Barriers to administering non-oral formulations in a paediatric population: A semi-structured interview study.

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1. Introduction

Approximately 200 million prescriptions are issued annually for children and young people in the UK (Costello et al., 2004). It has been estimated that 5 - 10% of young people worldwide suffer from chronic health conditions (Newacheck et al., 2000).

Children with chronic conditions may be prescribed a variety of medicines and have complex regimes. There is evidence to suggest that adherence with prescribed medication is lower amongst adolescents and children than in adults (Staples and Bravender, 2002). Medication adherence rates between 11% and 93% in paediatric patients have been reported (Winnick et al., 2005).

Acceptability has previously been defined as the overall ability of a patient/ caregiver to use a medicinal product as intended / authorised (Kozarewicz, 2014). Acceptability of a medicinal product has potential to significantly affect the patient's adherence and therefore is likely to influence safety and efficacy of a product (Kozarewicz, 2014). Usability has been used interchangeably with 'human factors' and defined as a 'multi-dimensional quality', which reflects human ability 'to interact easily

and relatively error-free with a system or product.' This may be translated in medical device terms, as the measure of how well a device works to meet user expectation, thus administration without frustration (BSI, 2015).

Over the past two decades, trends in post-market adverse events related to design issues affecting usability of medical devices have been reported. These use-related design issues have resulted in problems with therapies (BSI, 2015).

There is a paucity of research exploring barriers to non-oral formulations and devices used in the administration of formulations to paediatric patients within a pragmatic environment. However, barriers to medicines administration undoubtedly influence medicines adherence. Studies conducted with healthcare professionals have identified various issues with the usability and child acceptance of non-oral formulations and devices in children, (Venables et al., 2012; Walsh et al., 2015). In order to improve formulations for children in the future, it is inevitable that one needs to understand barriers to administration, thus usability can inform future drug development work to improve design of medicinal products and medical devices. Children have different sensory perceptions to adults and are therefore the most important participants for acceptability studies in paediatric patients; thus it was necessary to identify barriers to administration from their perspective to inform the design of future formulations and administration devices.

More information is needed to understand the factors that influence child and carers and their attitudes to medicines adherence to inform future paediatric formulation design. Regulatory agencies have also noted the importance of acceptability of devices for the administration of non-oral formulations including EMA (2014) guidelines and guidance from BSI on 'user interface design/evaluation' supports FDA (2011) draft guidance on optimizing medical device design, which

outlines potential human factors and usability engineering (HFE/UE) analyses that should be conducted for medical devices, which includes formative evaluations of medical devices.

The aims of the present study were: (i) to establish the prevalence and nature of barriers to administering non-oral formulations to paediatric patients with chronic conditions (ii) to determine how frequently any factors identified with non-oral formulations (including devices used to administer formulations) are involved in compromising acceptability and refusal and (iii) to inform future paediatric (non-oral) medicines formulation and device design, the pharmaceutical industry and prescribers.

1. Materials and Methods

1.1 Data collection tool

A semi-structured interview was selected for this study to obtain the qualitative data required and provide an appropriate balance in data collection and subsequent analysis (Malim and Birch, 1996). A multidisciplinary research team (Professor in Clinical Pharmacy, paediatric consultant and pharmacist) generated an outline of barriers to administering non-oral formulations to children; medicines administration 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), Paediatric AIDS Clinical Trials Group PACTG questionnaire (NIAID) and Morisky Scales (Morisky et al., 2008,1986) 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 used in the semi-structured interviews was designed to collect data exploring medicines acceptability and adherence. Open questions were used to elicit

barriers to medicines administration and a closed question was used to identify rates of refusal. The tool used has been previously reported by Venables et al. (2015).

A semi-structured interview was conducted by a single researcher 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 min) 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 from all participants.

1.2 Qualitative analysis

Thematic analysis was conducted using a frame-work approach to form a coding spine. Thematic content analysis (Pope et al., 2000) was used to identify and group common themes arising from the qualitative data, relating to administering non-oral formulations.

1.3 Study setting and 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 years old providing parent or carer consent was also obtained. Young people aged 16 – <18 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 empowerment over medicines administration. Parents' and carers' views were more useful for younger children where they did not

have the cognitive capability to participate alone or were not responsible for medicines administration.

Age-appropriate study information was provided to potential participants at least 24 h 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 medications; 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. 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.

1.4 Inclusion criteria

Children (aged 0–<18 years) with chronic conditions and their parents/ carers were recruited to the study. Patients were eligible for inclusion if they had been taking a prescribed medication for a chronic condition for at least one month prior to their outpatient appointment.

2 Results

A total of 280 participants consented to the FIND OUT study (Venables et al., 2015). In total, 90 participants were prescribed at least one non-oral formulation. Interviews exploring barriers to administering non-oral formulations were completed with 61 parents/guardians and 29 young people (in the presence of a parent/carer (n = 24), in the absence of a parent/carer (n = 5)).

