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Assessing the effects of solid versus liquid dosage forms of oral medications on adherence and acceptability in children (Protocol)

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[Intervention Protocol]

Assessing the effects of solid versus liquid dosage forms of oral medications on adherence and acceptability in children

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of solid versus liquid dosage forms on adherence to and acceptability of oral medications in children.

Secondary objectives include assessment of elements of the medication risk/benefit balance influenced by the drug dosage form, such as clinical efficacy and safety, treatment costs and adverse events related to oral administration.

BACKGROUND

Description of the condition

As medication use in children was historically considered to be rare and mainly limited to anti-infective drugs, its nature and extent have only recently been investigated (Clavenna 2009a; Rieder 2010). Epidemiological data from developed countries reveal that over a year, half of the paediatric population is prescribed medications, from a wide range of therapeutic agents, and mainly in younger children (Clavenna 2009a; Clavenna 2009b; Zhang 2013). Anti-infective drugs, especially antibiotics, remain the most frequently prescribed medication. Other commonly used medications are respiratory drugs, analgesics, psychoanaleptics, antiepileptics, or corticoids (corticosteroids). Low- and middle-income countries (LMIC) provide very limited data; the most widely used medications in children are antimalarials, antibiotics and analgesics/antipyretics (Clavenna 2009a).

Health authorities and organizations now recognise that medication use in children is a worldwide burden that cannot be addressed with the available medications that are primarily designed for use in adults (WHO 2008; WHO 2012; EMA 2013; FDA 2016).

Thus, there is an urgent need for the development and assessment of effective and safe medications for children (Standing 2005; Ivanovska 2014; Salunke 2016). In parallel, selecting and developing age-appropriate paediatric formulations that ensure success and safety of administration and adequate adherence is a critical objective for health authorities and paediatric researchers (Nunn 2005; EMA 2006; WHO 2008; Cram 2009; Rieder 2010; WHO 2012; EMA 2013; Batchelor 2015; Venables 2015).

Adherence can be defined as "the extent to which a person's behaviour corresponds with agreed recommendations from a healthcare provider" (WHO 2003). Medication adherence refers to the person taking the prescribed medication, according to the prescribed dosage with the prescribed schedule for the prescribed treatment duration. A child's refusal to take a medication, related to medication acceptability, is one of the most common reasons for non-adherence in paediatrics (Al-Shammari 1995; Sunakawa 1995; Craig 2009). For oral medications, adherence challenges due to swallowing difficulties and low tolerance to unacceptable dosage forms are of high concern in children (EMA 2006). Those features specific to the paediatric population can explain their poor adherence to medications, compared with adults, with an average adherence of only 50% (Matsui 1997).

Formulation-related factors influencing oral medication acceptability in children are mainly medication palatability, medication appearance (colour, shape), required dose (volume of liquid or number of tablets to be swallowed) and dosing frequency (Cram 2009; Salunke 2011; EMA 2013; Venables 2015). Medication palatability, defined as "the overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture (i.e. feeling in the mouth)", is a main element of oral medication acceptability in children (Davies 2008; Cram 2009; EMA 2013). Palatability of an oral medication is determined by the characteristics of both the active substance and the excipients (i.e. constituents of the pharmaceutical form that is taken by or administered to the person, other than the active substance) (European Commission 2003; Walsh 2014).

