# Barriers to administering non-oral formulations in a paediatric population

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*DOI:*
10.1016/j.ijpharm.2015.11.010



*Document Version*
Peer reviewed version

*Citation for published version (Harvard):*
Venables, R, Batchelor, H, Stirling, H & Marriott, J 2016, 'Barriers to administering non-oral formulations in a paediatric population: A semi-structured interview study', *International Journal of Pharmaceutics*, vol. 497, no. 1-2, pp. 12-17. https://doi.org/10.1016/j.ijpharm.2015.11.010

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# Abstract

Acceptability of medicines for children is a challenge, yet critical to ensure adherence to treatment. There is very little literature on formulation factors that influence acceptability of medicines, particularly in the domiciliary environment. This pragmatic study was conducted at University Hospital Coventry and Warwickshire (UHCW) with the aim of identifying the prevalence and nature of oral formulation-related barriers to medicines administration in children suffering from long-term conditions.

This study used semi-structured face-to-face interviews with 221 parents/carers of children (0-18 years) and 57 young people (12-18years).

Results showed significant medicines refusal and manipulation in the domiciliary environment. Nearly one-third (71/232) of respondents reported medicines refusal. This was associated significantly with the age of child ($p=0.016$), socioeconomic status (IMD 2010 score)($p=0.002$), taste ($p<0.001$), texture ($p=0.017$), and volume (of liquid/powder) or quantity (of solid dosage form) ($p<0.001$). 29%(74/252) of respondents reported manipulating medicines. P-values are based on multivariable statistical analysis models.

This study has indicated that formulations prescribed to children with chronic conditions are not meeting the needs of a significant number of patients based on self-report. Age-appropriate medicines are required to provide suitable dose units with an acceptable taste for children. This study should aid pharmaceutical companies to prioritise paediatric formulation work.

# 1 Introduction

Approximately 200 million prescriptions are issued annually for children and young people in the UK (Costello et al., 2004). Previous studies have investigated medicines adherence in children, however these have not explored potential barriers to adherence in the domiciliary setting. In this paper, barriers are defined as obstacles that could result in non-adherence of medicines (e.g. forgetting, refuse, hard to swallow, etc.).

There is a paucity of studies investigating barriers to medicines administration arising from oral formulations (particularly those related to organoleptic and physical properties) in children with chronic conditions. Those studies reported previously are limited to specific disease groups, e.g. antiretroviral medicines in Human Immunodeficiency Virus (HIV) (Boni et al., 2000; Gibb et al., 2003; Goode et al., 2003; Marhefka et al., 2004; Pontali et al., 2001; Wrubel et al., 2005). Further studies compare the acceptance and flavour preferences of a spectrum of drugs from one class (e.g. antibiotics) using a "one-off" taste test method, commonly with the aid of a visual analogue scale (VAS) most often in healthy children or adults (Bagger-Sjöbäck and Bondesson, 1989; Chan et al., 1997; Cohen et al., 2009; El-Chaar et al., 1996; Samulak et al., 1996; Toscani et al., 2000).

The present study targets a large paediatric population suffering from different chronic conditions.

The palatability of paediatric medicines is one of the most important formulation factors with potential to influence adherence to therapeutic regimens and outcomes (Salunke et al., 2011). It has been demonstrated that making medications more pleasing to the child can have a positive effect on compliance (Winnick et al., 2005). Refusal of a formulation was defined in the present study as, 'complete omission of a dose by intent on at least one occasion, including spitting the dose back out, and/or closing the mouth' and medicine manipulation was defined as 'a medicine physically adapted to facilitate medicines administration or for the purpose of giving a specific dose.'

The importance and incentive to study the palatability of paediatric formulations was discussed in the reflection paper (EMEA, 2006) and endorsed in the latest European Paediatric guideline on pharmaceutical development of formulations for paediatric use (EMA, 2013).

The aims of the present study were (i) to identify the prevalence and nature of oral formulation-related barriers to medicines administration in children suffering from long-term conditions in a domiciliary environment; (ii) to identify the prevalence of children refusing formulations and also determine which formulation factors influenced oral medicines refusal and (iii) to evaluate the prevalence and nature of oral medicines manipulation by parents, carers and children in the domiciliary environment.

