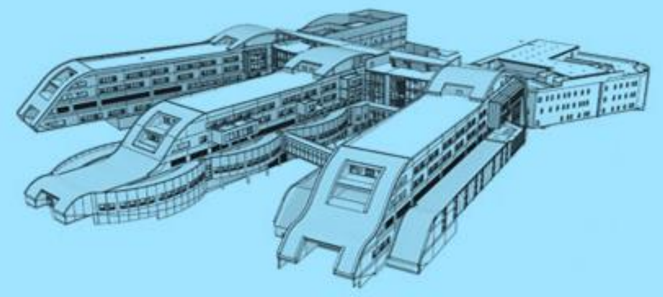
A feasibility study to assess the acceptability of solid dosage forms in children

[1]P.Mistry, [1]L.Bracken, [2]U.Ohia, [3]H.Jones, [3]N.Kanji, [4]F.Liu, [1,2]M.Peak

[1] Paediatric Medicines Research Unit, Alder Hey Children's NHS Foundation Trust, Liverpool, L12 2AP
www.alderhey.nhs.uk/research/paediatric-medicines
[2] NIHR Alder Hey Clinical Research Facility for Experimental Medicine, Alder Hey Children's NHS Foundation Trust, Liverpool, L12 2AP
[3] Co-Formulate Ltd, MediCity, Nottingham, NG90 6BH
[4] Department of Pharmacy, Pharmacology and Postgraduate Medicine, University of Hertfordshire, Hatfield, AL10 9AB



INTRODUCTION

Paediatric formulation development is currently a 'hot' topic within the pharmaceutical industry and substantial efforts are being invested into producing medicines that are acceptable to children. The administration of medicines to children poses a challenge to many parents and health care professionals; this is linked to the limited information available for age-appropriate oral formulations. Strategies such as crushing tablets or mixing medicine with food and drinks are used to aid this problem [1], yet these strategies can affect medicine efficacy, dosing accuracy and bioavailability. Developing medicines that are acceptable to children has the potential to influence adherence to therapeutic regimens and improve outcomes [2].

Tablets can be offered to children as an alternative to oral liquid medicines since they offer the potential of coating to taste-mask alongside their better stability profile and lower number of excipients used [3, 4]. However, limited evidence is available for the ability of children of different ages to swallow conventional tablets (>5 mm). Tablet size is a major determinant of whether they are swallowable, so acceptability and swallowability assessments can be linked during tablet formulation development. Acceptability has previously been defined as "an overall ability of the patient and caregiver (defined as "user") to use a medicinal product as intended" [5].

Evidence for the acceptability of tablets is still limited and additional studies are required to understand the impact of formulation factors (i.e. effect size, presence/absence of film coating or amount of dosage units per dose) on patient's acceptability.

We will conduct an ethically approved study (Ref: 17/NW/0410) to assess the feasibility of a trial of swallowability and acceptability of different sized placebo tablets in a hospital based population of children via patient-reported outcomes (PRO) and researcher observations. Evaluation of key feasibility parameters for a definitive trial will be undertaken alongside data capture on an estimate of the treatment effect on important outcomes.

MATERIALS AND METHODS

After informed consent is obtained, a short video will be shown to children with a demonstration of how a tablet can be swallowed. Children (aged 4-12 years) will be asked to swallow three different sized placebo tablets in a standardised order.
Each tablet will be placed on the child's tongue and the participant asked to swallow the tablet with up to 3 mouthfuls of still spring water [6]. The volume of water consumed will be measured, however unlimited water will be available to participants as required.
After each administration, the participant's mouth will be inspected by the investigator for any non-swallowed tablets [6]. The swallowability and acceptability of the samples will be assessed using a questionnaire that includes a 5-point hedonic facial scale [7] (Figure 1) and voluntary feedback.

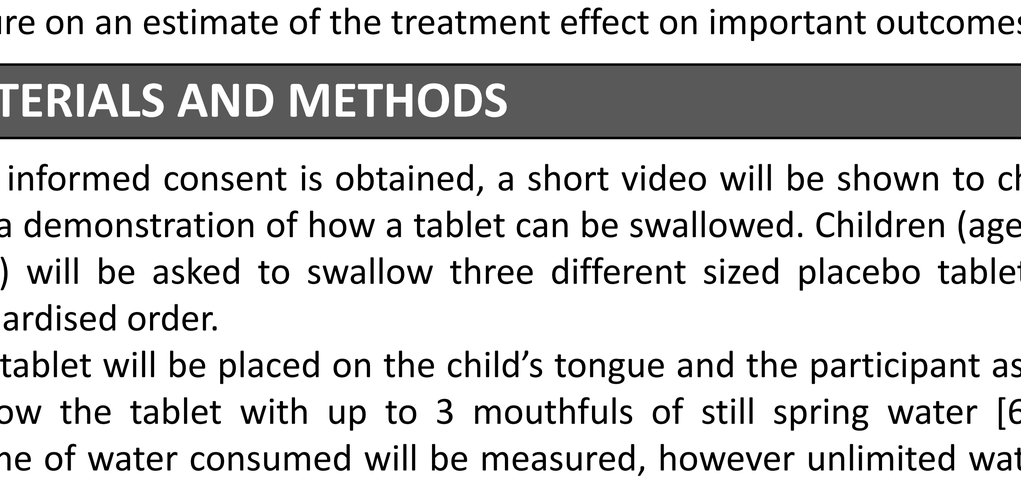


Figure 1: a. Example question to assess the swallowability of tablets using 5-point facial hedonic scale; b. Example of a multiple choice question

Participants' facial expressions and behaviours including chewing, choking and refusal will be recorded prior to, during and post intake using a 12-point tick chart based on the behavioural observations, of children tasting food [6, 8] (Figure 2).