Besides the above mentioned formulation-related factors, patient-related factors are also to be considered when assessing medication adherence and acceptability. Notably these include the child's age, developmental level and presence and severity of neurodevelopmental disorders, personal experience, perception of the disease, socioeconomic status, and parental/carer factors and family structure (biparental, monoparental, including grandparents, etc.) (Hoppe 1999; Matsui 2007; Dean 2010; Ivanovska 2013; Venables 2015). The child's age is a key element to consider when selecting an appropriate oral dosage form (Nunn 2005; EMA 2006; Salunke 2011; Venables 2015; Batchelor 2015). Whereas adherence in younger children depends on parents/carers' supervision, school age children and adolescents are capable of greater autonomy, and take partial or full responsibility for their own treatment (WHO 2003). Adolescents appear to have more difficulties in adhering to treatment compared to younger children; family conflict and a denial of disease are the most frequently mentioned reasons (WHO 2003; Matsui 2007). They are also more sensitive to the social stigma of taking medication in public and at school (Matsui 2007). Thus, factors determining the acceptability of a dosage form also differ across the wide age range of the paediatric population, with younger children being more likely to accept easy to swallow and pleasant tasting medications, while autonomous children who assume responsibility for their own treatment might prefer transportable and convenient dosage forms fitting their lifestyle. In this context, EMA 2006 defined six child age groups that reflect biological changes, developmental level, dependence on caregivers and school attendance, acceptance of flavour/textures, and ability to accept and handle different dosage forms: (i) preterm newborn infants, (ii) newborn infants (0 to 27 days), (iii) infants and toddlers (1 to 23 months), (iv) pre-school children (2 to 5 years), (v) school children (6 to 11 years) and (vi) adolescents (12 to 16 or 18 years).

Moreover, factors related to the disease, mainly whether the illness is short-term or long-term, treatment duration and number of treatments required are also major elements to be considered when assessing medication adherence and acceptability in the paediatric population (WHO 2003; Matsui 2007). Non-adherence in children has been primarily investigated in long-term (chronic) diseases, consensually defined as a disease lasting three months or more. Studies that were able to demonstrate the influence of improved medication adherence on clinical outcomes in children were conducted in chronic diseases (e.g. asthma, prevention of graft rejection, cancer, diabetes) (Hoppe 1999; Matsui 2007; Dean 2010). Despite the lack of literature on medication adherence in children receiving short-term treatments, paediatricians highlight the importance of selecting the appropriate formulation to facilitate adherence in acute disease (Kardas 2002). Indeed, actors contributing to medication acceptability are also related to treatment duration (WHO 2008; EMA 2013). For instance, whereas medication palatability is of major importance for both short-term and long-term treatments, other medication characteristics, such as safety of excipients, required dose, or convenience of the dosage form are of higher concern for long-term treatments (EMA 2006; EMA 2013).

Description of the intervention

The oral route is the most commonly used and the preferred route for administration of medications to paediatric patients (EMA 2006; WHO 2012). It is convenient and allows easy and safe administration compared to the intravenous route; it also offers the advantage of choice among various dosage forms suitable for the wide age range of the paediatric population (EMA 2006). To date, research on developing age-appropriate formulations mainly focuses on oral, solid dosage forms that would be easily swallowed and accepted by children (Nunn 2005; EMA 2006; Cram 2009; EMA 2013; Batchelor 2015; Lopez 2015).

Considering both acceptability and safety issues of oral administration in children, two main types of dosage forms can be distinguished: (1) liquids, including oral, liquid dosage forms (syrups, suspensions, oral drops) and solid dosage forms for reconstitution in semi-solid food or beverages (effervescent and dispersible preparations, powders, granules or sprinkles), and (2) solids, corresponding to oral solid single-unit dosage forms (tablets, capsules, orodispersibles and chewable preparations) (EMA 2013; Batchelor 2015).

How the intervention might work

According to paediatric experts' recommendations, an appropriate formulation for children allows minimal dosage and frequency; has minimal impact on lifestyle; contains non-toxic excipients; enables convenient, easy and reliable administration; and is easily produced and commercially viable (WHO 2008; Salunke 2011; EMA 2013).