# 2 Materials and Methods

## 2.1 Data collection tool

Understanding formulation acceptability in a domicilliary environment requries the use of alternative means of data collection compared to in-patient studies. A semi-structured interview was selected for this study to obtain the appropriate balance in data collection and subsequent analysis (Malim and Birch, 1996). During a semi-structured interview, the interviewer is able to show empathy and alter phrasing of questions in order to elicit detailed and considered responses from participants; these benefits have been previously shown to provide more detailed outputs (Gillham, 2000) and an increased response rate (Chambers, 2000) compared to paper-based questionnaires.

A multidisciplinary research team (Professor in Clinical Pharmacy, paediatric consultant and pharmacist) generated an outline of key problems with administering oral formulations to children; these issues were refined via four focus groups with healthcare professionals at the University Hospital Coventry and Warwickshire (UHCW) and Birmingham Children's Hospital (BCH). The data collected, in addition to self-report methodologies referenced in published studies (Medical Adherence Measure - MAM (Ingerski et al., 2009; Zelikovsky et al., 2008), Treatment Interview

Protocol - TIP (Marhefka et al., 2004), Pediatric AIDS Clinical Trials Group PACTG questionnaire (NIAID) and Morisky Scales (Morisky et al., 2008; Morisky et al., 1986) were used to inform the design of the self-report semi-structured interview tool. The Young Persons Advisory Group (YPAG) at Birmingham Children's Hospital (n=12 members) reviewed the tool to ensure that it was age appropriate.

The 13-item self-report tool (Supplementary File 1) used in the semi-structured interviews was designed to collect data exploring medicines adherence including medicines refusal (see Q5 in Supplementary File 1), medicines manipulation (see Q3a in Supplementary File 1) and barriers to medicines administration (see Q3b in Supplementary File 1) in parents, carers and children themselves. Open questions were used to elicit reasons for medicines refusal to avoid bias.

A semi-structured interview was conducted by a single researcher (post-graduate pharmacist (RV) - not previously known to the patients) to minimise variation in approach and the responses were entered manually onto a structured data record during each interview. The interviews (maximum duration of 45 minutes) were conducted in a private area at the paediatric outpatients department at UHCW at times scheduled to coincide with routine clinical appointments. Ethical approval was granted by the South Birmingham REC and informed consent was obtained for all participants.

Participants were invited to provide demographic information in order to generate an Index of Multiple Deprivation 2010 (IMD 2010) score.

## 2.2 Qualitative Analysis

Themes were identified using a frame-work analysis approach to form a coding spine. Thematic content analysis (Pope et al., 2000) was used to identify and group common themes,relating to medicines administration. Qualitative data was analysed using NVivo 8 software (QSR International).

## 2.3 Statistical Analysis

Statistical analysis was conducted using generalised estimating equations to explore the relationship between independent variables (e.g. child age, IMD score, formulation type) and dependent variables with binary outcomes (Refusal or Manipulation).

Patient, participant and data on formulations were converted into categorical variables (see Tables 2 & 3).

Data analysis was performed on an individual medicine level facilitating comparisons between medicine specific variables (e.g. different medicine groups and formulations), which are not possible at a patient level. In order to account possible non-independence of data owing to any response correlation to medicines taken by an individual, univariable generalised estimating equations were used. The univariable analysis did not control for potential relationships between independent variables therefore multivariable analysis was also conducted using the combination of independent variables found to be significant ($p<0.05$) for the dependent variables in the univariable model (medicines refusal, medicines manipulations). This generated Odds Ratios, 95% confidence intervals and associated p values. The data was analysed using SPSS version 20 software (IBM).

## 2.4 Study Setting and Study Participants

A pragmatic approach was employed to identify and recruit participants resulting in a total of 1559 study invitation letters being posted to patients (via their parent/carer) due to attend follow-up paediatric clinics (1448/1559) or handed out on the paediatric wards (111/1559) at UHCW. Study interviews were conducted with parents or carers (if legal guardians) of children or young people, or with young people directly. The opportunity to assent and participate alone was given to 12-16 year olds providing parent or carer consent was also obtained. Young people over 16 years of age were permitted to consent alone and encouraged to discuss the study with a parent or legal guardian before providing consent. It was necessary to include young people (those over 12 years of age),

where appropriate as this sub-population reported increased personal management of their medicines administration. Parents or carers views were more useful for younger children where they may not have the cognitive capability to participate alone.