The children prescribed only oral formulations will not be discussed in this paper; these have been published previously (Venables et al., 2015).

2.1 Participant demographics and non-oral formulations

The 90 children receiving non- oral formulations were categorised into three age groups: 0–4 years (n = 25), 5–11 years (n = 36) and 12– <18 years (n = 29), age bandings were based on pre-school; school-age and adolescents to match cognitive function. See Table 1 for the frequency of non-oral formulation types prescribed. In total, 148 non-oral formulations were prescribed across the cohort.

Table 1. Primary diagnoses and number of patients diagnosed

Main diagnosis	**Number of study patients with this primary diagnosis**
Gastro-intestinal	12
Neoplasm	2
Epilepsy	4
Allergies	2
CF	8
Arthritis / uveitis	14
Growth disorders	10
Thyroid condition	5
Blood-related disorder	2
Asthma	15
Renal disease	5
Cardiac disease	2
DM type 1	6
Chronic fatigue syndrome	2
Scleroderma	1

2.2 Medicines refusal

In total, data about the refusal of formulations was gained for 70% (103/148) non-oral formulations. Of these, 7% (7/103) of non-oral formulations were reported to have been completely refused

2.3 Barriers to non-oral medicines administration

In total, 88 barriers to medicines administration were reported across the 148 non-oral formulations. A barrier to administration in this study is defined as a factor which has potential to affect administration; this includes poor child acceptance and interference with daily living (more examples of reports are reported in the following results sections). See Figure 1 below for the frequency of reported barriers to administration across different non-oral formulations.

Figure 1. The frequency of reported barriers to administration across different non-oral formulations.

Over 60% of participants reported at least one barrier to non-oral medicines administration; the impact of age on reported barriers is shown in Figure 2 below.

Figure 2. The frequency of children/ parents reporting at least one barrier to administering non-oral formulations.

In addition to barriers to administration, for almost one quarter of non-oral formulations, problems with obtaining formulations were highlighted.

2.3.1 Inhaled formulations

49 children (0-4 years n=17, 5-11 years n=21, 12-<18 years n=11) were prescribed inhaled formulations. In total, 55% (27/49) of children prescribed inhaled medication reported a barrier to administration (0-4 years n=12, 5-11 years n=9, 12-<18 years n=6). See Fig.1 for the number of reported barriers to inhaled medication. See table 2 for themes arising from the data on inhaled formulations and associated reporting frequency.

Table 2. Themed barriers to administration of inhaled formulations reported by parents/carers and young people

Barrier theme	**Number of reports**
Difficulty with face mask/spacer devices doesn't	18

like face mask/spacer. Spacer too big inconvenient to transport/ difficulty washing.	
Difficulty with /inconvenience of preparation - Time consuming /preparation effort/puts off eating/interferes with daily living as have to be at home.	12
Measuring and delivering accurate dose - Device – unsure how much drug is delivered/hard to gauge how much is actually released relies on breath/ sometimes dose not released	6
Formulation options - doesn't like nebuliser prefer tablet, formulation difficult, not ideal	5
Age-appropriateness/appeal - Not child friendly or attractive to children	2
Palatability issues (texture/consistency/taste) - too powdery, bad taste when hits back of throat	3
Storage – nebuliser solution has to be kept in freezer storage bag when travelling	1

In addition, a positive comment was highlighted by a participant stating that inhalers with counters are valuable as they show how many doses are remaining.

2.3.2 Parenteral formulations

In total, data was explored for 43 parenteral formulations (including IM, IV and SC formulations) prescribed to 36 children (0-4 years n=6, 5-11 years n=15, 12-<18 years n=15). Three quarters - 75% (27/36) of children prescribed parenteral formulations reported a barrier to administration (0-4 years n=2, 5-11 years n=13, 12-<18 years n=12). See Fig.1 for the number of reported barriers to parenteral formulations. See table 3 for themes arising from the data on parenteral formulations and associated reporting frequency.

Table 3. Themed barriers to administration of parenteral formulations reported by parents/carers and young people

Barrier theme	Number of reports
Dislikes formulation/ prefer alternative formulation as dislikes injection, another formulation preferred, (e.g. tablets banana/strawberry liquid),does not like route of administration	13
Fear of pain / effects at site of administration - bruising, needle phobia (change to pen device like 'etanercept' so cannot see needle, prefer	10

diabetic pen), bleeding at site, stinging at site, preparation time increases anxiety.	
Difficulty with device (human error factors) - Device stiffness, difficult to administer, parents have to administer as too difficult for child yet child wants to be more independent, incompatibility with certain needles and the device, insulin pump does not test blood sugar still need to finger-prick.	6
Frequency of dosing - issue with twice daily dosing of injection	1
Difficulty with preparation of dose	1
Volume	1
Short expiry dates	1
Storage - fridge	1

2.3.3 Dermal/transdermal

In total, data was explored for 7 dermal/transdermal formulations prescribed to 5 children (0-4 years n=1, 5-11 years n=1, 12-<18 years n=3).