Historically, liquid formulations are considered to be the most appropriate oral dosage forms for children, as they are easy to swallow for younger children and provide good dosing flexibility. However, in long-term use, volumes to be swallowed and frequency of administration can lead to reduced acceptability of liquids in children, impacting medication adherence (Matsui 1997; Rieder 2010). Liquid oral medication's low stability (i.e. chemically low stability and risk of microbiological contamination after opening) and difficulties in taste masking are responsible for the use of large amounts of excipients (e.g. glycols, alcohols) and sweeteners (Bigeard 2000; Standing 2005). Their low transportability and storage difficulties (package size, conservation in the fridge, short expiry date) present practical and safety problems for caregivers and school-age children, especially for those with a long-term disease (Mattar 1975). Multiple preparation steps such as reconstitution, dose calculation, volume measurement, and multidose packaging are high risk factors for medication errors associated with liquid dosage forms in children (Mattar 1975; Wong 2004; Schillie 2009; EMA 2013). Liquid, oral dosage forms are also comparably expensive, due to the difficulties in developing liquid formulations (e.g. taste masking and ensuring active substance stability) and to the limited size of the paediatric market (Lajoinie 2014).

Conventional solid, single-unit, oral dosage forms, on the other hand, offer the advantages of greater pharmaceutical stability, dosing accuracy, improved transportability, ease of storage and lower cost compared to liquids (Standing 2005; Lajoinie 2014). The World Health Organization's (WHO) report of the informal expert meeting on dosage forms of medications for children (WHO 2008) states that suitable solid dosage forms should be used in preference to liquids for oral medications requiring precise dose measurement. Solid, oral dosage forms also allow the development of modified-release formulations, minimising administration frequency. This may indirectly improve medication adherence (Salunke 2011). The European Medicines Agency (EMA) highlights interest in the use of solid, oral dosage forms in young children with long-term illnesses, recommending that these children be trained to swallow pills from the relatively early age of three years (Walco 1986; Babbitt 1991; EMA 2006; Garvie 2007). These advantages are lost, however, if tablets are crushed. This can lead to preparation errors, loss of stability or modification of the drug's pharmacokinetic properties. Recently, studies have shown that very young children are able to safely swallow appropriately sized tablets, called mini-tablets (Thomson 2009; Spomer 2012; Van Riet-Nales 2013). Without strong and consistent evidence of safety and effectiveness in children, solid forms remain unpopular in paediatric practice mainly due to fear of choking (Nunn 2005; Salunke 2016; Walch 2016).

Besides efforts to improve medication formulation, worldwide accessibility should be considered, taking account of political, regulatory and economic features in different countries (WHO 2008; Rieder 2010; Ivanovska 2013). The development of suitable dosage forms for LMIC, in which most of the world's children reside, is one of the priorities of the WHO, with the aim of reducing childhood morbidity and mortality (WHO 2008; WHO 2012). Indeed, some features of oral dosage forms that are of high importance for high-income countries likely have even greater impact in LMIC, such as accessibility, stability, accurate dosing, storage conditions, and affordability (Craig 2009). LMIC also have additional concerns of restricted access to clean water and adequate staff training to use medications properly (WHO 2008; Salunke 2011). The WHO encourages the use of solid dosage forms for oral administration in young children, avoiding stability and storage issues of syrups and the need for clean water for suspensions (WHO 2008; Ivanovska 2013; Van Riet-Nales 2013).

Why it is important to do this review

One of the most important issues in the selection of an appropriate oral medication in children is the acceptability of the dosage form. Acceptability impacts on children's adherence to oral medications, and, consequently, on the safety and efficacy of a medicinal product (EMA 2013). Thanks to regulatory agency incentives and development of new oral medication formulations (i.e. minitablets, microgranules), the number of studies assessing the acceptability of oral dosage forms in children is growing. However, in the absence of sufficient consistent evidence, disagreement persists between regulatory authorities, paediatricians and parents concerning the most appropriate oral dosage form for paediatric use depending on children's age and illness (Salunke 2011). There is a growing recognition of the urgent need for research to address the lack of data on appropriate paediatric oral medication formulations and to address the very poor adherence typical in ambulatory paediatric settings (Cram 2009; Salunke 2011). This systematic review will help to identify those oral dosage forms with the best adherence and acceptability in children, depending, for

example, on the administered active drug, children's age group or disease duration.