Age-appropriate study information was provided to potential participants at least 24 hours before asking for participation in the study.

A total of 191 general and speciality outpatient clinics were targeted covering a wide range of chronic conditions (e.g. epilepsy, cystic fibrosis, neoplasms, cardiac disorders, endocrine disorders, tuberculosis, HIV, renal diseases, rheumatological diseases and survivors of neonatal intensive care). It should be noted that not all patients in clinics were prescribed medicines, therefore not all patients were eligible for study inclusion. There was a scheduled approach to accessing patients at these clinics on a rotating basis to ensure wide coverage of the target patient population. UHCW is a teaching hospital with three age-banded paediatric wards. All have a wide range of paediatric patients without specialism. Inpatients from all three paediatric wards at UHCW were included at the recruitment phase to minimise the risk of missing eligible patients who were hospitalised during the study period. The recruitment phase lasted 15 months from November 2010 to February 2012.

### 2.4.1 Inclusion criteria

The study included children (aged 0- <18 years) with chronic conditions and their parents or carers. Age bandings were based on pre-school; school-age and adolescents to match cognitive function. Patients were eligible for inclusion if they had been taking prescribed medication for a chronic condition for at least one month prior to their outpatient appointment.

# 3 Results

A total of 280 participants consented to the study (Figure 1). Interviews were completed with 221 parents/carers and 57 young people (in the presence of a parent/carer (n=42), in the absence of a parent/carer (n=15)). In total, (91%) 252/278 of the children included were prescribed at least one

oral formulation. The remaining 26 patients were not prescribed any oral formulations, only non-oral formulations. The data from these patients was analysed separately and is not included in the subsequent analyses.

## 3.1 Participant demographics and medicines

The 252 children receiving oral formulations were categorised into three age groups: 0-4 years (n=92), 5-11 years (n=93) and 12-18 years (n=67), see Table 1 for the frequency of oral formulation types prescribed.

**Table 1: The frequency of oral formulation types prescribed across child age ranges 0-4y, 4-12y and 12-18y**

| Age Group | 0-4 years (n=92) | 5-11 years (n=93) | 12-18 years (n=67) | Total in 252 children |
|---|---|---|---|---|
| **Liquids** | 130 | 86 | 36 | 252 |
| **Tablets or capsules** | 20 | 61 | 96 | 177 |
| **Other (granules, powders, soluble tablets and melts)** | 49 | 47 | 17 | 113 |
| **Totals** | 199 | 194 | 149 | 542 |

n represents the number of children in each age range (0-4, 5-11 and 12-18 years)

In total, 542 oral formulations were prescribed across the cohort (with the number of oral formulations prescribed to each patient ranging from 1 to 8).

Of these oral formulations, 8% (41/542) were identified as 'Specials' (i.e. unlicensed formulations prepared under the terms of a Marketing Authorisation, granted by the Medicines and Healthcare products Regulatory Agency) (MHRA).

## 3.2 Medicines refusal

In total, 232/252 of participants answered the question (Q5 see Supplementary File 1) about the refusal of formulations, resulting in data on 436/542 of formulations. Of these, 8% (44/542) of formulations were administered via nasogastric or percutaneous endoscopic gastrostomy tubes and medicine refusal was not permitted, therefore data is unavailable on these medications for 10

patients. The medicines refusal question was not delivered to a further 10 participants owing to time constraints. Almost one third (71/232) of respondents reported medicines refusal on at least one occasion; multivariable statistical analysis was conducted on this data set. The results are reported in Table 2.