5 barriers to medicines administration were reported across these formulations for 3 children (5-11 years n=1, 12-<18 years n=2). See table 4 for themes arising from the data on dermal/transdermal formulations and associated reporting frequency.

Table 4. Themed barriers to administration of dermal and transdermal formulations reported by parents/carers and young people

Barrier theme	Number of reports
Texture/ consistency - creams: greasy difficult for school, child avoids applying this. Ointments: very greasy difficult for school, child avoids applying this.	4
Measuring and delivering accurate dose - Transdermal patch – child is drowsy if cut in half inaccurately, other comment – mom was concerned as to whether she has cut the patch accurately for homogenous drug release; there is no score line, she reported using eye measurement	1

2.3.4 Ocular

In total, data was explored for 4 ocular formulations prescribed to 3 children (0-4 years n=1, 12-<18 years n=2). A single barrier to medicines administration was reported across these formulations;

difficulty with device – chloramphenicol eye ointment was described by a mother as very difficult to administer to a child owing to the child not wanting to sit still and not liking eyes to be touched (0-4 years n=1).

2.3.5 Nasal

In total, data was explored for 3 nasal formulations prescribed to 3 children (0-4 years n=1, 5-11 years n=1, 12-<18 years n=1). A single barrier to medicines administration was reported across these formulations; Issue with the volume of a nasal spray – '2 sprays for one dose is a large volume, child does not like this large volume' (5-11 years n=1).

2.3.6 Contraceptive implant device

No issue was reported for the contraceptive implant device prescribed (1 child prescribed a contraceptive implant device, 12-<18 years n=1).

2.3.7 Rectal

No issues were reported for the two enema formulations prescribed (2 children prescribed rectal formulations, 0-4 years n=1, 12-<18 years n=1).

3 Discussion

In total, 7% of doses were actually refused, however, a plethora of barriers (88 reported barriers across 148 non-oral formulations) to administration were reported. It was necessary to identify these barriers in order to improve usability, i.e. reduce frustration, resistance and potentially time delay of administration. Further to these barriers, reports of issues with obtaining medicines were reported.

64% (58/90) of participants reported at least one barrier to non-oral medicines administration (0-4 years n=15, 5-11 years n=24, 12-<18 years n=19). The highest rate of barriers (67% of children prescribed non-oral formulations) was reported by parents of children in the 5-11 years age band,

208 although similar frequency of reports were recorded for children aged 0-4 years and 12-<18 years
209 (60% and 66% respectively).

210 For inhaled formulations and associated devices, key issues identified in order of highest reporting
211 frequency (n=≥10 reports) were: Difficulty with face masks/ spacer devices and difficulty with/
212 inconvenience of preparation. Further barriers: measuring and delivering an accurate dose, difficulty
213 with other devices, age-appropriateness/appeal, texture/consistency, taste and storage were
214 reported in smaller frequencies.

215 Findings of this study demonstrate that barriers to administration of inhaled formulations were
216 reported more by children within the youngest age band (0-4 years). This may be related to high
217 frequency of prescribing of spacer devices (with a face mask where necessary) in children under the
218 age of 5 with chronic asthma, in-line with current NICE guidance (NICE, 2000). It is crucial that
219 findings inform formulation design and development, thus the pharmaceutical industry should
220 consider methods to improve patient acceptance and usability. It may be possible to improve child
221 acceptance if spacer devices were designed to appeal to children and be suitable in terms of age
222 appropriateness; it may be beneficial to use child-friendly designs in future design stages of both
223 products and patient information leaflets provided with these. Complementing some of these
224 findings, a study by Walsh et al. (2015) investigating healthcare professionals' perspectives identified
225 similar problems with respiratory devices including: too complicated to use, unpleasant taste,
226 coordination difficulties and lack of patient tolerance (especially to spacer/facemask). Similarly they
227 reported the use of child-friendly designs to improve child acceptance (Walsh et al., 2015).

228 With regard to parenteral formulations, key issues in order of highest reporting frequency (n=≥10
229 reports) were: disliking formulation/ preferring an alternative and fear of pain /effects at site of
230 administration. Other barriers reported in smaller frequencies were: difficulty with device, frequency
231 of dosing, difficulty with preparation of dose, volume, short expiry dates and storage.