OBJECTIVES

To assess the effects of solid versus liquid dosage forms on adherence to and acceptability of oral medications in children.

Secondary objectives include assessment of elements of the medication risk/benefit balance influenced by the drug dosage form, such as clinical efficacy and safety, treatment costs and adverse events related to oral administration.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) comparing outcomes in children receiving different oral formulations (solid versus liquid) containing the same active substance or both being free of an active drug. Medication adherence and acceptability could be compared in children acting as their own control (cross-over trials) or between parallel groups of children. Neither quasi-RCTs nor cluster RCTs will be considered for this review.

Types of participants

We will include children aged from 0 to 18 years old. Healthy volunteers or children with a clinical indication for therapy will be included. Studies that include both children and adults will be considered for the review, as we will search for outcome results for the paediatric population. Where children's specific outcomes are not available we will contact the study authors for details and, if still unavailable, studies including both adults and children will be eligible for inclusion if the majority of participants fall into the paediatric age group (< 25% of participants aged over 18 years).

Types of interventions

Medication adherence or acceptability will be compared in children receiving any kind of solid, single-unit, oral dosage forms (tablet, capsule, orodispersible, chewable) versus children receiving any kind of liquid, oral dosage form or solid form for reconstitution (syrups, suspensions, oral drops, sprinkle, granules, effervescent and dispersible preparations). The oral dosage forms could contain an active drug or be drug free. There will be no restriction on the dose duration or co-intervention (e.g. pill-swallowing training).

We will exclude RCTs where children or caregivers were recommended to crush tablets or open capsules in order to disperse drugs into food or beverages prior to administration, as they are no longer solid, oral dosage forms. We will not exclude RCTs where tablets were split, as they remain solids.

Types of outcome measures

Reporting of outcomes will not determine eligibility of studies for this review.

Primary outcomes

- Adherence to medication, commonly measured by the amount of medication consumed over a given period.
- Medication acceptability, defined as the overall ability of the child to use the medication as intended (EMA 2013).
- Adverse events related to oral administration (i.e. vomiting, inhalation, hypoxia, choking).

We will consider adherence as an outcome whether or not co-interventions were used (e.g. pill-swallowing training). We will collect information on how adherence was defined and measured in each RCT. We expect that adherence will be reported in RCTs with more than one outcome measure (e.g. pill count, self-reported). Thus, we will categorise outcomes for each included RCT from the most objective measurement to the least: (i) direct electronic monitoring will be considered as the gold standard, ahead of secondary count measures, (ii) pill count, (iii) self-recorded adherence (diaries), and (iv) pharmacy dispensing records (Farmer 1999). If multiple adherence measurements are available in an RCT, for preference we will consider the most objective one for analysis based on this categorisation. Two review authors will independently assign the adherence outcomes reported in each included RCT to these defined outcome categories and resolve any differences in categorisation, if they occur, by the involvement of a third review author.

Medication acceptability may be reported by children or caregivers (parents or health care professionals), and it is one of the most crucial factors influencing treatment adherence in children for oral administration. Medication acceptability can be assessed after a single administration or after completion of a course of treatment, using a visual analogue scale or other scales.

Since younger children are unable to report medication adherence themselves and, for the youngest, to express medication acceptability or palatability, caregivers may be requested to report child medication acceptability based on the child's behaviour. For children under 12 years old, where both the caregiver(s) and the child have reported adherence, we will consider the outcome that was

reported by the caregiver(s) for the review; we consider adolescents to be responsible for their own treatment and to be able to report adherence. Where both the caregiver(s) and the child have assessed medication acceptability or palatability, we will consider the outcome that was reported by the child for the review, as we consider the child's view to be the most relevant for this outcome.

Secondary outcomes

- Medication palatability (the overall appreciation of a medicinal product in relation to its smell, taste, aftertaste and texture) reported by children or caregivers.
- Child preference for one of the randomised oral dosage forms.
- Caregiver preference for one of the randomised oral dosage forms.
- Clinical or biological outcomes of treatment (beneficial or adverse effects with oral dosage forms containing active drug).
- Economic outcomes: differences between medication formulation treatment costs/cost saving investigations.