**Table 2: Multivariable analysis results: Reports of medicines refusal on at least one occasion**

| | Odds Ratio (95% CI) | p Value |
|---|---|---|
| **Age of child at Interview** | | **0.016*** |
| 0-4 years | 1 | |
| 5-11 years | 0.42 (0.19 - 0.89) | 0.024* |
| 12-18 years | 1.31 (0.54 - 3.20) | 0.554 |
| **IMD 2010 score** | | **0.002*** |
| <11.5 | 1 | |
| 11.5-19.8 | 1.32 (0.49-3.51) | 0.584 |
| 19.9-31.9 | 3.19 (1.37-7.43) | 0.007* |
| 32+ | 4.75 (2.02-11.18) | <0.001* |
| **Formulation type** | | **0.336** |
| Liquid | 1 | |
| Capsules and Tablets | 0.59 (0.27-1.30) | 0.193 |
| Other (granules, powders, soluble tablets and melts) | 0.64 (0.30-1.38) | 0.254 |
| **Problem with taste** | | **<0.001*** |
| No | 1 | |
| Yes | 3.82 (2.11-6.92) | <0.001* |
| **Problem with texture** | | **0.017*** |
| No | 1 | |
| Yes | 3.38 (1.24-9.22) | 0.017* |
| **Problem with volume or quantity** | | **<0.001*** |
| No | 1 | |
| Yes | 12.79 (4.41-37.12) | <0.001* |
| **Problem with smell** | | **0.776** |
| No | 1 | |
| Yes | 1.24 (0.28-5.46) | 0.776 |

p values marked with * identify statistically significant results (p<0.05).

The age of child at interview was found to be a significant predictor of refusal, with children aged between 5-11 the least likely to have refused medicines (OR=0.42, relative to the 0-4 year group; 95% CI: 0.19-0.89; p=0.024). However, no significant difference was detected between the likelihood of medicines refusal in the 12-18 years group, relative to the 0-4 years group (OR=1.31; 95% CI: 0.54-3.20; p=0.554). The likelihood of medicines refusal was found to increase significantly (p=0.002)

across the IMD score groups, peaking at an odds ratio of 4.75 (95% CI: 2.02-11.18; p<0.001) in the most deprived patient group (IMD=32+) relative to the least deprived (IMD<11.5).

A range of medicines related factors were also found to be associated with refusal in children. Patients who had problems with the volume or quantity of medication were considerably more likely to have a history of medicines refusal (OR=12.79; 95% CI: 4.41-37.12; p<0.001), with issues with either taste (OR=3.82; 95% CI: 2.11-6.92; p<0.001) or texture (OR=3.38; 95% CI: 1.24-9.22; p=0.017) also being significant predictors of refusal. However, after accounting for these factors, there was no significant evidence that either the smell (p=0.776), or the type of formulation (p=0.336), had any impact on refusal rates.

## 3.3 Medicines manipulation

Almost one third (74/252) of respondents reported manipulating formulations.

In total, 19% (94/499) of formulations were manipulated. Of these, the majority (93%, 87/94) were reported to be manipulated 'always' (i.e. prior to every dose administration).

Of the medicine manipulations reported, 26% (24/94) were performed for the purpose of administering a specific dose (e.g. one quarter of a tablet), whilst the majority of medicine manipulations, 79% (74/94) were performed to facilitate medicines administration (e.g. mixed into foodstuffs). Omeprazole soluble tablets, macrogol 3350 oral powder, co-trimoxazole tablets and mercaptopurine tablets were most often manipulated (by at least 40% of users). For over three quarters (78% 7/9) of children prescribed omeprazole soluble tablets, medicines manipulation was reported.

The age of the child at the interview was found to be a significant predictor of the reporting of medicines manipulation (p=0.005). Reports became progressively less likely with increasing age, with Odds Ratios of 0.29 (95% CI: 0.13-0.67; p=0.004) in the 5-11 year age group, and 0.18 (95% CI: 0.06-0.59; p=0.005) in the 12-18 year age group, relative to patients in the 0-4 year group.

The type of formulation was also associated significantly with reporting of medicines manipulation (p<0.001), with tablets and capsules (OR: 9.66; 95% CI: 3.48-26.87; p<0.001) and other formulations (granules, powders, soluble tablets and melts) (OR: 23.97; 95% CI: 9.14-62.84; p<0.001) both more likely to be manipulated than liquids. Manipulation was also found to be significantly more likely to be reported where patients had problems with either the size (OR: 4.52; 95% CI: 1.37-14.90; p=0.013) or the texture (OR: 3.15; 95% CI: 1.39-7.14; p=0.006) of the medicines. In cases where the child had partial responsibility for the administration of a medicine, significantly lower rates of manipulation were reported, relative to where the parent or guardian was solely responsible (OR: 0.28; 95% CI: 0.10-0.81; p=0.019). A similar effect was observed where the child was totally responsible for medicines administration, although this was not statistically significant (OR: 0.22; 95% CI: 0.02-1.94; p=0.171). The results are reported in Table 3.

