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Evaluation of patient reported outcome measurements as a reliable tool to measure acceptability of the taste of paediatric medicines

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10	4	Punam Mistry ¹ , Heather Stirling ² , Claire Callens ³ , James Hodson ⁴ and Hannah Batchelor ¹ on behalf of
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13	5	SPaeDD-UK project
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15	6	(Smart Paediatric Drug Development – UK, accelerating paediatric formulation development
16 17	7	http://www.paediatricscienceuk.com)
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31 Abstract

32 Objective: To evaluate the age-appropriateness and suitability of patient reported outcome
 33 measures to assess the acceptability of the taste of oral liquid medicines in children.

Design and setting: An observational mixed methods study involving children aged 2-16 years old taking oral liquid medicine in paediatric inpatient wards across the West Midlands (UK). Assessment tools included: patient-reported scores on the taste of medicines via a 5-point facial hedonic scale; a visual analogue scale (VAS); a question, "Did you think the medicine tasted OK?" and researcher observations of facial expressions and behaviours immediately before, during and after administration.

Results: 611 children participated. The percent unable to complete the scales were 7% (n=46) for the VAS; 2% (n=15) for the hedonic scale and 1% (n=7) for the question about taste. Significant correlations (Spearman's rho) were observed between the patient reported outcome measures: 0.80 and 0.78 for the taste question and hedonic and VAS respectively and 0.84 for the hedonic and VAS. Researcher observations demonstrated the ability of the patient to take the medicine as intended but did not provide sensitive measures of taste. 5% of administrations were not taken as intended by the children. Medicines known to have poor taste (clarithromycin and prednisolone) showed mean hedonic and VAS scores of \geq 3.5 and >65mm respectively.

48 Conclusions: Patient reported outcome measures correlate with each other and are a useful means
49 to assess the taste (and acceptability) of medicines. Hedonic scales are better understood by
50 children and should be the first choice tool in the assessment of medicines taste.

53 <u>Key words</u>: medicines, taste, acceptability, age-appropriate, hedonic scale, paediatric medicine,

- 54 patient-reported outcome measures, VAS
- 56 Strengths and limitations of this study
- This is the first study to compare methodologies to assess the acceptability of taste of liquid
 medicines in a large UK based paediatric population aged 2-16 years
- The sample size in this study provided large data sets of six key medicines, which provides a
- 60 representative comparison for newly developed products
 - This study was conducted within an inpatient environment and the acceptance of taste of
- 62 medicines in a domiciliary environment may differ
 - The study design captured the most relevant aspects of acceptability of taste whilst
- 64 minimising the burden to participants, it was not possible to measure every aspect.

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2 3	65	Suggestions for future research include measurement of: impact of the devices used to
4 5	66	administer medicines; use of alternative hedonic scales (e.g. those with 2-9 faces);
6 7	67	alternative anchor phrases; an endpoint of neutral and not positive within a hedonic scale;
8 9	68	further exploration of medicines that tasted OK as well as those with a reported negative
10 11	69	taste.
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71	Article Summary:		
72	What is already known about this subject?		
73	New medicines for children must be demonstrated to be acceptable to a paediatric		
74	population		
75	Measurement of acceptability of the taste of medicines is complex and a wide range of		
76	methods have been used previously, making comparison between studies complex.		
77	• There is a need for age-appropriate reproducible and reliable methods to measure the		
78	acceptability of medicines		
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80	What this study adds		
81	Patient reported outcome measures offer a pragmatic means to assess the taste of		
82	medicines		
83	5-point hedonic scales were better understood compared to visual analogue scales in		
84	children aged 2-16 years		
85	Although 41% of medicines were reported to have unacceptable taste only 5% were so bad		
86	that they could not be taken as intended		
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88			
89	Funding Statement		
90	This work was conducted as part of the SPaeDD-UK project (Smart Paediatric Drug Development –		
91	UK, a project co-funded by Innovate UK and the contributing companies of AstraZeneca, Bristol		
92	Myers Squibb, GlaxoSmithKline, Juniper Pharmaceuticals and Pfizer.		
93	(http://www.paediatricscienceuk.com).		
94	Competing interests: We have read and understood BMJ policy on declaration of interests and		
95	declare that we have no competing interests.		
96			

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2 3	97	Data sharing statement
4 5 6	98	Additional data is available in the Supplementary files. The full data set is held by the corresponding
7 8	99	author, please email with any requests for extra data.
9 10	100	
11 12	101	Authorship contributions
13 14	102	Punam Mistry contributed to the acquisition, analysis and interpretation of the data.
15 16	103	Heather Stirling contributed to the design, acquisition, analysis and interpretation of the data and
17 18	104	revising the manuscript following reviewers' comments.
19 20	105	Claire Callens contributed to the design of the study and acquisition of the data
21 22 22	106	James Hodson contributed to the design, statistical analysis and interpretation of the data and
23 24 25	107	revising the manuscript following reviewers' comments.
26 27	108	Hannah Batchelor contributed to the design, acquisition, analysis and interpretation of the data and
28 29	109	revising the manuscript following reviewers' comments. She is the corresponding author for this
30 31	110	work
32 33	111	work
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1. Introduction

Measurement of acceptability of paediatric medicines is important for two major reasons: (i) poor acceptability is likely to be associated with poor compliance and therefore suboptimal therapy; (ii) regulatory guidelines dictate that paediatric medicines' acceptability should be assessed (preferably in children) [1]. Patient acceptability has been defined as, "an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised)" [1]. A major barrier in the assessment of acceptability and subsequent interpretation of results is the lack of guidance on how an acceptability test should be conducted and the criteria used to determine acceptability in children [2]. It is unlikely that a single acceptability test will be valid for all medicines, due to the need to consider the benefit:risk balance on an individual basis.

Taste was previously identified as the biggest barrier in adherence and compliance in a paediatric population [3]. Previous techniques to evaluate acceptability focussed on taste and were based on methodology adapted from sensory analysis undertaken in the food industry. A variety of scales have been used to measure the acceptability of medicines, yet it remains unclear whether any of the scales is better for a particular purpose with regard to validity, reliability, feasibility, and preference [4, 5]. Patient reported measures of taste offer a pragmatic means to collect data on products. However, there is often concern about the reliability of these measures, particularly in a paediatric population [6]. Sensory analysis is commonly used to show a preference for one product over another, but this is not always relevant to medicines as often there is no alternative available. In addition, it can be rationalized that the therapeutic benefits of medicines outweigh the negative taste. It is complex to distinguish between acceptability and likeability of a medicine's taste, yet this difference may be critical for appropriate interpretation of resulting data.

137 The validity of any new method relies on how well it compares to other measures [7]. The 138 development of a reliable method to assess the taste of medicines requires comparison of a variety 139 of tools. This study compares a range of methods to assess the taste of medicines within a large

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140	paediatric inpatient population. Independent researcher observations are also compared to the self-
141	reported data. The results of this study will be used to propose a suitable method that can be used
142	for future taste assessments.
143	
144	2. Materials and Methods
145	Three patient-reported outcome (PRO) measures were compared to each other, and to researcher
146	observations of medicines administration in an observational mixed methods study. Bespoke PRO
147	tools were developed for this study based on previous methodologies and in consultation with the
148	National Institute for Health Research (NIHR) Children Specialty's Young Person's Advisory Group
149	(West Midlands) [8]. The young people (aged 11-18 years) reviewed the tools and provided feedback
150	that the tools were age-appropriate.
151	The hedonic scale selected was a genderless image where the mouth was the only expressive facial
152	feature (see Figure 1(a)). The images were yellow to ensure they stood out from the background
153	paper. They were obtained from S-cool the revision website (<u>http://www.s-cool.co.uk/gcse/food-</u>
154	technology/systems-and-control/revise-it/sensory-evaluation (accessed December 2015)). Children
155	and young people preferred simple faces and felt that this would be most appropriate for the
156	youngest age group [8]; anchor phrases were not included on the hedonic scale to keep this tool
157	basic. The visual analogue scale (VAS) included anchor phrases selected by the young persons'
158	group as the most clear and relevant [8], these were used at the extreme ends of the continuous
159	scale.
160	The direction of change was from positive to negative, which corresponds to the extensive data on
161	hedonic scales used for pain assessment in children [9]. Previous studies in adult studies of foods
162	showed no difference based on structural variations that read from positive to negative or vice versa
163	[10].
164	The third PRO was a question, 'Did you think the medicine tasted OK?' with the response options of:
165	yes, no, not sure.
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1 2		
3 4	166	
5 6	167	2.1. Participants and Setting
7 8 9	168	Paediatric inpatients aged between 2 to 16 years taking any oral liquid medicine as part of their
10 11	169	medical care were recruited from inpatient wards at 11 sites across the West Midlands. The study
12 13	170	was conducted between December 2015- April 2016. Ethical approval was granted by London Surrey
14 15	171	borders ethical committee (REC reference: 15/LO/1253; IRAS project ID: 179684).
16 17	172	Demographic information was obtained on participant's age and whether this was their first dose of
18 19	173	the medicine under evaluation. The medicine name; brand; manufacturer; concentration (strength);
20 21	174	dose administered and product batch number was recorded.
22 23 24	175	Each participant was observed by a researcher as they took their medicine. Some medicines were
24 25 26	176	provided to the patient as an oral liquid following extemporaneous preparation within the clinical
20 27 28	177	setting, for example, dispersion of prednisolone tablets immediately prior to dosing. Depending on
29 30	178	the capability of the child, the medicines were either self-administered, or administered by nursing
31 32	179	staff and/or parents. Participants were asked not to mix the medicine with any other food product,
33 34	180	as this might influence the participant's responses.
35 36	181	
37 38	182	2.2. Patient-reported outcome tools
39 40	183	Participants were asked to complete (a) 5-point facial hedonic scale and (b) 10cm VAS (Figure 1)
41 42	184	immediately after administration of their medicine; both scales were provided on separate paper
43 44 45	185	documents in a randomized order. Children were free to ask for support in completing the
46 47	186	questionnaires from parents, nursing staff or the researcher present. Both reporting documents
48 49	187	included a third PRO (Figure 1 (c)) as a question, 'Did you think the medicine tasted OK?' with the
50 51	188	response options of: yes, no, not sure. The purpose behind this question was to endorse the
52 53	189	reliability of the participant's reporting from both scale-based questionnaires.
54 55	190	Figure 1
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The data from the scales (a and b) were transformed into numbers for subsequent statistical
analysis. Hedonic expressions were converted to scores of 1 to 5 with 1 being the most positive
expression and 5 the most negative. VAS scores were reported as measurements from the extreme
left hand side of the scale in mm; this provided scores of 0-100 mm (although scale was written as 010 cm).