We will prepare a 'Summary of findings' table to present the results of analyses, based on the methods described in chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017). We will present the results of analysis for the major comparisons of the review, for each of the two major primary outcomes and adverse events related to oral administration, and for medication palatability, child preference, caregiver preference, and economic outcomes.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases from their start date:

- Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, latest issue);
- MEDLINE (OvidSP);
- Embase (OvidSP);
- PsycINFO (OvidSP); and
- CINAHL (EBSCOhost).

We present the strategy for MEDLINE (OvidSP) in Appendix 1. We will tailor strategies to other databases and report them in the review.
There will be no language nor date restrictions.

Searching other resources

We will search grey literature sources, such as reports and conference proceedings (e.g. Global Research in Paediatrics (GRIP) Webinars and Workshop, EMA Workshop on Paediatric Formulations, European Paediatric Formulation Initiative (EuPFI) Conferences).
We will search the reference lists of all included studies.
We will handsearch the following journals: International Journal of Pharmaceutics (from 1978), AAPS (American Association of Pharmaceutical Scientists) Journal (from 1999), Journal of Pediatrics (from 1980), Pediatrics (from 1980), and the Journal of Behavioral Medicine (from 1978).
We will contact experts in the field and authors of included studies for advice as to other relevant studies. We will search reference lists of relevant studies and seek expert advice about other potentially relevant studies, such as the EuPFI and GRIP.
We will also search online trial registers including the WHO trials portal (www.who.int/ictrp/en/) and Clinicaltrials.gov (www.clinicaltrials.gov) for ongoing and recently completed studies.

Data collection and analysis

Selection of studies

Two authors will independently screen all titles and abstracts identified to determine which ones meet all the inclusion criteria. We will retrieve the full text of any papers identified as potentially relevant by at least one review author (over-inclusion of selected references) (Higgins 2011a). Two review authors will independently screen full-text articles for inclusion or exclusion, with discrepancies resolved by discussion and by consulting a third review author if necessary to reach consensus. All potentially relevant papers excluded from the review at this stage will be listed as excluded studies, with reasons provided in the 'Characteristics of excluded studies' table. We will also provide citation details and any available information about ongoing studies. We will collate duplicates and report details, so that each study (rather than each report) is the unit of interest in the review. We will report the screening and selection process in an adapted PRISMA flow chart (Liberati 2009).

Data extraction and management

Two review authors will extract data independently from included studies. Any discrepancies will be resolved through consultation with a third review author when necessary. We will develop a data extraction form using the Cochrane Consumers and Communication Group Data Extraction Template (cccrg.cochrane.org/author-resources). Data to be extracted will include the following

items: article information (authors, title, year of publication), outcomes, timing and measurement scales, study design, intervention and comparison groups (dosage form, active substance or placebo, treatment duration, co-interventions), participants (age range, inclusion/exclusion criteria, clinical condition, country, method for recruitment), and aim of the study. One review author will enter all the extracted data into Review Manager (RevMan) 5 (RevMan 2014), and a second review author, working independently, will check them for accuracy against the data extraction sheets.

Assessment of risk of bias in included studies

We will assess and report the methodological risk of bias of included studies in accordance with the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2017) and Cochrane Consumers and Communication's guidelines (Ryan 2013). The latter recommends the explicit reporting of the following individual elements for RCTs: random sequence generation; allocation sequence concealment; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data, selective outcome reporting; other biases, relating for example to particular trial designs (e.g. carry-over effect in cross-over trials). We will assess these domains using the Cochrane tool for assessing risk of bias (Higgins 2011b). We will judge each item as being at a high, low or unclear risk of bias as set out in the criteria provided by Higgins 2011b. We will provide a quote from the study report and a justification for our judgement for each item in the risk of bias table.