**Table 3: Multivariable analysis results: Reports of medicines manipulation**

| | **Odds Ratio (95% CI)** | **P Value** |
|---|---|---|
| **Age of child at Interview** | | **0.005*** |
| 0-4 years | 1 | |
| 5-11 years | 0.29 (0.13-0.67) | 0.004* |
| 12-18 years | 0.18 (0.06-0.59) | 0.005* |
| **Is English first language of participant** | | **0.085** |
| Yes | 1 | |
| No | 0.26 (0.06-1.20) | 0.085 |
| **Formulation type** | | **<0.001*** |
| Liquid | 1 | |
| Tablets and Capsules | 9.66 (3.48-26.87) | <0.001* |
| Other (granules, powders, soluble tablets and melts) | 23.97 (9.14-62.84) | <0.001* |
| **Problem with size of dosage form or aversion to/difficulty swallowing dosage form** | | **0.013*** |
| No | 1 | |
| Yes | 4.52 (1.37-14.90) | 0.013* |
| **Problem with texture** | | **0.006*** |
| No | 1 | |
| Yes | 3.15 (1.39-7.14) | 0.006* |
| **Problem related to other formulation and administration problems** | | **0.206** |
| No | 1 | |
| Yes | 1.89 (0.70-5.08) | 0.206 |

| | | |
|---|---|---|
| **Who is responsible for medicines administration** | | **0.049*** |
| Parent/Guardian | 1 | |
| Child plus Parent/Guardian | 0.28 (0.10-0.81) | 0.019* |
| Child | 0.22 (0.02-1.94) | 0.171 |
| **Problem with volume or quantity** | | **0.157** |
| No | 1 | |
| Yes | 2.17 (0.74-6.35) | 0.157 |
| **Frequency of dosing** | | **0.404** |
| 1x daily | 1 | |
| 2x daily | 0.70 (0.34-1.45) | 0.345 |
| ≥3x daily | 0.20 (0.03-1.46) | 0.113 |
| <1x daily (not including medicines prescribed on a 'when required' basis) | 0.76 (0.23-2.46) | 0.647 |

p values marked with * identify statistically significant results (p<0.05).

## 3.4 Barriers to oral medicines administration

### 3.4.1 Taste

Taste was the most commonly reported barrier to medicines administration affecting 35% (188/542) of all prescribed oral formulations, and associated with 64% (54/85) of formulations that were refused.

Formulations with the highest incidence of taste issues were ranitidine liquid (82%; 9/11 children), prednisolone soluble tablets (81%; 13/16 children) and trimethoprim liquid (75%; 6/8 children) of total users. However, taste issues were reported for at least 50% of children prescribed other common drugs (lactulose liquid, macrogol 3350 oral powder sachets, co-trimoxazole tablets, sodium valproate liquid, levetiracetam liquid, penicillin liquid, ibuprofen liquid and prednisolone tablets). See Figure 2 for reported taste problems.

### 3.4.2 Texture

Texture was reported to affect 8% (42/542) of all prescribed oral formulations, and was a significant predictor of medicines refusal. Co-trimoxazole liquid (38%), omeprazole soluble tablets (33%) and lactulose liquid (25%) were most commonly reported to have texture-related problems. Specific medicines identified with textural issues included: lactulose which was described as "oily" and co-trimoxazole liquid described as "thick and gelatinous"

### 3.4.3 Volume or Quantity

Of the medicines prescribed, 5% (29/542) were reported to have “too large” a volume or “too many” solid dosage units to be administered at one dosing interval. Volume or quantity were reported as barriers to administration for 63% (5/8) of children prescribed pancrealipase capsules, 40% (12/30) of children prescribed macrogol 3350 oral powders and 19% (3/16) of children prescribed prednisolone soluble tablets.

### 3.4.4 Size and aversion to or difficulty with swallowing

Problems related to i) the size of a solid dosage form or ii) aversion to or difficulty swallowing a solid dosage form was associated with 5% (28/542) of the total medicines prescribed (16% if only solid dosage forms considered).