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198 2.3. Researcher Observations

199 A facial expression and behavioural scale to capture researcher observations was a 12-point tick 200 chart designed in-house (Figure 2), based on an existing scale used to measure behavioural distress 201 in children undergoing medical procedures [11], the Procedural Behavior Rating Scale (PBRS). The 202 PBRS was developed specifically for infants and children with cancer, who were undergoing bone 203 marrow aspirations or lumbar punctures. It contained 13 behavioural codes including: cry, cling, pain 204 verbal, flail, stall, scream, refuse position, restrain, emotional support, muscular rigidity and requests 205 termination [11]. The in-house tool was based on this scale plus other scales used to measure 206 behavioural distress in children [12]. The facial expressions included on the scale were derived from 207 previous studies that assessed food-liking in children based on their facial expressions; typically 208 negative tastes are associated with eyes squeezing, brow bulge, nose wrinkle and pursed lips [13].

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209 Figure 2

210

- 211 A series of nine short films or still pictures of children were made available to researchers
- 212 participating in the study to assess the inter-rater agreement in the facial expressions displayed.

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215 2.4. Statistical analysis

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2 3	216	A sample size was not fixed for this study at the outset as there was no appropriate power
4 5	217	calculation. Advice from a statistician was to ensure we had sufficient numbers (<50) paired data to
6 7	218	ensure that selectivity and sensitivity of the methods could be demonstrated.
8 9 10	219	Initially, the mean age of participants that were unable to understand the assessments were
10 11 12	220	compared to those who could using Mann-Whitney tests. The same approach was also used to
13 14	221	compare the scores for patients receiving their first dose, relative to those who had previously
15 16	222	received the medicine. Age was then divided into categories, and the proportions of participants
17 18	223	scoring in the extreme categories for the scales were compared using Fisher's exact tests.
19 20	224	Spearman's correlation coefficients were used to assess the degree of correlation between the
21 22	225	assessments for the cohort as a whole, and within each of the age categories. In this analysis, the
23 24	226	"Did you think the medicine tasted OK?" question was treated as an ordinal scale, with the response
25 26	227	of Don't Know being between Yes and No. Where responses were not recorded for all criteria, the
27 28 20	228	outcome was calculated based on those that were available
29 30 31	229	The assessments were then dichotomised, and compared using McNemar's tests to assess for
32 33	230	marginal homogeneity in the 2x2 tables, and Kappa to assess agreement. The three assessments
34 35	231	were then combined into a composite score, which was compared with reported behaviours using
36 37	232	Kendall's tau correlation coefficients. All analyses were performed using IBM SPSS 22 (IBM Corp.
38 39	233	Armonk, NY), and p<0.05 deemed to be indicative of statistical significance throughout.
40 41	234	
42 43	235	
44 45	236	3. Results and discussion
46 47 48	237	Data were available for 628 administrations to 611 children aged between 2-16 years. The median
49 50	238	participant age was 6 years. Further details on the distribution of the participant ages can be found
51 52	239	in supplementary material 1.
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To ease analysis of data, the population for this study was stratified by age into three groups: 2-4 years (n=237); 5-9 years (n=227) and 10-16 years (n=147). The medicine was administered as the first dose in 162 cases. There was no evidence of a significant

difference in the hedonic or VAS scores between those receiving their first dose of a medicine, compared to those who had previous administrations (p=0.336, 0.909 respectively). For all subsequent analysis the data was pooled for those receiving their first and subsequent doses of medicine.

3.1. Completeness of patient-reported assessment scales

The assessment scales were not completed by all of the study participants. The VAS had the lowest completion rate, where 46 (7%) were not completed due to lack of understanding by the child, compared to 15 (2%) for the hedonic scale. There were 7 (1%) cases where the child did not understand the question, "Did you think the medicine taste OK?". The range and mean age of those unable to complete the scales were 2-5 years with a mean of 2.4 years for the hedonic; 2-6 years with a mean of 3.1 years for the VAS and 2-3 years with a mean of 2.3 years for the taste question. In each case, participants unable understand the assessment methods were significantly younger than the remainder of the cohort (p<0.001 each assessment). The cognitive function of children was not assessed within this study and there was an assumption of cognitive normal for age for all participants.

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3.2. Distribution of responses to patient-reported assessment scales

In the patient reported scales (VAS and hedonic), the responses tended to be biased towards the extreme responses, with 56% of responses being in the highest or lowest categories for hedonic score (Figure 3a) and, 55% within 1cm from either end of the scale in the VAS (Figure 3b).

Fiaure 3

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The use of the extreme ends of the scales was greater in the younger populations (p<0.001) (data is shown in Supplementary material 2). For those that completed the hedonic scale, 64% of those aged 2-4 years used the extreme ends of the scale compared to 60% of those aged 5-9; 35% of those aged 10-16 years. A similar trend was observed in the VAS data where 66% of those aged 2-4 years were within 10mm of either end of the scale compared to 60% of 5-9 year olds and 39% of 10-16 year olds.

- **3.3.** Reliability of assessment, "Did you think the medicine tasted OK?"

The question, "Did you think the medicine tasted OK?" was asked to participants on two occasions for each medicine administration; once following the hedonic and once following the VAS (which were presented in a randomized order). In the 600 cases where participants responded to both questions, the same response was given in 569 (95%) of cases, giving a Kappa statistic of 0.91. In cases where the answers were not consistent, the median age of the respondents was 5 years (mean age = 6.3 years). For subsequent analysis, the two versions of this question were merged, with discrepancies resolved by taking the most positive response given by the participant.

- - **3.4.** Correlation between patient reported outcome measures

Significant correlations were observed between the hedonic scale score, VAS and "Did you think the medicines tasted OK?" question (all p<0.001 Table 1), with the strongest correlation observed between the hedonic and VAS scores (Spearman's rho=0.84). The weakest correlations were consistently observed in the youngest patients (age 2-4 years), implying that this group of patients had the lowest consistency in scores given across the different assessments. However, despite this,

- the consistency between the scores was still reasonable, with correlation coefficients ranging from
- 290 0.68- 0.77.

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The assessments were dichotomised, to identify those responses that classified a medicine as tasting acceptable. For the hedonic scale, this was defined as a neutral to positive response (the leftmost three faces of Figure 1a). For the "Did you think the medicine tasted OK?" question, grouping the "yes" and "not sure" responses was considered most appropriate, as the overall purpose is the assessment of acceptability of taste of a medicine; the response "no" is clearly aligned to an unacceptable taste, making other responses acceptable. The level of agreement between the resulting dichotomised scores was high (90%), with a Kappa statistic of 0.782, and no indication of bias (McNemar's test: p=0.519).

Correlation of the hedonic scale to the "tastes OK" question is simple; however interpretation of the VAS is more complex. The VAS had anchor phrases at either end to maintain the continuous scale, so it was not obvious where neutral or positive was ranked on the scale. Initially, an arbitrary cut-off of <50mm in the VAS was used to define acceptability, which gave reasonable agreement with both the dichotomised hedonic (88%) and "tastes OK" (86%) measures. However, McNemar's test indicted significant bias in both cases (p<0.001), with a tendency for the VAS score of 0-50mm to underestimate the number of tastes-acceptable responses, compared to the hedonic and "tastes OK" assessments. As a result, alternative VAS cut-offs were explored, with 0-70mm selected to approximately match the cut-off on the hedonic scale where the neutral face becomes the negative. Using 70mm rather than 50mm in the VAS marginally increased the agreement with both the dichotomised hedonic and "tastes OK" measures to 91% but, more importantly, eliminated the previously observed bias (McNemar's test p=1.000, 0.683 respectively). All subsequent analysis used the cut-off of >70mm as a measure of unacceptable taste.

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3.5. Associations with researcher observations and patient reported outcome measures

One patient did not have a record of facial expression/behaviours, hence they were excluded, and
 the analysis was based on n=620 cases. Associations between facial expressions and behaviours

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- 321 on those that were available. In total, 255/620 (41%) of assessments identified the taste of
- able. 322 medicines to be unacceptable. The associations between this outcome, and the various facial
- 323 expressions and behaviours that were recorded were then assessed.
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Table 2 shows the incidence of the facial expression or behaviour as a fraction of the total population. The behaviours are listed in order of Kendall's tau correlation coefficients, with those behaviours most strongly associated with unacceptable taste having the highest value of tau. Based on this metric, voicing disgust was the behaviour most strongly associated with negative taste. Of the 105 patients that voiced disgust, 95 (90%) reported the taste of the medicine to be negative. This rate was almost three-fold higher than the 160/515 (31%) who reported negative taste after not voicing disgust. Ordering the data in this way puts 'vomits' in last place, despite the fact that 100% of patients who vomited found the taste of their medicine to be unacceptable. Since so few children vomited (n=7), the proportion of the total number of children who identified the taste as unacceptable and also displayed this behaviour (i.e. the sensitivity) was low, at 3%. Hence, although a vomiting child is almost certain to find the taste unacceptable, using this behaviour in isolation as a predictor of negative taste would miss the vast majority of patients who reported taste to be negative

339 Inter-rater agreement assessed via the use of short films and images were mixed; prevalent

340 expressions were detected in >95% of cases, whereas some mild expressions were only detected in

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341 40-50% of those viewing the images.

3.6. Analysis of medicine-specific taste assessment

Fifty-seven different drugs were observed in this study and the six most commonly administered were paracetamol, ibuprofen, prednisolone, co-amoxiclav, amoxicillin and clarithromycin, which made up 76% (n=477) of the total data set.

Comparisons were made across the six most commonly prescribed drugs. Table 3 ranks these drugs in order of taste, and reports the means scores on the hedonic scale and VAS, as well as the proportion of patients answering "no" to the, "Did you think the medicine tasted OK?" question.