232 Results show a higher frequency of reporting of barriers to parenteral administration amongst the 5-
233 11 and 12-<18 years age band compared to children aged 0-4 years. This may be associated with
234 children at the middle and upper end of the paediatric spectrum desiring more empowerment over
235 their medication, thus being involved with the administration process. As a child matures in to
236 adolescence, generally reduced parental guidance and supervision is observed. Often, parents
237 become less responsible for administering medication and also reminding their child to administer
238 medication as the child gets older (WHO, 2003). One factor which may affect adherence is the
239 interference of the treatment with needs and lifestyles of the young person (Michaud et al., 2004).
240 The majority of young people strive to lead a stereotypical 'teenage life' and are likely to undergo
241 peer pressure, and feel the stigma associated with administering medication (e.g. when attending
242 social events) (Michaud et al., 2004). This should be taken into account when designing parenteral
243 devices for the paediatric spectrum. Parenteral formulations are often prescribed for conditions
244 such as juvenile diabetes, haemophilia and rheumatoid arthritis; research exploring young people
245 with these conditions has revealed the potential vulnerability of young people to medication non-
246 adherence (WHO, 2003). This correlates with the findings of the current study, which highlights the
247 prevalence of barriers to parenteral administration across a paediatric population.

248 There is a steady increase in both pinch strength and grasp which correlates to increase in
249 chronological age (Ager et al., 1984; Häger-Ross et al., 2002) and development (Ager et al., 1984). It
250 has been previously reported that the peak grip strength of a 9 year old is comparable to that of a
251 healthy man/woman (Nordenskio¨ld & Grimby 2003), thus this should be considered when designing
252 devices that are 'usable' for children of different ages and abilities. Furthermore, it is vital that the
253 pharmaceutical industry recognise and inform device design with respect to dexterity issues which
254 may be experienced by certain paediatric patient groups whom often require devices, e.g. children
255 with juvenile idiopathic arthritis. The ethos is that parents/young people should be able to use
256 medical devices safely and effectively, without unintentionally making errors that could compromise
257 positive outcomes.

Reports of palatability issues for three inhaled formulations included the 'powdery' texture and 'bad taste when hits back of throat'; such findings should be explored further and used to direct future formulation design. 'Greasy' consistency was reported as a barrier to administration for a child prescribed ointments and creams. This has been similarly reported in other studies. Santer et al. (2013) described carers' reports which included "waxy and slippery and very sticky". Similarly a further study reports the unappealing formulation, such as smell or greasiness of my child's topical treatments, making it difficult to treat the disease (Ellis et al., 2011). Methods used to overcome child resistance to topical application have been reported to include bribes, games and distraction therapy during application (e.g. Television) (Santer et al., 2013). Such methods, alongside parental/ young person educational techniques may help to overcome barriers to administration and should be explored further in future studies.

The current study findings identify barriers to administering non-oral formulations and provide insight into improving the design of future devices. Such findings should be used alongside existing guidance on acceptability of formulations (EMA, 2014), draft guidance on usability (FDA, 2011) and BSI guidance on 'user interface design/evaluation' to inform the pharmaceutical industry and optimise medical device design.

Both the FDA and IEC 62366 stress the importance of a UI design process that is driven by iterative formative evaluations conducted early-on and throughout the design process of a device; this is crucial in view of minimising risk thus human error and also improving usability of devices (BSI, 2015). If usability is not optimal, medicines administration may be slower and more prone to error; this could affect medicines adherence and patient/parent safety. Furthermore, if a product has improved usability, this may result in a competitive advantage from a marketing perspective.

It is imperative that children and young people are involved in the design or medical devices as well as in the writing of appropriate instructions for use to optimise this process, in order to inform future formulation development at an age-appropriate level. This should promote the production of

devices that are suitable across the paediatric spectrum. In addition, the role of educating and communicating with parents and young people effectively to optimise adherence to medication regimens should be explored further. Current research evidence highlights the importance of effective communication to support paediatric adherence (DiMatteo, 2004).

Further studies should be conducted to explore barriers to usability and patient acceptance of non-oral formulations and device on a larger scale, noting specific brands to inform pharmaceutical industry.

4 Conclusions

This pragmatic and novel study provides insight on the acceptance of non-oral formulations across a paediatric population suffering from various chronic conditions. This study complements the work conducted by: the EUPFI on acceptability (Kozarewicz, 2014); Walsh et al. (2015) on healthcare professionals' perceptions of devices and Venables et al. (2015) exploring barriers to oral medicines administration. This work complements BSI guidance on human factors and usability engineering (BSI, 2015) and that drafted by FDA (2011) on the need for evaluations of medical devices from users to determine usability. As children must not be considered mini-adults it is vital to ensure that data used to inform future pharmaceutical development of non-oral formulations and devices is from the representative patient group.

The findings of the current study should be used to inform future development of non-oral formulations and medical devices, suitable in terms of safety, efficacy usability and acceptability to paediatric patients and their parents/carers.

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