For 16% (28/177) of solid dosage forms prescribed to patients, problems experienced either with the size of a solid dosage form or where children were averse to swallowing a solid dosage form were reported. Problems specifically related to the sizes of particular solid dosage forms were reported for 68% (19/28) of these medicines, and aversion to, or difficulty swallowing solid dosage forms was reported for the remaining 32% (9/28) of medicines. It should be noted that these patients were not physically unable to swallow (i.e. not patients fitted with an NG or PEG tube). The majority (7/8= 88%) of patients prescribed co-trimoxazole tablets reported a problem with their large size or difficulties swallowing them. These children were aged from 4 to 15 years. Although specific data on brand of formulation was not collected from parents, the size of co-trimoxazole tablets (480mg) was measured to be an average of 11mm (based on the average diameter of two different manufacturers).This could be expected based on the large amount of active ingredient within the formulation. In contrast, there were no problems reported with the size of levothyroxine tablets, owing to their significantly lower dose (micrograms) and therefore a comparatively smaller tablet.

### 3.4.5 Colour/appearance and smell

An unfavourable colour (descriptions provided included “alarming”, off-putting, and colourless) was associated with 2% (11/542) of medicines prescribed. Two of eighteen children prescribed sodium

valproate liquid highlighted its “alarming colour” .. Similarly, one of nine patients prescribed paracetamol liquid described its unappealing colour.

In addition, 2% (11/542) of medicines prescribed were identified as having “off-putting” smells. For 25% (2/8) of children prescribed trimethoprim liquid, an unfavourable smell was reported.

# 4 Discussion

This study has indicated that formulations prescribed to children with chronic conditions are not meeting the needs of a significant number of patients based on self-report. Medicines refusal was associated significantly with barriers to oral medicines administration: taste, texture, quantity/volume (see Table 2). Palatability needs to be considered carefully by pharmaceutical companies when designing new formulations and also by prescribers in order to optimise effective prescribing, maximising adherence, therapeutic effects and reducing wastage with cost savings. Other statistically significant factors associated with medicines refusal were child age at interview and IMD 2010 score. Recent EMA guidance (EMA, 2013) states that age-appropriateness of formulations needs to be prominent in pharmaceutical development and also when designing prescribing protocols for prescribers. Further research is required to investigate the relationship between socio-demographic factors and medicines refusal.

The formulations highlighted to be problematic are also often prescribed to treat patients with acute conditions, e.g. soluble prednisolone tablets. Evaluation of the study data can inform changes in prescribing practice, e.g. prescribing prednisolone tablets in preference to soluble prednisolone tablets for children; even though intuitively soluble tablets are considered to be age-appropriate for paediatric populations. This change has been implemented at UHCW and it is estimated that this will generate a cost saving of £5000 per annum in the Paediatric Department (Personal Communication, 2012).

This study identified that almost one third (29%) of participants reported manipulating medicines. Studies conducted in specific patient groups (HIV (Byrne et al., 2002; Goode et al., 2003; Wrubel et al., 2005) and oncology (Christiansen et al., 2008)), reported similar findings. Several examples of medicines manipulation that could affect drug bioavailability and thus therapeutic response were identified and their potential physicochemical effects are reported in Table 4 below.

**Table 4: Potential physicochemical effects of medicines manipulation**

| Manipulation techniques reported within this study | Potential physicochemical effects of manipulation techniques (general examples; not tested with specific formulations reported within this study) |
|---|---|
| Splitting tablets (co-trimoxazole tablets) or sachets manually (Gaviscon infant oral powders) | Inaccurate segmentation resulting in administration of inaccurate dose (underdose versus overdose) |
| Mixing non-soluble tablets with liquids (azathioprine tablets) | Non-uniform dosing, aggregation and sedimentation of insoluble drug particles |
| Crushing tablets (hydrocortisone tablets) | Thermal degradation |
| Mixing with foodstuffs (sodium valproate liquid) | Fruit juices (altering pH), drug binding to dairy proteins, formation of insoluble complexes |

Limited evidence is available on the effects of mixing drugs with various foodstuffs. Prolonging the contact time of a drug with a foodstuff is likely to increase the binding capability and therefore may risk reducing drug bioavailability, thus affect therapeutic response. Additionally, if a drug-foodstuff mixture is not consumed in its entirety, the desired dose will not be administered.

