusion, if the investigational centres have access to the diagnostic, the comorbidities, the concomitant treatments and information on the patient, they are invited to enter this information via the website with the personal code of the participant. If no corresponding data on medicine use are entered within one month, the information on treatment and patient entered at inclusion will be automatically deleted as described in the "data management and storage" section.

4.4 Data collection

4.4.1 Data collected by the healthcare professionals

<u>At inclusion:</u>

The healthcare professional should report information on the prescribed treatments, if the information are available at the investigational sites:

- Number of prescribed treatments

- For each prescribed treatment:
    - the name of the medicine (brand name or international non-proprietary name + strength + dosage form)
    - the required dose (e.g. the dosing volume, number of tablets, etc.)
    - the required dosing frequency
    - the duration of treatment
    - the disease treated
- Other comorbidities

The healthcare professional should also report information on the patient, if the information are available at the investigational sites:

- Patient characteristics
    - gender
    - age
    - geographical origin of parents (according to the EMA the child's culture affects the acceptability)
    - whether the medicine is being taken for the first time or has been taken before

If the healthcare professional observes the first medicine's administration, he has to provide the name of the observed medicine (brand name + strength + dosage form).

- Observational measures performed during the medicine use
    - the patient's reaction during the administration
    - the result of the administration
    - the time needed to prepare the medicine
    - the time needed to administrate the medicine
- The methods used to achieve administration
    - divide the required dose intake
    - halve the medicine (e.g. tablet)
    - crush the medicine (e.g. tablet)
    - open the medicine (e.g. capsule)
    - mix the medicine with water or other drink or food
    - eat/drink something before or after the medicine to mask the taste or ease swallowing
    - use of a not provided preparation/administration device
    - use of a reward
    - use of restraint
- Subjective information on medicine use
    - general feelings about ease of preparing the medicine
    - general feelings about ease of administrating the medicine

  - additional remarks on medication acceptability
- Objective information on care
  - the person(s) in charge of preparing the medicine
  - the person(s) in charge of administrating the medicine
  - the place where the medicine is administered

The healthcare professional should complete a simplified questionnaire described in the following section after the medicine administrations occurring 24 hours later and 15 days later (or after the last medicine administration, if the duration of treatment is less than 15 days), if the required dosing frequency allows it. To perform patient follow-up, the healthcare professional will register the link between patient identity and access code into a confidential written document. The document will be stored in the investigational site and deleted after patient participation in the study (15 days maximum).

4.4.2 Data collected by the assistants and/or the patients

Participants are not obliged to answer each question. Once validated, participants will not be able to modify their answers.

<u>After the first medicine administration:</u>

Participants have to provide information on the observed medicine

- The characteristics of the first treatment administered
  - the name of the medicine (brand name + strength + dosage form)
  - the required dose (e.g. the dosing volume, number of tablets, etc.)
  - the required dosing frequency
  - the duration of treatment
  - the disease treated

Participants have to provide information on the medicine use

- Observational measures performed during the medicine use
  - the patient's reaction during the administration
  - the result of the administration
  - the time needed to prepare the medicine
  - the time needed to administrate the medicine
- The methods used to achieve administration
  - divide the required dose intake
  - halve the medicine (e.g. tablet)
  - crush the medicine (e.g. tablet)
  - open the medicine (e.g. capsule)
  - mix the medicine with water or other drink or food

  - eat/drink something before or after the medicine to mask the taste or ease swallowing
  - use of a not provided preparation/administration device
  - use of a reward
  - use of restraint
- Subjective information on medicine use
  - general feelings about ease of preparing the medicine
  - general feelings about ease of administrating the medicine
  - additional remarks on medication acceptability

Participants have to provide information on the patient

- Objective information on care
  - the person(s) in charge of preparing the medicine
  - the person(s) in charge of administrating the medicine
  - the place where the medicine is administered
- Patient characteristics
  - gender
  - age
  - geographical origin of parents (according to the EMA the child's culture affects the acceptability)
  - whether the medicine is being taken for the first time or has been taken before
- Comorbidities & concomitant treatments
  - comorbidities
  - concomitant treatments

At the end, participants are invited to complete the questionnaire again after the medicine administration occurring 24 hours later (if the required dosing frequency allows it). They could provide their email address in order to be reminded to login again. Email addresses will be automatically deleted 15 days later.

<u>24 hours after the first administration:</u>

Participants have to provide information on the medicine use

- Observational measures performed during the medicine use
  - the patient's reaction during the administration
  - the result of the administration
  - the time needed to prepare the medicine
  - the time needed to administrate the medicine
- The methods used to achieve administration
  - divide the required dose intake
  - halve the medicine (e.g. tablet)

  - crush the medicine (e.g. tablet)
  - open the medicine (e.g. capsule)
  - mix the medicine with water or other drink or food
  - eat/drink something before or after the medicine to mask the taste or ease swallowing
  - use of a not provided preparation/administration device
  - use of a reward
  - use of restraint

At the end, participants are invited to complete the questionnaire again after the medicine administration occurring 15 days after the first one or after the last medicine administration, if the duration of treatment is less than 15 days (if the required dosing frequency allows it). They could provide their email address in order to be reminded to login again. Email addresses will be automatically deleted 15 days later.