Facial Expressions	Behaviours
Eyes squeezed/ shut	Voices disgust
Brow bulge	Resistance/ Cries
Nose wrinkled	Spits out/ vomits
Pursed lips	Refusal
-	Chews sample

Figure 2: Facial expressions and behaviours to record if displayed by participant

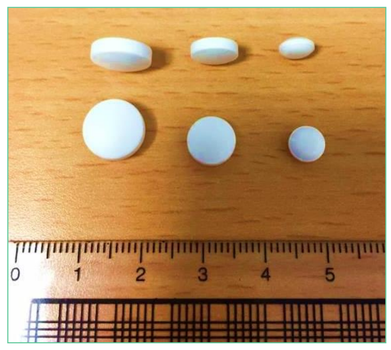
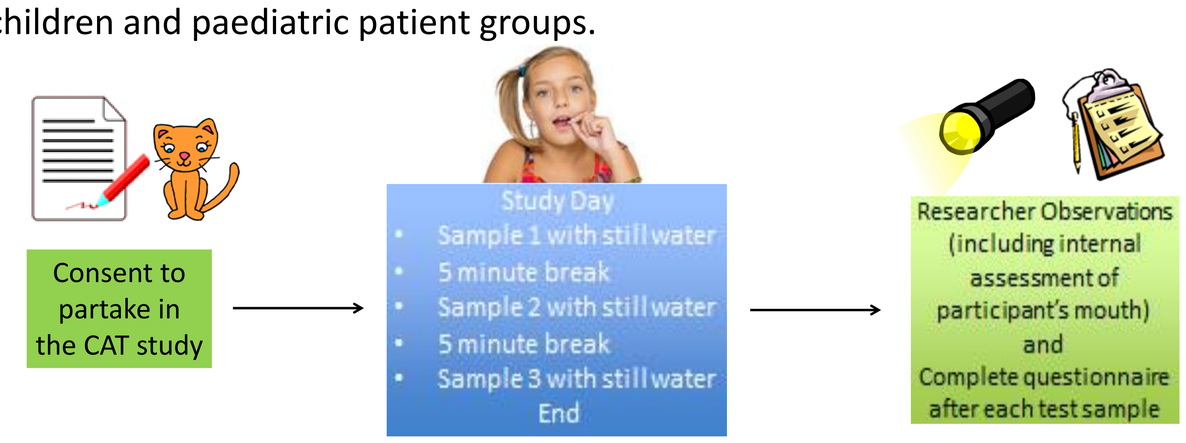


Figure 3. Placebo solid dosage forms made of PROSOLV® EASYtab SP. The solid dosage form sizes vary from left to right: 10mm, 8mm and 6mm diameters respectively with a standard round biconvex shape.

GMP manufactured placebo tablets containing microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate and sodium stearyl fumarate (PROSOLV® EASYtab SP, JRS Pharma, Germany) will be used as model tablets. All samples are produced as film coated versions (OPADRY®, Colorcon, UK). Tablet diameters are 6, 8 and 10 mm (Figure 3).

We aim to recruit a minimum of 50 participants between the healthy children and paediatric patient groups.



RESULTS

The feasibility study will provide estimates on important variables for the design of a definitive trial:

- Estimate of recruitment rate of eligible participants for a larger trial.
- Estimate of proportion of children who are willing and able to swallow all three tablets in relation to age.
- Ability to measure intended outcomes in healthy and hospital based paediatric populations.
- Estimate of effect size of proposed primary outcome.
- Participant feedback on process evaluation of trial methodology including willingness to be randomised to a single tablet size in a future trial.

CONCLUSIONS

Interdisciplinary research groups with expertise in recruitment of children at high volume into clinical trials are required to undertake rigorous studies of formulation acceptability in this age group. This study will gain understanding of whether swallowability studies are feasible in healthy and hospital paediatric populations and generate effect size estimates for important outcomes to inform future trials.

Findings from this study via PRO will provide the basis for further clinical trials to determine acceptable solid dosage formulations.

ACKNOWLEDGMENTS

This work is conducted with combined expertise from paediatric clinical researchers (NIHR Alder Hey Clinical Research Facility for Experimental Medicine & Liverpool Paediatric Medicines Research Unit), university academics (University of Hertfordshire) and pharmaceutical industry partners (Co-Formulate Ltd).

REFERENCES

[1] Richey et al., A systematic review of the use of dosage form manipulation to obtain accurate doses to inform use of manipulation in paediatric practice. 2017; Int J Pharm. 518 (1-2). 155 – 166
[2] Venables R, Batchelor HK, Hodson J, Stirling H, Marriott J. Determination of formulation factors that affect oral medicines acceptability in a domiciliary paediatric population. Int J Pharm. 2015;480(1–2):55–62.
[3] European Medicines Agency. Guideline on pharmaceutical development of medicines for paediatric use. 2013;**44**:1–24
[4] World Health Organisation. Development of paediatric medicines: points to consider in formulation. 2012.
[5] Kozarewicz P. Regulatory perspectives on acceptability testing of dosage forms in children. *Int J Pharm* 2014;**469**:245–8. doi:10.1016/j.ijpharm.2014.03.057European Medicines Agency. Guideline on pharmaceutical development of medicines for paediatric use. 2013;**44**:1–24
[6] Klingmann, V. et al. 2013. Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children. Journal of Pediatr, 163, 1728-1732 e1.
[7] Chen, A. W. et al 1996. Age appropriate hedonic scales to measure food preferences of young children. Journal of Sensory Studies, 11, 141-163
[8] Zeinstra, G. G. et al.. 2009. Facial expressions in school-aged children are a good indicator of 'dislikes', but not of 'likes'. Food Quality and Preference, 20, 620-624