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350 The drugs can be divided into three groups based on this data: clarithromycin and prednisolone 351 were found to be the worst tasting; amoxicillin and co-amoxiclav were mid-range, and ibuprofen and 352 paracetamol were the best tasting medicines. The effect of brand was also investigated and the data 353 is presented in Supplementary material 3. 354 355 In addition to reports of taste, the proportion of children who refused, vomited or spat out the 356 medicines, was calculated and classified as unable to "use a medicinal product as intended". In total, 357 this occurred in 33/620 (5%) administrations, which are reported for the six most commonly used 358 drugs in Table 4. 359 360 Clarithromycin was the most commonly not taken as intended and was also the drug most 361 frequently identified as having unacceptable taste, based on the previously defined composite 362 outcome. However, there was insufficient data to suggest that the taste of the medicine was directly 363 related to the ability to take the medicine as intended. Children may vomit due to their underlying 364 illness rather than as a direct result of the taste of their medicine. 365 366 4. Discussion 367 Few studies have categorised acceptability of the taste of medicines. The results within this study 368 agree with previous reports, where a neutral to positive hedonic response indicates acceptable taste 369 [14-17]; Sjovall et al (1984) compared two brands of penicillin and reported that the acceptable taste 370 mean hedonic score was within the neutral to positive range and an unacceptable taste was in the 371 negative range [18]. Children were free to ask for support in completing the PRO measured and we 372 did not collect data on how many received help in this aspect; it would be of value to consider how 373 many, particularly in the youngest age group received support. 374

4.1. Interpretation of facial expressions and behaviours

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Voicing disgust was the behaviour most strongly associated with unacceptable taste whilst, perhaps counterintuitively, vomiting was the behaviour least strongly correlated with unacceptable taste. Despite the fact that 100% of patients who vomited found the taste of their medicine to be unacceptable, only a small number of patients vomited (n=7). As a result, whilst vomiting was a highly specific predictor of unacceptable taste, it had very low sensitivity. A similar pattern was also observed for the other facial expressions and behaviours, with sensitivity ranging from 10%-51%, and specificity from 84%-99%. This can be interpreted as indicating that, whilst it was uncommon to observe these facial expressions and behaviours in patients who found the taste of the medicine acceptable, displaying facial expressions and behaviours was not a strong indicator of unacceptability. The behaviours used to inform the researcher observations were not always clearly defined; for example the use of physical restraint was not explicitly stated and further work is required to better understand what physical restraint may be considered acceptable. The explicit definition of an acceptable medicine being "an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised)" (Kozarewicz, 2014), includes the patient/caregiver's ability to access the medicine and comply with packaging requirements and for this study to demonstrate that the medicine was swallowed without incident. In total, 33/620 (5%) of medicines were spat out or vomited, and therefore unacceptable within this in patient population. This demonstrates that, although some of the behaviour and expressions observed may link more strongly to a negative taste, they do not automatically mean that the medicine was unacceptable. In future studies, observations should ensure that the medicine was taken as intended; this may require a simple tool to ensure that the dose was completely swallowed without spitting out or vomiting. There is no need to include additional observations, as these were not strongly correlated to patient reported outcomes on the taste of medicines.

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4.2. Medicine-specific taste assessment

Our results correlate well with other reports in the literature on the taste of medicines. Both paracetamol and ibuprofen have previously been reported to demonstrate acceptable taste (mid-range in a 5 point hedonic scale) in paediatric populations [19, 20]. Co-amoxiclav and amoxicillin were reported to have acceptable taste to 57-67% of children within this study, which is consistent with previous literature, which has reported co-amoxiclav to be preferred to other antibiotics in terms of taste, including amoxicillin [21-27]. Previous work suggested that 60% of children accepted amoxicillin without problems and 63% of children liked the taste of co-amoxiclav [27]. Prednisolone and clarithromycin were the least liked medicines, again consistent with published data, with results showing predominantly negative scores in hedonic scales or the equivalent of >70mm in a VAS [28-30, 23, 31, 32, 3]. This study identified differences in acceptance of certain brands of medicines; however, there was insufficient sample numbers to undertake a detailed analysis of the impact of brand on taste and acceptance. A future study that explored brand preference would be of value to patients and those purchasing commonly used medicines.

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Using our criteria, the proportion of patients classifying taste as acceptable for the most liked of the frequently prescribed medicines (ibuprofen and paracetamol) was over 70%; the proportion classifying taste as acceptable for the least liked medicines (prednisolone and clarithromycin) was less than 30%. This study provides some standardised values for medicines used within a UK population, the thresholds reported here provide guidance for future medicines development where in addition to taste scores the overall risk-benefit of the medicine will need to be considered.

5. Conclusions

This study has generated data on the taste of medicines commonly used in paediatric populations aged 2-16 years. The results of this study suggest that patient reported outcome measures are a reliable and valid assessment of the taste of children's medicines, for children aged from 2-16 years.

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2 3 4	428	These assessment tools offer a mechanism to evaluate the taste of other medicines (either novel
5	429	products and formulations or medicines used orally in an off-label or unlicensed manner) to
7 8	430	generate comparative data on the taste of medicines.
9 10	431	The data from this study coupled with previous literature on the taste of medicines provides
11 12	432	evidence to suggest criteria to demonstrate acceptability of taste of medicines.
13 14	433	Our results suggest that criteria to demonstrate acceptability of taste are: a mean VAS score of
15 16	434	<70mm; a mean hedonic score of \leq 3 (neutral or positive face) and a non-negative response to the
17 18	435	"Tastes OK?" question. Pragmatically, there is no need to use all methods. As the hedonic scale was
19 20	436	understood across the widest age range, this should be the first choice method going forwards.
21 22	437	It would be prudent to ensure that any new product exceeds these scores to demonstrate that it is
23 24 25	438	likely to have acceptable taste in practice.
25 26 27	439	
28 29	440	
30 31	441	Acknowledgements
32 33	442	The authors would like to thank the NIHR Clinical Research Network: West Midlands - Young
34 35	443	Person's Steering Group (YPSG) for their input and advice in the development, conduct and
36 37	444	dissemination of this study.
38 39	445	All patients, families and researchers at the participating sites are acknowledged for their
40 41	446	participation in this study.
42 43	447	
44 45 46	448	
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49 50	449	Figure Legends
51	450	Figure 1. Scales used within PRO tools completed by paediatric participants immediately after
52	451	administration of their medicine. (a) Hedonic scale; (b) Anchored visual analogue scale (VAS); (c)
53	452	direct question on taste.
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55	454	Figure 2. Researcher observation sheet completed by the researcher prior to, during and post
56 57	455	medicine administration.
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Figure 3. Hedonic and VAS score distribution

459 Table headings

Table 1. Spearman's rho correlation values between patient-reported outcome measures.

	"Tastes OK" vs. Hedonic	"Tastes OK" vs. VAS	Hedonic vs. VAS
Overall	0.80	0.78	0.84
Age (Years)			
2-4	0.77	0.68	0.76
5-9	0.83	0.85	0.90
10-16	0.80	0.81	0.86

462 Table 2. Relationship between facial expression or a behaviour and a patient report of an 463 unacceptable tasting medicine 464

	Cases When	re Taste was			
	Reported as una	cceptable (n=255)			
Behaviour	Not Displayed	Displayed	Tau	Sens.	Spec.
Voices disgust	160/515 (31%)	95/105 (90%)	0.45	37%	97%
Eyes squeezed	131/460 (28%)	124/160 (78%)	0.44	49%	90%
Nose Wrinkle	125/433 (29%)	130/187 (70%)	0.38	51%	84%
Voices resistance	184/539 (34%)	71/81 (88%)	0.37	28%	97%
Refusal	192/551 (35%)	63/69 (91%)	0.36	25%	98%
Pursed Lips	168/505 (33%)	87/115 (76%)	0.33	34%	92%
Cries/Screams	201/559 (36%)	54/61 (89%)	0.32	21%	98%
Brow bulge	149/463 (32%)	106/157 (68%)	0.31	42%	86%
Physical restraint	219/579 (38%)	36/41 (88%)	0.25	14%	99%
Cries	216/573 (38%)	39/47 (83%)	0.24	15%	98%
Spits out	229/590 (39%)	26/30 (87%)	0.21	10%	99%
Vomits	248/613 (40%)	7/7 (100%)	0.13	3%	100%

467 Table 3. Patient reported taste scores by medicine

	Hee	donic Score	V	AS Score	Tastes OK?	Composite Outcome
		%	Mean	%		%
Drug	Mean	unacceptable	(mm)	unacceptable	(% "No")	unacceptable
Clarithromycin (n=26)	3.5	62%	70	58%	65%	77%
Prednisolone (n=86)	3.6	58%	68	54%	61%	70%
Amoxicillin (n=30)	2.7	37%	37	23%	33%	43%

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Co-Amoxiclav (n=50)	2.5	30%	39	24%	29%	33%
Paracetamol (n=193)	2.4	22%	37	21%	21%	29%
lbuprofen (n=92)	2.1	14%	27	12%	12%	20%

Table 4. Percentage unable to take medicine as intended

Medicine	% spat out/vomited the medicine	Composite Outcome % unacceptable
Clarithromycin (n= 26)	23%	77%
Amoxicillin (n=30)	13%	43%
Prednisolone (n= 86)	9%	70%
Co-amoxiclav (n= 50)	6%	33%
Ibuprofen (n= 92)	2%	20%
Paracetamol (n= 193)	1%	29%

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Figure 1. Scales used within PRO tools completed by paediatric participants immediately after administration of their medicine. (a) Hedonic scale; (b) Anchored visual analogue scale (VAS); (c) direct question on taste.

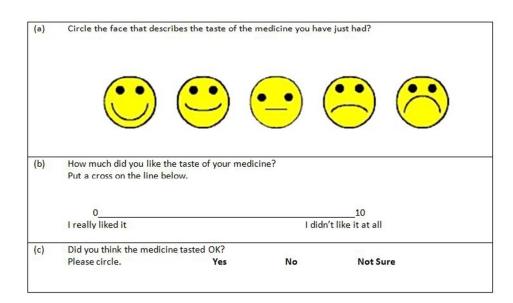


Figure 1. Scales used within PRO tools completed by paediatric participants immediately after administration of their medicine. (a) Hedonic scale; (b) Anchored visual analogue scale (VAS); (c) direct question on taste.

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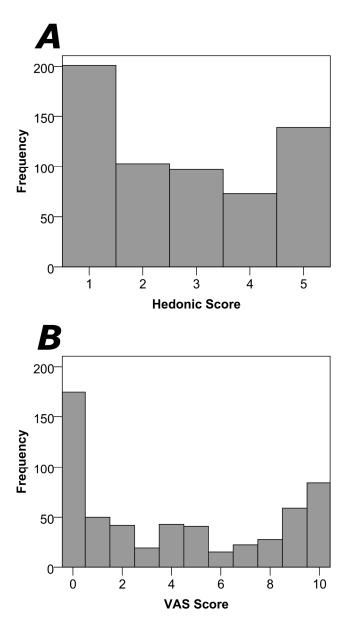
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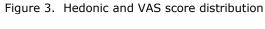
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Expression		Tick if observed prior to administration		Tick if observed during administration	
Eyes squeezed shut or towar	ds shut				
Brow bulge/lower (frown)					
Nose wrinkle					
Pursed lips					
Behaviours observed					
		if observed prior to ninistration	Tick if observed during administration		
Child refuses medicine	0				=unacceptable
Child cries/screams					=unacceptable
Child requires physical restraint					=unacceptable
Child voices resistance					=unacceptable
	imn	t if observed nediately after ninistration			
Child voices disgust					=unacceptable
Child vomits					=unacceptable
Child spits out medicine					=unacceptable
Child cries					=unacceptable

Figure 2. Researcher observation sheet completed by the researcher prior to, during and post medicine administration.

