Protocol

STUDY ON MEDICINES ACCEPTABILITY IN CHILDREN

Norwegian sub study

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Project group

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Norsk sammendrag (Study synopsis in Norwegian)

Studien er en substudie under en internasjonal studie. Prosjektet startet opprinnelig i Frankrike, men det planlegges substudier i flere land, deriblant Storbritannia. Hovedansvarlig for studien er Fabrize Ruiz, ClinSearch, Frankrike.

Hensikten i studien er å undersøke hvilke egenskaper ved medisiner som har betydning for hvorvidt barn finner dem akseptable. Forskingsprosjektet har etablert en standardisert, validert statistisk metode for å vurdere ulike legemidler, ClinSearch Acceptability Score Test®. Nå ønsker man å styrke modellen med data fra flere land og flere barn.

Dette er en internasjonal, multisenter, longitudinell observasjonsstudie. Foreldre som henter legemidler til sine barn på apoteket vil bli bedt om å delta i studien. De vil få utlevert informasjon om studien, en webadresse for pålogging og en personlig kode. Innlogging med personlig kode ansees som samtykke til å delta i studien. Websiden og databasen tilhører ClinSearch.

Inklusjonskriterer er barn under 18 år som får minst et legemiddel på resept, og hvor foreldre har tilstrekkelige norskkunnskaper til å kunne fylle ut spørreskjemaet.

På websiden blir foreldrene bedt om å fylle ut en del spørsmål knyttet til barnets inntak av den første legemiddeldosen etter inklusjon til studien. Deltakerne bli bedt om å fylle ut skjemaet ved tre tidspunkt:

- Ved første inntak av legemiddel etter inklusjon
- Ved legemiddeladministreringen som skjer 24 timer etter den første
- Ved legemiddeladministreringen som skjer 15 dager etter den første, eller etter siste legemiddeldose hvis behandlingen har kortere varighet enn 15 dager.

Spørreskjemaet inneholder spørsmål om hvilket medikament, dosering og for hvilken lidelse barnet blir behandlet. Videre hvem som er ansvarlig for å gjøre i stand og administrere legemidlet, barnets reaksjon på legemidlet, hvorvidt hele dosen ble tatt, hvor lang tid det tok å få i barnet legemidlet og hvilke metoder man eventuelt måtte ty til. Til slutt skal man fylle inn opplysninger om barnet, som kjønn, alder.

I dataanalysen har vi utviklet en metode som klassifiserer pasientopplevelser til ulike aksept-skår klasser (grader av aksept), basert på kombinasjoner av ulike variabler i pasientopplevelsen. Ved å kombinere pasientopplevelser for ulike forklaringsvariabler (for eksempel alle pasientopplevelser for et spesifikt legemiddel eller pasientkarakteristika), kan man da analysere hvilke variable som påvirker grad av aksept..

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List of abbreviations

CAST – ClinSearch Acceptability Score Test®

EMA – European Medicines Agency

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 adherence to the treatment as agreed with the prescribing physicians. Ensuring patient's adherence contributes to the prevention of under- or over consumption of medicines and reduce the risk of treatment failure or adverse events. Therefore, a medicine should be designed to be accepted by patients but not necessarily to be their preferred product of choice [1].

Consideration of patient acceptability becomes of utmost importance in paediatric or geriatric populations: Due to lack of well accepted, age-appropriate formulations, unauthorized crushing of tablets or capsule opening for children and elderly patients is frequently reported in literature [2, 3, 11]. Such procedures may cause dosing inaccuracies, impair bioavailability and affect taste [2, 3].

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 adherence. Acceptability is in this guideline 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 which have to be considered in testing acceptability may depend on the medicines to be studied and the patient 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 the latter population [6].

According to this guideline, which came 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 the 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 paediatric population an observational, multicentre, longitudinal and international study has been designed to collect data from a wider population, using the developed model. This sub study will involve pharmacists in community or hospital dispensaries in Norway as recruiting centres. In addition, longitudinal data will be collected to study the acceptability of medicines over time and the impact over time of the required dosing frequency and duration of treatment.

This document is the protocol of the Norwegian sub study.

2. OBJECTIVE

The objective of this study is to increase the knowledge on which factors that affects medicines acceptability in the paediatric population, using a standardized assessment tool developed by ClinSearch, the ClinSearch Acceptability Score Test (CAST)

3. STUDY DESIGN

Observational, multicentre, longitudinal study using web-based questionnaire.

4. METHODOLOGY

4.1. Investigational centres

Recruiting centres will be Norwegian pharmacies, including both community and hospital pharmacies. Centres will be enlisted in collaboration with the pharmacy chain head offices.

Written information about the study shall be provided to each recruiting 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, recruiting centres will receive participation leaflets to be handed over to each participating subject. These leaflets will contain general information about the aims of the study and the observational measures that need to be performed during the medicine use. In addition, the leaflet will provide a personal login code, which will allow the participants to connect to the online questionnaire. Thus, the leaflet delivered to the participants are pre-identified with a unique pre-printed code.