We will deem studies to be at the highest risk of bias if we score them as at unclear risk of bias on the sequence generation domain, or at high or unclear risk of bias on the allocation concealment domain, based on growing empirical evidence that these factors are particularly important potential sources of bias (Higgins 2011b). We will investigate the effects of excluding studies at the highest risk of bias through sensitivity analyses. The nature of the intervention does not allow the blinding of participants, caregivers or investigators to the allocated dosage form. We will therefore rate the risk of bias for this blinding domain (participants, personnel) as unclear for all included RCTs. Concerning the blinding of outcome assessment, we will classify adherence measures using electronic monitoring devices as at low risk of bias, while we will consider other measurement methods as at unclear or high risk. Acceptability and preference measures will be unblinded and subjective; we will classify them as at unclear or high risk of bias.

The cross-over study conducted by Van Riet-Nales and colleagues showed a period effect (see 'Unit of analysis issues' Van Riet-Nales 2013). Thus, we will base the analysis of cross-over RCTs on the first period of any included cross-over study (Higgins 2011b).

In all cases, two review authors will independently assess the risk of bias of included studies and resolve any disagreements by discussion to reach consensus. We will contact study authors for additional information about the included studies, or for clarification of the study methods if needed. We will incorporate the results of the 'Risk of bias' assessment into the review through standard tables, and systematic narrative description and commentary about each of the elements, leading to an overall assessment of the risk of bias of included studies and a judgment about the internal validity of the review's results.

Level of risk of bias will not determine eligibility for inclusion of studies for this review. However, we will conduct sensitivity analysis, if possible, based on 'Risk of bias' ratings on the sequence generation or allocation concealment domains of the tool, or both.

Measures of treatment effect

For RCTs comparing solid versus liquid oral dosage forms of the same pharmacological agent or placebo, if sufficient trials are available and similar enough, we will perform meta-analysis of primary and secondary outcomes.

For dichotomous outcomes, we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups, which we will use to calculate the odds ratio (OR) and 95% confidence interval (CI). For continuous measures, we will analyse data based on the mean, standard deviation (SD) and number of people assessed for both the intervention and comparison groups to calculate mean differences (MD) and 95% CI. If the MD is reported without data from each individual group, we will report summarised MD (effect size) for each trial. If continuous outcomes are not measured on the same scale, we will calculate the standardised mean difference (SMD) and 95% CI. Following recommendations for data analysis set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017), we will use the software provided by Cochrane, RevMan 5, to perform the statistical analysis (RevMan 2014).

There are numerous different ways to measure medication adherence, both dichotomous and continuous. Where possible we will re-express all adherence outcomes, together with their confidence intervals, as log OR using Chinn's formula (Chinn 2000) together with their standard errors, and combine them in RevMan 5 using the generic inverse-variance method (Deeks 2017).

Unit of analysis issues

In the cross-over RCT by Van Riet-Nales and colleagues, where children were administered four different oral placebo dosage forms - minitablet (4 mm), powder, suspension and syrup - following a randomised order, study authors found a significant period effect on dosage form acceptability (Van Riet-Nales 2013). Oral formulations administered earlier tended to have higher scores compared to oral formulations tested later in the sequence for the same child. On the basis of this example, we will include only data from the first period after randomisation of cross-over RCTs, similar to a parallel-group design.

In case of multiple comparisons (e.g. one liquid dosage form versus two types of solid dosage form), we will include each pair-wise

comparison separately in the meta-analysis, but with the shared intervention group (liquid form) divided approximately evenly to make relatively independent comparisons with each of the solid dosage forms (Higgins 2011b). This method does not completely avoid unit-of-analysis error due to the unaddressed correlation between intervention effects. However, it ensures the distinction between important dosage form characteristics is maintained, limiting heterogeneity, and allowing subgroup and sensitivity analysis, notably: formulation appropriateness depending on children's age, solid dosage form diameter, drug-containing or drug-free (placebo) oral dosage forms. For dichotomous outcomes, we will divide both the number of events and the total number of participants between comparisons. For continuous outcomes, we will only divide the total number of participants between comparisons and will leave the means and standard deviations unchanged.