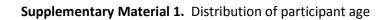
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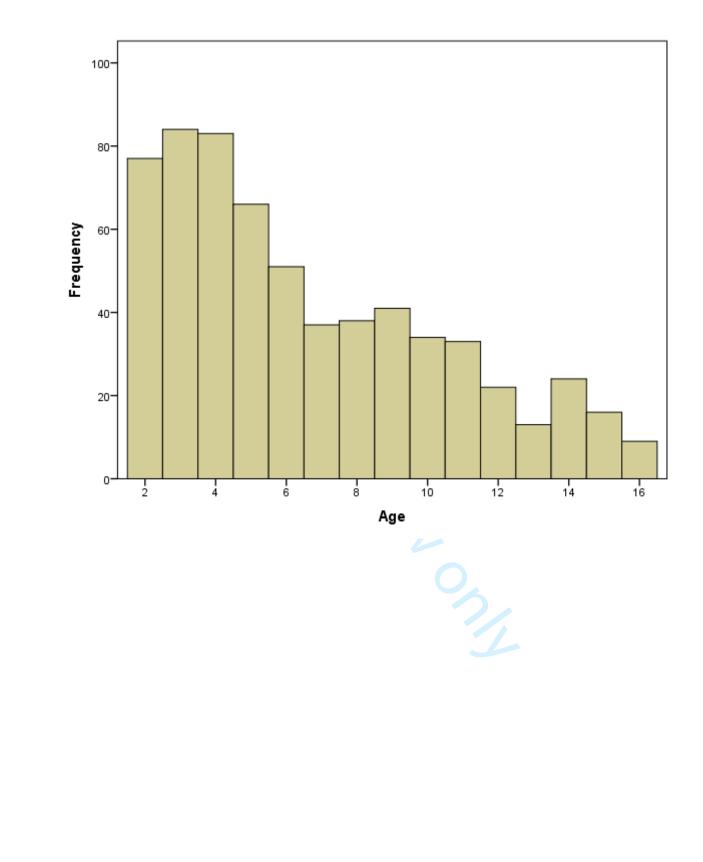


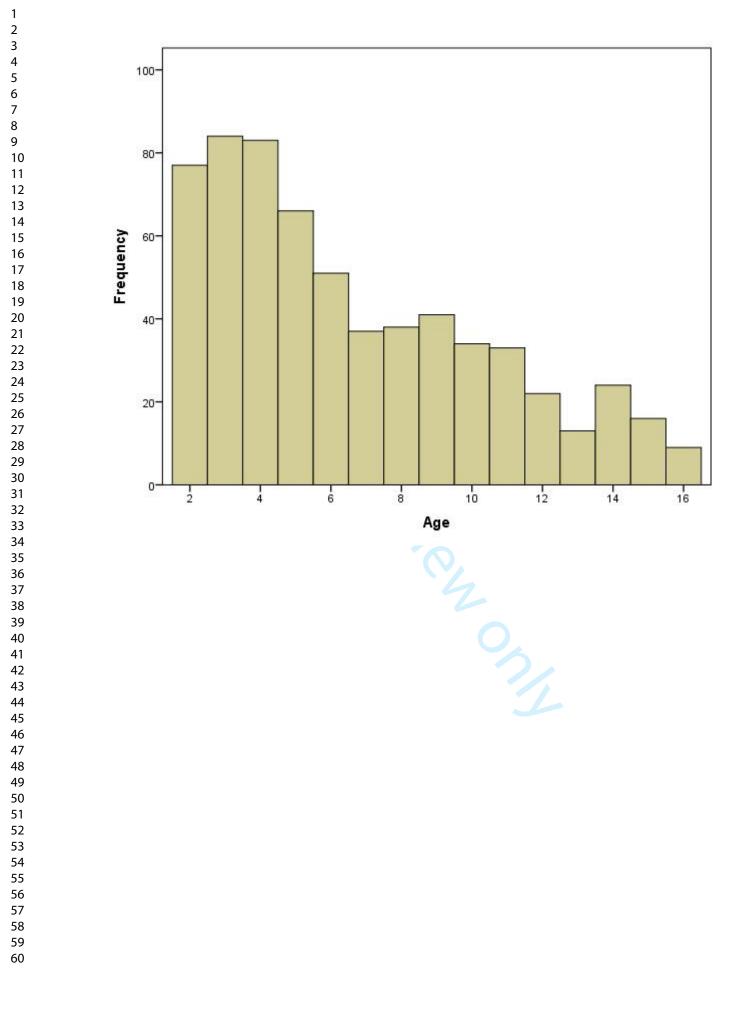


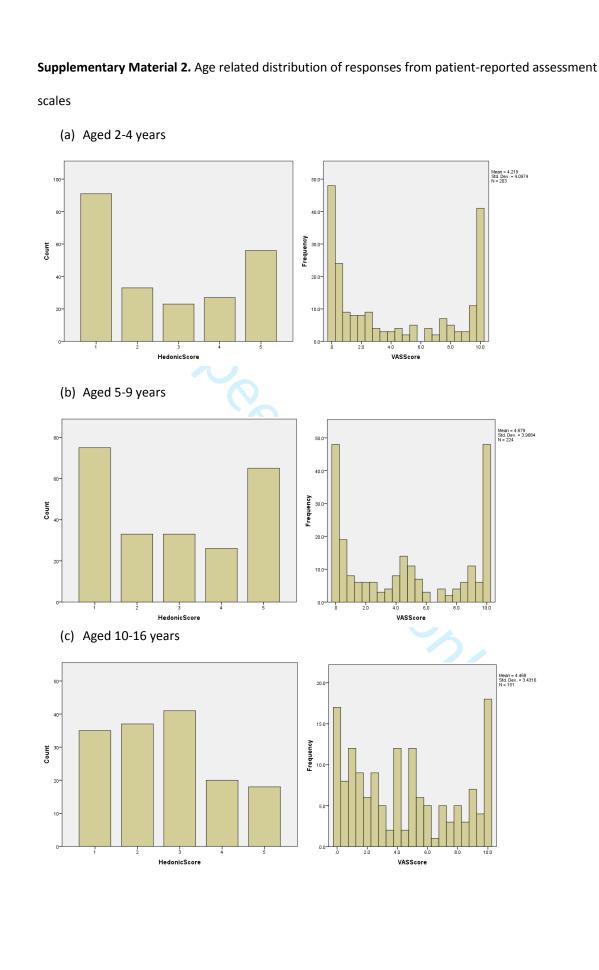
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Supplementary material 3. Table of taste scores for the six most commonly administered drugs by

brand

		Mean	Mean	Tastes
		Hedonic	VAS	ОК
Drug/Manufacturer	Ν	Score	Score	(% "No")
Amoxicillin			-	-
Athlone Laboratories	21	2.8	4.4	33%
Clamo	2	5.0	0.3	100%
Kent Pharmaceuticals	2	1.0	1.3	0%
Medreich PLC	1	3.0	10.0	100%
PL Holder	4	2.0	1.3	0%
Clarithromycin				
Abbott	11	3.7	7.4	82%
Klaricid	1	5.0	9.9	100%
MA Holder	1	2.0	4.2	0%
Sandoz Ltd.	13	3.4	6.7	54%
Co Amoxiclav				
Medreich PLC	1	3.0	5.0	0%
Rosemont Pharmaceutical Ltd	1	2.0	2.4	0%
Sandoz Ltd.	48	2.5	4.0	30%
Ibuprofen				
Fenpaed	9	2.1	3.4	22%
MA Holder	1	5.0	5.2	0%
McNeil Products	1	5.0	10.0	100%
Pinewood	78	2.0	2.5	10%
Reckitt Benckiser Healthcare	3	2.3	3.7	0%
Paracetamol				
Bristol Laboratories	1	3.0	4.0	100%
MA Holder	38	1.9	2.4	3%
McNeil Products	6	2.3	2.5	17%
Pinewood	113	2.6	4.3	28%
Rosemont Pharmaceutical Ltd	35	2.4	3.0	17%
Prednisolone				
Actavis	12	3.1	4.7	42%
Amdipharm	64	3.6	7.0	63%
Genetic SPA	1	3.0	5.2	0%
Teva UK Ltd	9	4.5	8.6	86%

This checklist was used and all items are provided within the manuscript: Evaluation of patient reported outcome measurements as a reliable tool to measure acceptability of the taste of paediatric medicines

	Item No	Recommendation	Appears in manuscript (line number)
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	34-35
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2 – Abstract
Introduction		6	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	115-123
Objectives	3	State specific objectives, including any prespecified hypotheses	139-142
Methods			
Study design	4	Present key elements of study design early in the paper	145-150
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up,	167-180
		and data collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants.	168-171
		Describe methods of follow-up	
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and	
		control selection. Give the rationale for the choice of cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed	n/a
		Case-control study-For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give	183-208
		diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	172-174; 183-208
measurement		Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	211-212
Study size	10	Explain how the study size was arrived at	216-218
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings	193-196; 219-232

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		were chosen and why	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for confounding	220-222; 215-232
		(b) Describe any methods used to examine subgroups and interactions	240-241
		(c) Explain how missing data were addressed	227-228
		() Colored at the 16 and include method have been to fully more and a damaged	222.224
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(<u>e</u>) Describe any sensitivity analyses	284-290
		(a) Conor study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	

Results			Appears in manuscript
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	250-259
		(b) Give reasons for non-participation at each stage	250-259
		(c) Consider use of a flow diagram	n/a
Descriptive 1 data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	237-239
		(b) Indicate number of participants with missing data for each variable of interest	250-259
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	250-259
		Case-control study-Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study-Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95%	261-364
		confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	301-313
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses	343-364
Discussion			
Key results	18	Summarise key results with reference to study objectives	366-422
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both	56-69
		direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results	425-438
		from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	433-438
Other informati	on		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	90-95

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 ** epidem.com/). Information on the STROBE Init.

 Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluation of patient reported outcome measurements as a reliable tool to measure acceptability of the taste of paediatric medicines

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Primary Subject Heading :	Paediatrics
Secondary Subject Heading:	Patient-centred medicine, Pharmacology and therapeutics
Keywords:	THERAPEUTICS, PAEDIATRICS, palatability, ORAL MEDICINE



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2	1	Evaluation of patient reported outcome measurements as a reliable tool to measure
3 4	1	Evaluation of patient reported outcome measurements as a reliable tool to measure
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10	4	Punam Mistry ¹ , Heather Stirling ² , Claire Callens ³ , James Hodson ⁴ and Hannah Batchelor ¹ on behalf of
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13	5	SPaeDD-UK project
14	-	
15	6	(Smart Paediatric Drug Development – UK, accelerating paediatric formulation development
16 17	7	http://www.paediatricscienceuk.com)
18	,	<u>Intep.//www.paeulatitescienceuk.com</u> /
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36 37	23	Connected the set the set of Detailed and a Colored of Discovery set to the set Officiary College
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31 Abstract

32 Objective: To evaluate the age-appropriateness and suitability of patient reported outcome
 33 measures to assess the acceptability of the taste of oral liquid medicines in children.

Design and setting: An observational mixed methods study involving children aged 2-16 years old taking oral liquid medicine in paediatric inpatient wards across the West Midlands (UK). Assessment tools included: patient-reported scores on the taste of medicines via a 5-point facial hedonic scale; a visual analogue scale (VAS); a question, "Did you think the medicine tasted OK?" and researcher observations of facial expressions and behaviours immediately before, during and after administration.

Results: 611 children participated. The percent unable to complete the scales were 7% (n=46) for the VAS; 2% (n=15) for the hedonic scale and 1% (n=7) for the question about taste. Significant correlations (Spearman's rho) were observed between the patient reported outcome measures: 0.80 and 0.78 for the taste question and hedonic and VAS respectively and 0.84 for the hedonic and VAS. Researcher observations demonstrated the ability of the patient to take the medicine as intended but did not provide sensitive measures of taste. 5% of administrations were not taken as intended by the children. Medicines known to have poor taste (clarithromycin and prednisolone) showed mean hedonic and VAS scores of \geq 3.5 and >65mm respectively.

48 Conclusions: Patient reported outcome measures correlate with each other and are a useful means
49 to assess the taste (and acceptability) of medicines. Hedonic scales are better understood by
50 children and should be the first choice tool in the assessment of medicines taste.

53 Key words: medicines, taste, acceptability, age-appropriate, hedonic scale, paediatric medicine,

- 54 patient-reported outcome measures, VAS

1		
2 3	57	Strengths and limitations of this study
4 5	58	• This is the first study to compare methodologies to assess the acceptability of taste of liquid
6 7	59	medicines in a large UK based paediatric population aged 2-16 years
8 9 10	60	• The sample size in this study provided large data sets of six key medicines, which provides a
11 12	61	representative comparison for newly developed products
13 14	62	• This study was conducted within an inpatient environment and the acceptance of taste of
15 16	63	medicines in a domiciliary environment may differ
17 18	64	The study design captured the most relevant aspects of acceptability of taste whilst
19 20	65	minimising the burden to participants, it was not possible to measure every aspect.
21 22 23	66	Suggestions for future research include measurement of: impact of the devices used to
23 24 25	67	administer medicines; use of alternative hedonic scales (e.g. those with 2-9 faces);
26 27	68	alternative anchor phrases; an endpoint of neutral and not positive within a hedonic scale;
28 29	69	further exploration of medicines that tasted OK as well as those with a reported negative
30 31	70	taste.
32 33	71	What is already known about this subject?
34 35	72	What is already known about this subject?
36 37	73	New medicines for children must be demonstrated to be acceptable to a paediatric
38 39 40	74	population
40 41 42	75	Measurement of acceptability of the taste of medicines is complex and a wide range of
43 44	76	methods have been used previously, making comparison between studies complex.
45 46	77	• There is a need for age-appropriate reproducible and reliable methods to measure the
47 48	78	acceptability of medicines
49 50	79	
51 52	80	What this study adds
53 54	81	Patient reported outcome measures offer a pragmatic means to assess the taste of
55 56 57	82	medicines in children aged from 2-16 years
58 59		3
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83	• 5-point hedonic scales were better understood compared to visual analogue scales in
84	children aged 2-16 years
85	• Although 41% of medicines were reported to have unacceptable taste only 5% were so bad
86	that they could not be taken as intended
87	
88	
89	Funding Statement
90	This work was conducted as part of the SPaeDD-UK project (Smart Paediatric Drug Development –
91	UK, a project co-funded by Innovate UK and the contributing companies of AstraZeneca, Bristol
92	Myers Squibb, GlaxoSmithKline, Juniper Pharmaceuticals and Pfizer.
93	(http://www.paediatricscienceuk.com).
94	Competing interests: We have read and understood BMJ policy on declaration of interests and
95	declare that we have no competing interests.
96	
97	Data sharing statement
98	Additional data is available in the Supplementary files. The full data set is held by the corresponding
99	author, please email with any requests for extra data.
100	
101	Authorship contributions
102	Punam Mistry contributed to the acquisition, analysis and interpretation of the data.
103	Heather Stirling contributed to the design, acquisition, analysis and interpretation of the data and
104	revising the manuscript following reviewers' comments.
105	Claire Callens contributed to the design of the study and acquisition of the data
106	James Hodson contributed to the design, statistical analysis and interpretation of the data and
107	revising the manuscript following reviewers' comments.

1 2		
2 3 4	108	Hannah Batchelor contributed to the design, acquisition, analysis and interpretation of the data and
5	109	revising the manuscript following reviewers' comments. She is the corresponding author for this
7 8	110	work
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1. Introduction

Measurement of acceptability of paediatric medicines is important for two major reasons: (i) poor acceptability is likely to be associated with poor compliance and therefore suboptimal therapy; (ii) regulatory guidelines dictate that paediatric medicines' acceptability should be assessed (preferably in children) [1]. Patient acceptability has been defined as, "an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised)" [1]. A major barrier in the assessment of acceptability and subsequent interpretation of results is the lack of guidance on how an acceptability test should be conducted and the criteria used to determine acceptability in children [2]. It is unlikely that a single acceptability test will be valid for all medicines, due to the need to consider the benefit:risk balance on an individual basis.

Taste was previously identified as the biggest barrier in adherence and compliance in a paediatric population [3]. Previous techniques to evaluate acceptability focussed on taste and were based on methodology adapted from sensory analysis undertaken in the food industry. A variety of scales have been used to measure the acceptability of medicines, yet it remains unclear whether any of the scales is better for a particular purpose with regard to validity, reliability, feasibility, and preference [4, 5]. Patient reported measures of taste offer a pragmatic means to collect data on products. However, there is often concern about the reliability of these measures, particularly in a paediatric population [6]. Sensory analysis is commonly used to show a preference for one product over another, but this is not always relevant to medicines as often there is no alternative available. In addition, it can be rationalized that the therapeutic benefits of medicines outweigh the negative taste. It is complex to distinguish between acceptability and likeability of a medicine's taste, yet this difference may be critical for appropriate interpretation of resulting data.

137 The validity of any new method relies on how well it compares to other measures [7]. The 138 development of a reliable method to assess the taste of medicines requires comparison of a variety 139 of tools. This study compares a range of methods to assess the taste of medicines within a large

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140	paediatric inpatient population. Independent researcher observations are also compared to the self-
141	reported data. The results of this study will be used to propose a suitable method that can be used
142	for future taste assessments.
143	
144	2. Materials and Methods
145	Three patient-reported outcome (PRO) measures were compared to each other, and to researcher
146	observations of medicines administration in an observational mixed methods study.
147	
148	2.1. Patient and Public Involvement
149	Bespoke PRO tools were developed for this study based on previous methodologies and in
150	consultation with the National Institute for Health Research (NIHR) Children Specialty's Young
151	Person's Advisory Group (West Midlands) [8]. The young people (aged 11-18 years) reviewed the
152	tools and provided feedback that the tools were age-appropriate. The same young people provided
153	feedback on the trial materials including information sheets and how to minimise the burden to
154	participants during the conduct of the study. The results are available to participants as a poster
155	summary from the corresponding author's personal webpage (www.hannahbatchelor.com); this
156	poster was also reviewed by the young person's group.
157	
158	2.2. Patient reported outcome measures used
159	The hedonic scale selected was a genderless image where the mouth was the only expressive facial
160	feature (see Figure 1(a)). The images were yellow to ensure they stood out from the background
161	paper. They were obtained from S-cool the revision website (http://www.s-cool.co.uk/gcse/food-
162	technology/systems-and-control/revise-it/sensory-evaluation (accessed December 2015)). Children
163	and young people preferred simple faces and felt that this would be most appropriate for the
164	youngest age group [8]; anchor phrases were not included on the hedonic scale to keep this tool
165	basic. The visual analogue scale (VAS) included anchor phrases selected by the young persons'