4.2. Inclusion criteria

- Patient's age < 18 years
- Receiving any medicine on prescription
- Verbal agreement to participate by the patient's parent/guardian and by the patient if its age and its all-over health status allows him to do that
- Adequate Norwegian language skills to understand and complete the web-questionnaire

4.3. Study period

The inclusion of patients into the study will start during the second quarter of 2018. Two one-month periods will be studied to cover a broader treatment settings and potential seasonal variations. For each patient included, the study duration will be maximum 15 days with questionnaire to be filled on day 1, 2 and 15 if relevant.

4.4. Study participation

Volunteers will be invited to complete the web-questionnaire.

The web-questionnaire could be completed by a parent or a relative hereafter referred to as care giver and/or by the patient if its age (above the age of 12) and its all-over health status allows him to do so.

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. The use of the unique access code for each patient will serve as consent to participate.

The questionnaire focuses on the first administration of the relevant medicine prescribed following study inclusion. If the child receives more than one medicine on prescription at the time of inclusion, the parent/guardian/patient will be encouraged to fill in the questionnaire for each medicine. In these situations, one access code per medicine will need to be provided.

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

- After the first medicine administration;
- After administration of the medicine on the second day (if the required dosing frequency allows it);
- After administration of medicine after 15 days, or after the last medicine administration if the duration of treatment is shorter than 15 days (if the required dosing frequency allows it).

4.5. Data collection

Information on medicines

Product identification will be enabled by a pop-up menu, triggered by product name or product identification number.

Information on the medicines in the database/web solution will be based on the prescribing and dispensing support database (Forskrivnings- og ekspedisjonsstøtte (FEST)) delivered by The Norwegian Medicines Agency (https://legemiddelverket.no/andre-temaer/fest).

Information given by the care giver and/or the patients

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

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

Participants will be asked to provide information related to the treatment with the medicine

- 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 will be asked to provide information on the experience with administrating the medicine

- Observational measures performed during the medicine use
    - the patient's reaction during the administration
    - the result of the administration (dose fully taken, partly taken, not taken)
    - 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 will be asked to provide information on the patient

- Objective information on care
    - the person(s) in charge of preparing the medicine (pharmacist, care giver, patient)
    - the person(s) in charge of administrating the medicine (care giver, patient)
    - the place where the medicine is administered (home, hospital)
- Patient characteristics
    - gender
    - age
    - 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 administration of the medicine the next day. The same web address and login details will be applicable.

<u>Second day of administration of medicine:</u>

Participants will be asked 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
    - o use of a reward
    - o use of restraint

If a dose is not given on the second day, the participant can tick a “not applicable”-box.

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).

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

Participants will be asked 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

4.6. Data storage

Recorded and validated data are stored on an external server and will then be transferred to a database in a ClinSearch internal server where they will be stored in a secured and completely anonymous environment. Data will not allow in any means to identify patients.

Only duly authorized and authenticated ClinSearch employees will be allowed to follow the database evolution.

The database will support statistical analyses.

4.7. Data analysis

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.

4.8. Sample size

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 position of medicines will become more accurate.

5. ADHERENCE TO REGULATORY AND ETHICAL CONSIDERATIONS - ADMINISTRATIVE ASPECTS

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 results of the study could contribute to better and more appropriate formulations of medicines for children.

No record will be kept that connects the personal log in code the participants receive to any personal information, i.e. the data collected is anonymous.

The Norwegian Regional Ethics Committee considered the data in this study to be anonymous and therefore that the study was not subject to an ethical approval from the Committee (ref 2017/272).

5.1. 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.

Norwegian translation of all study material has been performed according to Certificate for Translation (ref) and in agreement with the Norwegian sub study team.

5.2. 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 collaborative research group.

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 between ClinSearch and the national research team.

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

5.3. Time schedule and milestones

The time schedule for the Norwegian sub study is as follows:

	Mile stone reached by (date)
Translated web site for use in Norway finalised	January 2018
Protocol for Norwegian sub study finalised (including appendices)	January 2018
Start of inclusion of recruiting centres	February 2018
Final version of information material printed and ready for delivery to centres	March 2018
First inclusion period	9 April – 5 May 2018
Second inclusion period	3 – 29 Sept 2018
Data analysis finalised	ClinSearch opinion Jan 2019?
Paper submitted	Mar 2019?

5.4. Budget

The contribution from members of the Norwegian research team will be covered by their respective employers, i.e. the Norwegian Medicines Agency and the School of Pharmacy, University of Oslo. The analysis of the results will be handeled by ClinSearch.

Costs for editing and printing the information material to the recruiting centres and study participants will be covered by ClinSearch

There are no conflict of interests to declare in relation to the performance of this study.

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7. APPENDICES

- Written information to recruiting centres
- Patient information leaflet
- Description of the study database/ web site