Dealing with missing data

We will attempt to contact study authors to obtain missing data (participant, outcome, or summary data). For participant data, we will, where possible, conduct analysis on an intention-to-treat basis; otherwise we will analyse data as reported. We will report on the levels of loss to follow-up and assess this as a source of potential bias.

If we are not able to collect missing data, review authors will describe the proportion of missing observations. We do not plan to undertake any imputation for missing outcome data.

For studies that may have missing summary data, we will calculate these summary data where possible. As an example, if the standard deviation (SD) is missing, review authors will calculate SD from the standard error (SE), CIs or P value, if these are available.

Assessment of heterogeneity

For studies that we consider similar enough (based on consideration of participants, interventions and study designs) to allow pooling of data using meta-analysis, we will assess the degree of heterogeneity through a visual inspection of forest plots and the Chi^2 test of heterogeneity (Deeks 2017). We will use the I^2 statistic to quantify heterogeneity. We will consider an I^2 value of 50% or more to represent substantial heterogeneity (Higgins 2003).

If we detect substantial clinical, methodological or statistical heterogeneity across the included studies we will not report pooled results from meta-analysis but will instead use a narrative approach to data synthesis. We will provide an explanation and justification for this approach should we choose not to statistically pool data. We will attempt to explore possible clinical or methodological reasons for this variation by grouping studies that are similar in terms of population (paediatric age group, clinical condition), intervention (dosage form, active substance) or methodological features to explore differences in intervention effects.

Assessment of reporting biases

We will assess reporting bias qualitatively based on the characteristics of the included studies (e.g. if only small studies that indicate positive findings are identified for inclusion), and if information that we obtain from contacting experts and authors of studies suggests that there are relevant unpublished studies.

If we identify sufficient studies (at least 10) for inclusion in the review we will construct a funnel plot to investigate small study effects, which may indicate the presence of publication bias. We will formally test for funnel plot asymmetry, with the choice of test made based on advice in Sterne 2017, and bearing in mind that there may be several reasons for funnel plot asymmetry when interpreting the results.

Data synthesis

We will decide whether to meta-analyse data based on whether the interventions in the included trials are similar enough in terms of participants, settings, intervention, comparison and outcome measures to ensure meaningful conclusions from a statistically pooled result.

Due to the anticipated variability in the interventions (e.g. placebo or active-medication dosage forms, treatment duration) and participants (e.g. wide age ranges of children, healthy volunteers or children with clinical indication for therapy, short-term or long-term disease, baseline level of adherence) of included studies, we will use random-effects meta-analyses (Borenstein 2010).

If we are unable to pool the data statistically using meta-analysis we will conduct a narrative synthesis of results. We will present the major results for the comparison of solid versus liquid dosage forms, organised by outcomes. Depending on the assembled research, we may also explore the possibility of organising the data by children's age groups. We will explore the main comparisons of the review.

Subgroup analysis and investigation of heterogeneity

If we identify a sufficient number of RCTs, we will perform subgroup analyses looking at effects on medication adherence and acceptability in children.

- Paediatric age groups defined by the EMA (EMA 2006):
  - infants and toddlers (1 month to 23 months);
  - children (2 to 11 years); and
  - adolescents (12 to 18 years)
- Tested formulation appropriateness depending on children's age:
  - for solid forms: based on solid diameter considered as acceptable depending on children's age from EMA's draft *Guideline on pharmaceutical development of medicines for paediatric use* (EMA 2011) (0 to 5 mm: small, 5 to 10 mm: medium, 10 to 15 mm: large; more than 15 mm: very large);
  - for liquid forms: based on the volume of liquid to be swallowed considered as acceptable from EMA's

recommendations (EMA 2013) (less than 5 mL per dose for children younger than five years old and less than 10 mL per dose for children over five years)

- Study conducted in LMIC or high-income countries
- Long-term or short-term disease, based on the list of long-term conditions published by the National Institute for Health Research (Taylor 2014)
- Study conducted in children with illness or in healthy volunteers
- Children's physiological ability to swallow: that is, children with swallowing difficulties due to neurologic or muscular disorders (e.g. myasthenia, muscular dystrophy, multiple sclerosis) or any cause of dysphagia (e.g. severe psychiatric disorders, neurodevelopmental disorders), compared with children without any medical cause for dysphagia.