1

3	166	group as the most clear and relevant [8], these were used at the extreme ends of the continuous
4 5	167	scale.
6 7 8	168	The direction of change was from positive to negative, which corresponds to the extensive data on
9 10	169	hedonic scales used for pain assessment in children [9]. Previous studies in adult studies of foods
11 12	170	showed no difference based on structural variations that read from positive to negative or vice versa
13 14	171	[10].
15 16	172	The third PRO was a question, 'Did you think the medicine tasted OK?' with the response options of:
17 18	173	yes, no, not sure.
19 20	174	
21 22	175	2.3. Participants and Setting
23		
24 25	176	Paediatric inpatients aged between 2 to 16 years taking any oral liquid medicine as part of their
26 27	177	medical care were recruited using convenience sampling, from inpatient wards at 11 sites across the
28 29 30	178	West Midlands. The study was conducted between December 2015- April 2016. Ethical approval was
31 32	179	granted by London Surrey borders ethical committee (REC reference: 15/LO/1253; IRAS project ID:
33 34	180	179684).
35 36	181	Demographic information was obtained on participant's age and whether this was their first dose of
37 38	182	the medicine under evaluation. The medicine name; brand; manufacturer; concentration (strength);
39 40	183	dose administered and product batch number was recorded.
41 42	184	Each participant was observed by a researcher as they took their medicine. Some medicines were
43 44	185	provided to the patient as an oral liquid following extemporaneous preparation within the clinical
45 46	186	setting, for example, dispersion of prednisolone tablets immediately prior to dosing. Depending on
47 48	187	the capability of the child, the medicines were either self-administered, or administered by nursing
49 50 51	188	staff and/or parents. Participants were asked not to mix the medicine with any other food product,
52 53	189	as this might influence the participant's responses.
54 55	190	
56 57	191	2.4. Patient-reported outcome tools
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192 Participants were asked to complete (a) 5-point facial hedonic scale and (b) 10cm VAS (Figure 1) 193 immediately after administration of their medicine; both scales were provided on separate paper 194 documents in a randomized order. Children were free to ask for support in completing the 195 questionnaires from parents, nursing staff or the researcher present. The cognitive function of 196 children was not assessed and age may not always predict a child's ability to complete the 197 questionnaire, therefore all children were free to ask for support if requried. Both reporting 198 documents included a third PRO (Figure 1 (c)) as a question, 'Did you think the medicine tasted OK?' 199 with the response options of: yes, no, not sure. The purpose behind this question was to endorse the 200 reliability of the participant's reporting from both scale-based questionnaires. 201 Figure 1 202 203 The data from the scales (a and b) were transformed into numbers for subsequent statistical 204 analysis. Hedonic expressions were converted to scores of 1 to 5 with 1 being the most positive 205 expression and 5 the most negative. VAS scores were reported as measurements from the extreme 206 left hand side of the scale in mm; this provided scores of 0-100 mm (although scale was written as 0-207 10 cm). 208 209 2.5. Researcher Observations 210 A facial expression and behavioural scale to capture researcher observations was a 12-point tick 211 chart designed in-house (Figure 2), based on an existing scale used to measure behavioural distress 212 in children undergoing medical procedures [11], the Procedural Behavior Rating Scale (PBRS). The 213 PBRS was developed specifically for infants and children with cancer, who were undergoing bone 214 marrow aspirations or lumbar punctures. It contained 13 behavioural codes including: cry, cling, pain 215 verbal, flail, stall, scream, refuse position, restrain, emotional support, muscular rigidity and requests 216 termination [11]. The in-house tool was based on this scale plus other scales used to measure 217 behavioural distress in children [12]. The facial expressions included on the scale were derived from

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previous studies that assessed food-liking in children based on their facial expressions; typically negative tastes are associated with eyes squeezing, brow bulge, nose wrinkle and pursed lips [13]. Figure 2 A series of nine short films or still pictures of children were made available to researchers participating in the study to assess the inter-rater agreement in the facial expressions displayed. 2.6. Statistical analysis A sample size was not fixed for this study at the outset as there was no appropriate power calculation. Advice from a statistician was to ensure we had sufficient numbers (<50) paired data to ensure that selectivity and sensitivity of the methods could be demonstrated. Initially, the mean age of participants that were unable to understand the assessments were compared to those who could using Mann-Whitney tests. The same approach was also used to compare the scores for patients receiving their first dose, relative to those who had previously received the medicine. Age was then divided into categories, and the proportions of participants scoring in the extreme categories for the scales were compared using Fisher's exact tests. Spearman's correlation coefficients were used to assess the degree of correlation between the assessments for the cohort as a whole, and within each of the age categories. In this analysis, the "Did you think the medicine tasted OK?" question was treated as an ordinal scale, with the response of Don't Know being between Yes and No. Where responses were not recorded for all criteria, the outcome was calculated based on those that were available The assessments were then dichotomised, and compared using McNemar's tests to assess for marginal homogeneity in the 2x2 tables, and Kappa to assess agreement. The three assessments were then combined into a composite score, which was compared with reported behaviours using

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2 3	243	Kendall's tau correlation coefficients. All analyses were performed using IBM SPSS 22 (IBM Corp.
4 5	244	Armonk, NY), and p<0.05 deemed to be indicative of statistical significance throughout.
6 7	245	
8		
9 10	246	
11 12	247	3. Results and discussion
13 14	248	Data were available for 628 administrations to 611 children aged between 2-16 years. The median
15 16	249	participant age was 6 years. Further details on the distribution of the participant ages can be found
17 18	250	in supplementary material 1.
19 20	251	
21 22	252	To ease analysis of data, the population for this study was stratified by age into three groups: 2-4
23 24 25	253	years (n=237); 5-9 years (n=227) and 10-16 years (n=147).
25 26 27	254	The medicine was administered as the first dose in 162 cases. There was no evidence of a significant
28 29	255	difference in the hedonic or VAS scores between those receiving their first dose of a medicine,
30 31	256	compared to those who had previous administrations (p=0.336, 0.909 respectively). For all
32 33	257	subsequent analysis the data was pooled for those receiving their first and subsequent doses of
34 35	258	medicine.
36 37	259	
38 39	260	3.1. Completeness of patient-reported assessment scales
40 41	261	The assessment scales were not completed by all of the study participants. The VAS had the lowest
42 43	262	completion rate, where 46 (7%) were not completed due to lack of understanding by the child,
44 45	263	compared to 15 (2%) for the hedonic scale. There were 7 (1%) cases where the child did not
46 47	264	understand the question, "Did you think the medicine taste OK?". The range and mean age of those
48 49 50	265	unable to complete the scales were 2-5 years with a mean of 2.4 years for the hedonic; 2-6 years
50 51 52	266	with a mean of 3.1 years for the VAS and 2-3 years with a mean of 2.3 years for the taste question. In
53 54	267	each case, participants unable understand the assessment methods were significantly younger than
55 56	268	the remainder of the cohort (p<0.001 each assessment). The cognitive function of children was not
57 58		11

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assessed within this study and there was an assumption of cognitive normal for age for all participants. 3.2. Distribution of responses to patient-reported assessment scales In the patient reported scales (VAS and hedonic), the responses tended to be biased towards the

extreme responses, with 56% of responses being in the highest or lowest categories for hedonic score (Figure 3a) and, 55% within 1cm from either end of the scale in the VAS (Figure 3b).

Figure 3

The use of the extreme ends of the scales was greater in the younger populations (p<0.001) (data is shown in Supplementary material 2). For those that completed the hedonic scale, 64% of those aged 2-4 years used the extreme ends of the scale compared to 60% of those aged 5-9; 35% of those aged 10-16 years. A similar trend was observed in the VAS data where 66% of those aged 2-4 years were within 10mm of either end of the scale compared to 60% of 5-9 year olds and 39% of 10-16 year olds.

3.3. Reliability of assessment, "Did you think the medicine tasted OK?"

3.4. Correlation between patient reported outcome measures

The question, "Did you think the medicine tasted OK?" was asked to participants on two occasions for each medicine administration; once following the hedonic and once following the VAS (which were presented in a randomized order). In the 600 cases where participants responded to both questions, the same response was given in 569 (95%) of cases, giving a Kappa statistic of 0.91. In cases where the answers were not consistent, the median age of the respondents was 5 years (mean age = 6.3 years). For subsequent analysis, the two versions of this question were merged, with discrepancies resolved by taking the most positive response given by the participant.

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Significant correlations were observed between the hedonic scale score, VAS and "Did you think the
medicines tasted OK?" question (all p<0.001 Table 1), with the strongest correlation observed
between the hedonic and VAS scores (Spearman's rho=0.84). The weakest correlations were
consistently observed in the youngest patients (age 2-4 years), implying that this group of patients
had the lowest consistency in scores given across the different assessments. However, despite this,
the consistency between the scores was still reasonable, with correlation coefficients ranging from
0.68- 0.77.

The assessments were dichotomised, to identify those responses that classified a medicine as tasting acceptable. For the hedonic scale, this was defined as a neutral to positive response (the leftmost three faces of Figure 1a). For the "Did you think the medicine tasted OK?" question, grouping the "yes" and "not sure" responses was considered most appropriate, as the overall purpose is the assessment of acceptability of taste of a medicine; the response "no" is clearly aligned to an unacceptable taste, making other responses acceptable. The level of agreement between the resulting dichotomised scores was high (90%), with a Kappa statistic of 0.782, and no indication of bias (McNemar's test: p=0.519).

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Correlation of the hedonic scale to the "tastes OK" question is simple; however interpretation of the VAS is more complex. The VAS had anchor phrases at either end to maintain the continuous scale, so it was not obvious where neutral or positive was ranked on the scale. Initially, an arbitrary cut-off of <50mm in the VAS was used to define acceptability, which gave reasonable agreement with both the dichotomised hedonic (88%) and "tastes OK" (86%) measures. However, McNemar's test indicted significant bias in both cases (p<0.001), with a tendency for the VAS score of 0-50mm to underestimate the number of tastes-acceptable responses, compared to the hedonic and "tastes OK" assessments. As a result, alternative VAS cut-offs were explored, with 0-70mm selected to approximately match the cut-off on the hedonic scale where the neutral face becomes the negative.

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Using 70mm rather than 50mm in the VAS marginally increased the agreement with both the dichotomised hedonic and "tastes OK" measures to 91% but, more importantly, eliminated the previously observed bias (McNemar's test p=1.000, 0.683 respectively). All subsequent analysis used the cut-off of >70mm as a measure of unacceptable taste.

3.5. Associations with researcher observations and patient reported outcome measures

327 One patient did not have a record of facial expression/behaviours, hence they were excluded, and

328 the analysis was based on n=620 cases. Associations between facial expressions and behaviours

329 (listed in Figure 2) were linked to cases where the medicines were reported to have an unacceptable

330 taste, based on a composite outcome (Table 2). This was defined using the criteria defined

331 previously. Where responses were not recorded for all criteria, the outcome was calculated based

332 on those that were available. In total, 255/620 (41%) of assessments identified the taste of

333 medicines to be unacceptable. The associations between this outcome, and the various facial

334 expressions and behaviours that were recorded were then assessed.

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Table 2 shows the incidence of the facial expression or behaviour as a fraction of the total population. The behaviours are listed in order of Kendall's tau correlation coefficients, with those behaviours most strongly associated with unacceptable taste having the highest value of tau. Based on this metric, voicing disgust was the behaviour most strongly associated with negative taste. Of the 105 patients that voiced disgust, 95 (90%) reported the taste of the medicine to be negative. This rate was almost three-fold higher than the 160/515 (31%) who reported negative taste after not voicing disgust. Ordering the data in this way puts 'vomits' in last place, despite the fact that 100% of patients who vomited found the taste of their medicine to be unacceptable. Since so few children vomited (n=7), the proportion of the total number of children who identified the taste as unacceptable and also displayed this behaviour (i.e. the sensitivity) was low, at 3%. Hence, although a vomiting child is almost certain to find the taste unacceptable, using this behaviour in isolation as a predictor of negative taste would miss the vast majority of patients who reported taste to be negative Inter-rater agreement assessed via the use of short films and images were mixed; prevalent

351 expressions were detected in >95% of cases, whereas some mild expressions were only detected in

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352 40-50% of those viewing the images.