To minimise unnecessary medicines manipulation it is essential that prescribers consider age-appropriateness, type of formulation (in relation to ease of administration), swallowing problems and patient capability to swallow tablets according to size and also acceptance of different textures. These factors were associated significantly with manipulation of medicines (see Table 3). The lower reported refusal of solid dosage forms compared to liquids (see Table 2) may be associated with the adoption of *ad hoc* manipulation techniques, and supporting this, medicines manipulation was significantly associated with administering solid dosage forms (see Table 3).

Future formulation work needs to be implemented to develop age-appropriate formulations that are accepted by children and are also available in appropriate unit doses, ideally pre-measured, covering child dosing ranges and also small enough to taper doses accurately. Dosage form technologies such

as mini-tablets (Spomer et al., 2012; Thomson et al., 2009) may help to reduce the perceived need to manipulate some medicines. However, it should be acknowledged that for some medicines, it may be more feasible for practical and economical reasons to use safe and effective manipulation techniques. Owing to the limited data available and also poor understanding of healthcare professionals regarding the safety and efficacy of medicines manipulation (Akram and Mullen, 2012; Venables et al., 2012) it is vital that laboratory work is conducted to provide a robust scientific evidence base to support safe and effective medicines manipulation.

It would be useful for future studies to investigate if education to help children to learn to swallow tablets could improve medicines adherence. Studies investigating infant acceptance of different tastes and textures of foodstuffs (Harris, 2008; Northstone et al., 2001) agree that encouraging children to accept solid dosage forms from a younger age may be beneficial. This could minimise child aversion to some formulations and also reduce unnecessary modification to medication.

The present study is pragmatic, of multi-perspective design and has a large paediatric sample size. It has expanded the pre-existing, narrowly focussed literature and identified the prevalence and nature of barriers to oral medicines administration in children with chronic conditions. Complementing the findings of this study, two other studies (Richey et al., 2011; Skwierczynski and Conroy, 2008) identified the nature and frequency of manipulations to formulations administered to children on paediatric wards. Identification of the difficulties experienced by families when administering formulations to children is essential for directing future formulation development work. User involvement has played a fundamental role throughout the present study.

A limitation within the present study is the reporting of generic formulations as opposed to specific products (e.g. brands and manufacturers). This results from the nature of this pragmatic study which relies upon parent/carer/patient reports. Nonetheless, this is the first study to explore barriers to oral medicines administration in children with a wide range of chronic conditions. Further research is

required to identify whether similarly, problems are encountered with non-oral medicines and in paediatric populations outside of the UK.

A limitation of using a self-report tool is the risk of inaccurate reporting (Butz, 2006). In this study, one mother reported that medication had not been omitted, however the adolescent in her care provided an opposing report. This finding reinforces the need for future studies to investigate parent and teenager reports independently. In the present study, there was insufficient time and resources for parents and young people to be interviewed independently and the study was designed to be pragmatic, thus reflect a family environment. A study by Buchanan and co-workers (2012) found significant similarity between independent reports of 'taste/cannot get it down' ($p<0.001$), forgetting ($p<0.001$), and also refusing doses ($p=0.01$) amongst young people with HIV and their carers. These findings suggest that reporting of such outcomes is fairly consistent between carers and young people, however this is only one study, conducted in children with HIV.

The statistical results may have been subject to confounding by other factors that were not considered in the analysis and should be interpreted in light of this. However, since a range of variables were considered in the analysis and a multivariable statistical approach was used, confounding factors have been accounted for as far as was possible.

# 5 Conclusions

Almost one third (31%) of respondents reported medicines refusal on at least one occasion and 29% reported manipulating formulations. Study findings indicate that oral formulations prescribed to children are not suitable for a significant number of patients. Adherence and hence expected therapeutic response will be potentially affected. Medicines manipulation can be a serious burden for parents or carers, particularly when children are prescribed several formulations. Age-appropriate formulations should be developed to provide both suitable dose units and acceptable taste. Further laboratory work is required to provide robust scientific evidence to support medicines

manipulation techniques suitable for use in the domiciliary environment with attention to patient safety and drug efficacy. In addition, prescribers and pharmacists need to be vigilant when making prescribing and supply decisions respectively, to ensure that they are choosing the most appropriate formulation for an individual patient.

We would like to acknowledge the West Midlands Medicines for Children Research Network (WM-MCRN) for funding this research. We would like to thank Sarah Thomas, University of Birmingham for reviewing the systematic literature review which identified this original research.

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