Sensitivity analysis

If we identify a sufficient number of RCTs, we will perform sensitivity analyses to assess the robustness of the results, as follows.

- Level of risk of bias based on sequence generation or allocation concealment domains;
    - RCTs with an unclear risk of bias for sequence generation or high or unclear risk of bias for the allocation concealment domain will be excluded from a first analysis;
    - RCTs with an unclear risk of bias on the sequence generation domain will be excluded from a second analysis;
- Adherence outcome measurement method; only RCTs that used direct electronic monitoring (i.e. gold standard) will be included in the analysis (excluding other forms of measurement).

'Summary of findings' table

Based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), we will prepare a 'Summary of findings' table to present the results of the review. For each of the primary outcomes as outlined in the Types of outcome measures section we will present the results of analyses, whether meta-analysis or narrative synthesis, for the major comparisons of the review. We will provide a source and rationale for each assumed risk cited in the tables, and we will use the GRADE criteria to rank the quality of the evidence by means of GRADEpro GDT software (Schünemann 2017).

Ensuring relevance to decisions in health care

The protocol and review will receive feedback from one consumer referee in addition to a health professional as part of Cochrane Consumers and Communication's standard editorial processes.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp child/
2. exp infant/
3. adolescent/
4. minors/
5. exp pediatrics/
6. (child* or infan* or toddler* or newborn or neonat* or baby or babies or preschool* or pre-school* or boy? or girl? or schoolchild* or adolescen* or pediatric* or paediatric* or youth* or juvenile* or teen*).tw,hw.
7. or/1-6
8. exp tablets/
9. capsules/

10. (solid or tablet* or capsule* or encapsul* or caplet* or pill? or minitab* or minicapsule* or pellet* or orodispersible or chewable).ti,ab,kw.
11. or/8-10
12. exp pharmaceutical solutions/
13. suspensions/
14. powders/
15. (liquid or fluid or syrup* or solution* or suspension* or drink* or beverage* or spoon* or sprinkle* or powder* or granule* or dispersible* or drop?).ti,ab,kw.
16. or/12-15
17. 11 and 16
18. (dosage form* and (oral* or compar*)).mp.
19. (oral* and formulation*).ti,ab,kw.
20. or/17-19
21. 7 and 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.
26. clinical trials as topic.sh.
27. randomly.ab.
28. trial.ti.
29. or/22-28
30. exp animals/ not humans.sh.
31. 29 not 30
32. 21 and 31

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- Conceiving the review and performing previous work that was the foundation of the current review protocol: Audrey Lajoinie, Emilie Henin, Jean-Cédric Gleize, Clémentine Berlion, Behrouz Kassaï
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- Writing the protocol: Audrey Lajoinie, Perrine Janiaud, Emilie Henin, Patrice Nony, Behrouz Kassaï
- Guarantor of the protocol: Behrouz Kassaï.

DECLARATIONS OF INTEREST

Audrey Lajoinie, Jean-Cédric Gleize, Clémentine Berlion, Kim An Nguyen, Patrice Nony, Delphine Maucort-Boulch, and Behrouz Kassaï Koupaï have no known conflicts of interest.

Perrine Janiaud is currently receiving a PhD grant from GlaxoSmithKline France as part of an Industrial Agreement of Training through Research through a private and public partnership between GSK and Claude Bernard University, Lyon, France. Her PhD focuses on the extrapolation of the medicine benefit risk ratio from adults to children.

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