3.6. Analysis of medicine-specific taste assessment

Fifty-seven different drugs were observed in this study and the six most commonly administered were paracetamol, ibuprofen, prednisolone, co-amoxiclav, amoxicillin and clarithromycin, which made up 76% (n=477) of the total data set.

358 Comparisons were made across the six most commonly prescribed drugs. Table 3 ranks these drugs 359 in order of taste, and reports the means scores on the hedonic scale and VAS, as well as the 360 proportion of patients answering "no" to the, "Did you think the medicine tasted OK?" question.

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The drugs can be divided into three groups based on this data: clarithromycin and prednisolone were found to be the worst tasting; amoxicillin and co-amoxiclav were mid-range, and ibuprofen and paracetamol were the best tasting medicines. The effect of brand was also investigated and the data is presented in Supplementary material 3. In addition to reports of taste, the proportion of children who refused, vomited or spat out the medicines, was calculated and classified as unable to "use a medicinal product as intended". In total, this occurred in 33/620 (5%) administrations, which are reported for the six most commonly used drugs in Table 4. Clarithromycin was the most commonly not taken as intended and was also the drug most frequently identified as having unacceptable taste, based on the previously defined composite outcome. However, there was insufficient data to suggest that the taste of the medicine was directly related to the ability to take the medicine as intended. Children may vomit due to their underlying illness rather than as a direct result of the taste of their medicine. 4. Discussion Few studies have categorised acceptability of the taste of medicines. The results within this study agree with previous reports, where a neutral to positive hedonic response indicates acceptable taste [14-17]; Sjovall et al (1984) compared two brands of penicillin and reported that the acceptable taste mean hedonic score was within the neutral to positive range and an unacceptable taste was in the negative range [18]. Children were free to ask for support in completing the PRO measured and we did not collect data on how many received help in this aspect; it would be of value to consider how many, particularly in the youngest age group received support. Many of the children aged 2-5 years were able to provide reliable data on the taste of medicines demonstrating that the scales and questions used within this study are suitable for very young participants.

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2	387	
3 4	387	
5 6	388	4.1. Interpretation of facial expressions and behaviours
7 8	389	Voicing disgust was the behaviour most strongly associated with unacceptable taste whilst, perhaps
9 10	390	counterintuitively, vomiting was the behaviour least strongly correlated with unacceptable taste.
11 12	391	Despite the fact that 100% of patients who vomited found the taste of their medicine to be
13 14	392	unacceptable, only a small number of patients vomited (n=7). As a result, whilst vomiting was a
15 16	393	highly specific predictor of unacceptable taste, it had very low sensitivity. A similar pattern was also
17 18	394	observed for the other facial expressions and behaviours, with sensitivity ranging from 10%-51%,
19 20	395	and specificity from 84%-99%. This can be interpreted as indicating that, whilst it was uncommon to
21 22	396	observe these facial expressions and behaviours in patients who found the taste of the medicine
23 24	397	acceptable, displaying facial expressions and behaviours was not a strong indicator of
25 26 27	398	unacceptability.
27 28 29	399	The behaviours used to inform the researcher observations were not always clearly defined; for
30 31	400	example the use of physical restraint was not explicitly stated and further work is required to better
32 33	401	understand what physical restraint may be considered acceptable.
34 35	402	The explicit definition of an acceptable medicine being "an overall ability of the patient and caregiver
36 37	403	(defined as 'user') to use a medicinal product as intended (or authorised)" (Kozarewicz, 2014),
38 39	404	includes the patient/caregiver's ability to access the medicine and comply with packaging
40 41	405	requirements and for this study to demonstrate that the medicine was swallowed without incident.
42 43	406	In total, 33/620 (5%) of medicines were spat out or vomited, and therefore unacceptable within this
44 45 46	407	in patient population. This demonstrates that, although some of the behaviour and expressions
40 47 48	408	observed may link more strongly to a negative taste, they do not automatically mean that the
49 50	409	medicine was unacceptable.
51 52	410	In future studies, observations should ensure that the medicine was taken as intended; this may
53 54	411	require a simple tool to ensure that the dose was completely swallowed without spitting out or
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vomiting. There is no need to include additional observations, as these were not strongly correlatedto patient reported outcomes on the taste of medicines.

4.2. Medicine-specific taste assessment

Our results correlate well with other reports in the literature on the taste of medicines. Both paracetamol and ibuprofen have previously been reported to demonstrate acceptable taste (mid-range in a 5 point hedonic scale) in paediatric populations [19, 20]. Co-amoxiclav and amoxicillin were reported to have acceptable taste to 57-67% of children within this study, which is consistent with previous literature, which has reported co-amoxiclav to be preferred to other antibiotics in terms of taste, including amoxicillin [21-27]. Previous work suggested that 60% of children accepted amoxicillin without problems and 63% of children liked the taste of co-amoxiclav [27]. Prednisolone and clarithromycin were the least liked medicines, again consistent with published data, with results showing predominantly negative scores in hedonic scales or the equivalent of >70mm in a VAS [28-30, 23, 31, 32, 3]. This study identified differences in acceptance of certain brands of medicines; however, there was insufficient sample numbers to undertake a detailed analysis of the impact of brand on taste and acceptance. A future study that explored brand preference would be of value to patients and those purchasing commonly used medicines.

Using our criteria, the proportion of patients classifying taste as acceptable for the most liked of the frequently prescribed medicines (ibuprofen and paracetamol) was over 70%; the proportion classifying taste as acceptable for the least liked medicines (prednisolone and clarithromycin) was less than 30%. This study provides some standardised values for medicines used within a UK population, the thresholds reported here provide guidance for future medicines development where in addition to taste scores the overall risk-benefit of the medicine will need to be considered.

4.3. Recommended tools to assess acceptability

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This study has correlated three simple patient reported measures of medicines taste acceptability. It has also provided comparative data from existing medicines. Regulations mandate that all new medicines need to be demonstrated to be acceptable to children [1]. This study provides pragmatic and reliable tools to conduct this assessment. Furthermore, comparison of the results from a new medicine using these tools can be directly compared to existing medicines to support evidence of acceptance.

- 444
- 445 5. Conclusions

This study has generated data on the taste of medicines commonly used in paediatric populations aged 2-16 years. The results of this study suggest that patient reported outcome measures are a reliable and valid assessment of the taste of children's medicines, for children aged from 2-16 years. These assessment tools offer a mechanism to evaluate the taste of other medicines (either novel products and formulations or medicines used orally in an off-label or unlicensed manner) to generate comparative data on the taste of medicines.

- 452 The data from this study coupled with previous literature on the taste of medicines provides
- 453 evidence to suggest criteria to demonstrate acceptability of taste of medicines.

454 Our results suggest that criteria to demonstrate acceptability of taste are: a mean VAS score of
455 <70mm; a mean hedonic score of ≤3 (neutral or positive face) and a non-negative response to the

456 "Tastes OK?" question. Pragmatically, there is no need to use all methods. As the hedonic scale was

- 457 understood across the widest age range, this should be the first choice method going forwards.
- 458 It would be prudent to ensure that any new product exceeds these scores to demonstrate that it is
- 459 likely to have acceptable taste in practice.
- 460
- 461

462 Acknowledgements

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470 Figure Legends

471 Figure 1. Scales used within PRO tools completed by paediatric participants immediately after
472 administration of their medicine. (a) Hedonic scale; (b) Anchored visual analogue scale (VAS); (c)
473 direct question on taste.
474

475 Figure 2. Researcher observation sheet completed by the researcher prior to, during and post476 medicine administration.

- **Figure 3.** Hedonic and VAS score distribution

480 Table headings

Table 1. Spearman's rho correlation values between patient-reported outcome measures.

	"Tastes OK" vs. Hedonic	"Tastes OK" vs. VAS	Hedonic vs. VAS	
Overall	0.80	0.78	0.84	
Age (Years)				
2-4	0.77	0.68	0.76	
5-9	0.83	0.85	0.90	
10-16	0.80	0.81	0.86	

Table 2. Relationship between facial expression or a behaviour and a patient report of anunacceptable tasting medicine

	Cases Wher	Cases Where Taste was					
	Reported as unac	Reported as unacceptable (n=255)					
Behaviour	Not Displayed	Not Displayed Displayed					
Voices disgust	160/515 (31%)	160/515 (31%) 95/105 (90%)					

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Eyes squeezed	131/460 (28%)	124/160 (78%)	0.44	49%	90%
Nose Wrinkle	125/433 (29%)	130/187 (70%)	0.38	51%	84%
Voices resistance	184/539 (34%)	71/81 (88%)	0.37	28%	97%
Refusal	192/551 (35%)	63/69 (91%)	0.36	25%	98%
Pursed Lips	168/505 (33%)	87/115 (76%)	0.33	34%	92%
Cries/Screams	201/559 (36%)	54/61 (89%)	0.32	21%	98%
Brow bulge	149/463 (32%)	106/157 (68%)	0.31	42%	86%
Physical restraint	219/579 (38%)	36/41 (88%)	0.25	14%	99%
Cries	216/573 (38%)	39/47 (83%)	0.24	15%	98%
Spits out	229/590 (39%)	26/30 (87%)	0.21	10%	99%
Vomits	248/613 (40%)	7/7 (100%)	0.13	3%	100%

488 Table 3. Patient reported taste scores by medicine

	Hedonic Score		VAS Score		Tastes OK?	Composite Outcome
Drug	Mean	% unacceptable	Mean (mm)	% unacceptable	(% "No")	% unacceptable
Clarithromycin (n=26)	3.5	62%	70	58%	65%	77%
Prednisolone (n=86)	3.6	58%	68	54%	61%	70%
Amoxicillin (n=30)	2.7	37%	37	23%	33%	43%
Co-Amoxiclav (n=50)	2.5	30%	39	24%	29%	33%
Paracetamol (n=193)	2.4	22%	37	21%	21%	29%
lbuprofen (n=92)	2.1	14%	27	12%	12%	20%

Table 4. Percentage unable to take medicine as intended

Medicine	% spat out/vomited the medicine	Composite Outcome % unacceptable
Clarithromycin (n= 26)	23%	77%
Amoxicillin (n=30)	13%	43%
Prednisolone (n= 86)	9%	70%
Co-amoxiclav (n= 50)	6%	33%
lbuprofen (n= 92)	2%	20%
Paracetamol (n= 193)	1%	29%

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Figure 1. Scales used within PRO tools completed by paediatric participants immediately after administration of their medicine. (a) Hedonic scale; (b) Anchored visual analogue scale (VAS); (c) direct question on taste.