<u>15 days after the first administration or after the last administration of medicine if the duration of treatment is inferior to 15 days:</u>

Participants have to provide information on the medicine use

- Observational measures performed during the medicine use
  - the patient's reaction during the administration
  - the result of the administration
  - the time needed to prepare the medicine
  - the time needed to administrate the medicine
- The methods used to achieve administration
  - divide the required dose intake
  - halve the medicine (e.g. tablet)
  - crush the medicine (e.g. tablet)
  - open the medicine (e.g. capsule)
  - mix the medicine with water or other drink or food
  - eat/drink something before or after the medicine to mask the taste or ease swallowing
  - use of a not provided preparation/administration device
  - use of a reward
  - use of restraint

Participants have to provide information on the patient's adherence

- Information relative to treatment follow-up
  - whether the patient stopped the treatment prematurely
  - what percentage of the prescribed dose has actually been taken
  - if adherence was poor, for what reasons:

- child activities (school, sports, etc)
- difficulties to prepare the medicine
- difficulties to administer the medicine

4.5 Data management and storage

An electronic report form available online allows data collection. It was designed specifically for the study using Oracle Java EE 7™.

Recorded and validated data will be stored within a secured ClinSearch server. SSL protocol ensuring data encryption during data transfer. That provides communications security.

Daily batch processes will automatically delete the email address after 15 days and the data on patient and treatment entered at inclusion if no corresponding data on medicine use are entered within one month.

Only duly authorized and authenticated ClinSearch employees will be allowed to extract data from the database for statistical analyses. Email address won't be extracted. So data for analysis will be completely anonymous.

4.6 Data analysis

Because medicines and persons are randomly selected, a description of the obtained sample, medicines and patients, will be performed.

Categorical variables will be described by the size and the percentage of each category. Numerical variables will be described by the size, the minimum value, the first quartile, the median, the mean and the standard deviation, the third quartile and the maximum value.

Each medicine's assessment will be associated with one of the response options (categories) for each objective measure (variables). Multiple Correspondence Analysis (MCA) will be used as the mapping process to produce the acceptability map. The Hierarchical Classification on the Principal Components (HCPC) will be used as the clustering process to define acceptability profiles.

The use of a given medicine will be assessed several times with different patients. The barycentre of these assessments will define the medicine's position on the map and will be linked to an acceptability profile. A confidence ellipse will be drawn around the barycentre. The ellipse held the true medicine's position in the population with a defined probability. Acceptability of two medicines will be significantly different if their ellipses do not overlap on the acceptability map.

The R packages FactoMineR [9] and MissMDA [10] will be used to perform MCA and HCPC and to handle missing data. Data analyses in R and results will be checked with SAS 9.4 for patients with complete data.

4.7 Sample

This methodology aims at designing a model that fits with the real-life data collected. Hence the number of patients to be included in order to obtain statistically significant results cannot be predicted. By continuously feeding the model with new data, new medicines will

be plotted on the acceptability map and the positions of medicines will become more accurate.

Data collection, enrolment of new centres and inclusion of new participants, could continue until new data do not improve the model any more. This study will be carried out during 18 months following the approval.

5 ADHERENCE TO REGULATORY AND ETHICAL CONSIDERATIONS - ADMINISTRATIVE ASPECTS

5.1 Regulatory and ethical considerations

The study is strictly observational. As such, it does not influence patient treatment and usual child medical care. Furthermore, this study does not impact on the physical or psychological integrity of participants and does not require additional follow-up visits.

The European Union Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data, apply to the present study. Consequently, prior to the study start, the protocol and the data management process will be submitted for approval and/or authorisation to the local authorities, when applicable. Additionally, the study will start in each country after appropriate local ethics committees and/or health authorities' approvals and/or authorisations are granted.

5.2 Quality assurance

The study will be conducted in accordance with the Standardised Operating Procedures of ClinSearch.

All study-related documents will be retained electronically on removable media by ClinSearch, so that data could be analysed and published, and audits could be carried out by the Quality assurance Department of ClinSearch.

5.3 Pharmacovigilance

Physicians participating in the study will ensure their obligations in terms of pharmacovigilance process, according to local regulation.

5.4 Confidentiality

The physicians and pharmacists who participate in, and any person who collaborates to the study must keep professional confidentiality in particular concerning the assessments performed, the patients involved, and the obtained results.

5.5 Publication and communication

This study may generate publications and/or communications in a peer-reviewed journal and/or in a scientific meeting jointly chosen by ClinSearch.

All information produced by this study is considered as being confidential, at least until appropriate analysis and control of data has been performed by ClinSearch. Results must only be published or presented with the agreement of ClinSearch.

Moreover, any communication or presentation must at least refer to ClinSearch.

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