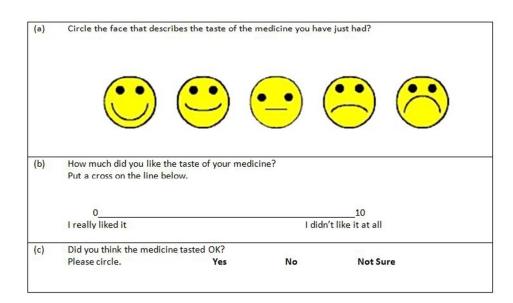


Figure 1. Scales used within PRO tools completed by paediatric participants immediately after administration of their medicine. (a) Hedonic scale; (b) Anchored visual analogue scale (VAS); (c) direct question on taste.

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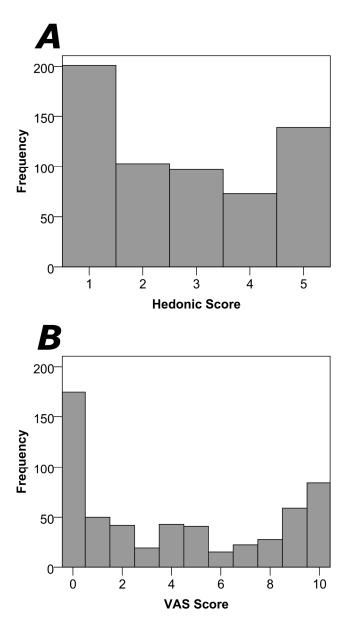
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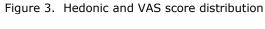
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Expression		Tick if observed prio administration		Tick if observed during administration	
Eyes squeezed shut or towar	ds shut				
Brow bulge/lower (frown)					
Nose wrinkle					
Pursed lips					
Behaviours observed					
Behaviour		if observed prior to ninistration	Tick if observed during administr	ation	
Child refuses medicine					=unacceptable
Child cries/screams					=unacceptable
Child requires physical restraint					=unacceptable
Child voices resistance					=unacceptable
	imn	c if observed nediately after ninistration			
Child voices disgust					=unacceptable
Child vomits					=unacceptable
Child spits out medicine					=unacceptable
Child cries					=unacceptable

Figure 2. Researcher observation sheet completed by the researcher prior to, during and post medicine administration.

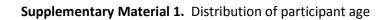
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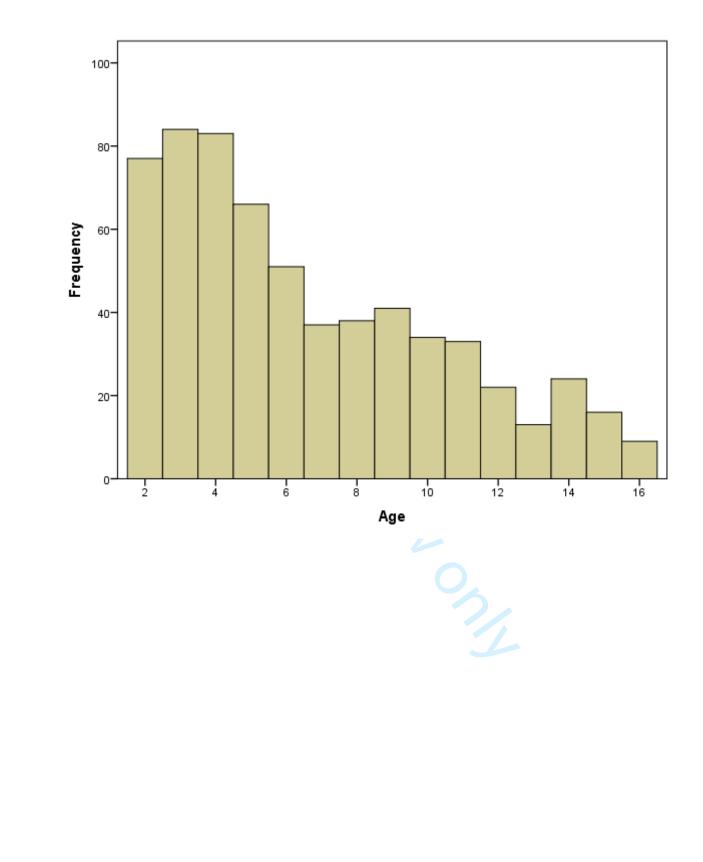


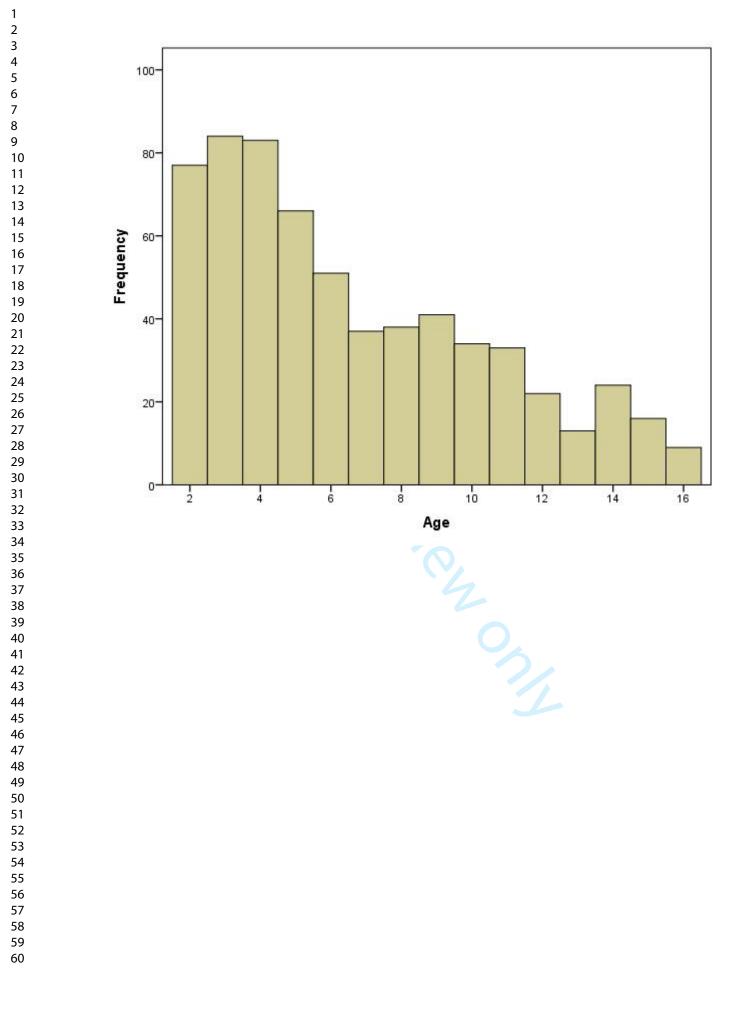


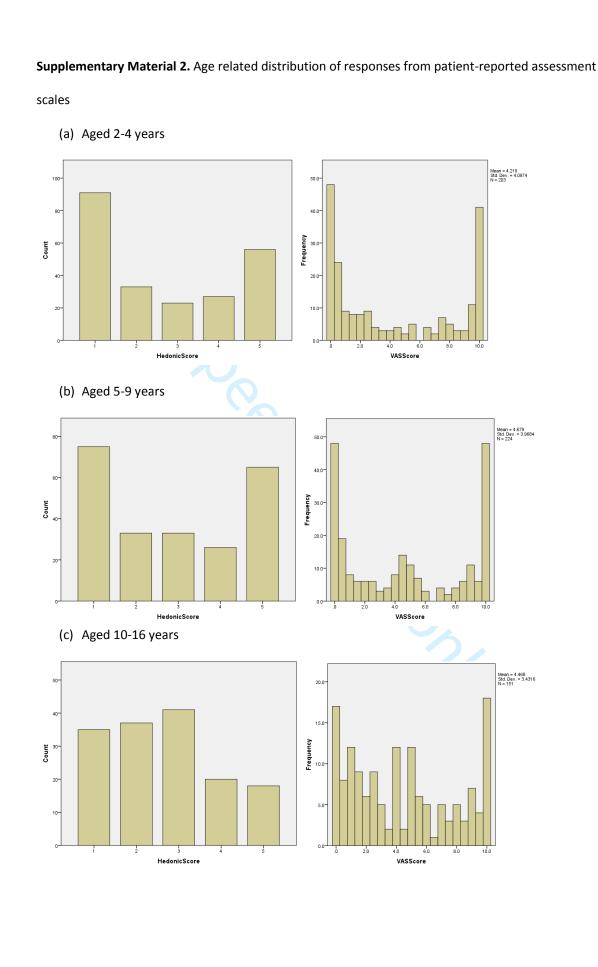
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Supplementary material 3. Table of taste scores for the six most commonly administered drugs by

brand

		Mean	Mean	Tastes
		Hedonic	VAS	ОК
Drug/Manufacturer	Ν	Score	Score	(% "No")
Amoxicillin			-	-
Athlone Laboratories	21	2.8	4.4	33%
Clamo	2	5.0	0.3	100%
Kent Pharmaceuticals	2	1.0	1.3	0%
Medreich PLC	1	3.0	10.0	100%
PL Holder	4	2.0	1.3	0%
Clarithromycin				
Abbott	11	3.7	7.4	82%
Klaricid	1	5.0	9.9	100%
MA Holder	1	2.0	4.2	0%
Sandoz Ltd.	13	3.4	6.7	54%
Co Amoxiclav				
Medreich PLC	1	3.0	5.0	0%
Rosemont Pharmaceutical Ltd	1	2.0	2.4	0%
Sandoz Ltd.	48	2.5	4.0	30%
Ibuprofen				
Fenpaed	9	2.1	3.4	22%
MA Holder	1	5.0	5.2	0%
McNeil Products	1	5.0	10.0	100%
Pinewood	78	2.0	2.5	10%
Reckitt Benckiser Healthcare	3	2.3	3.7	0%
Paracetamol				
Bristol Laboratories	1	3.0	4.0	100%
MA Holder	38	1.9	2.4	3%
McNeil Products	6	2.3	2.5	17%
Pinewood	113	2.6	4.3	28%
Rosemont Pharmaceutical Ltd	35	2.4	3.0	17%
Prednisolone				
Actavis	12	3.1	4.7	42%
Amdipharm	64	3.6	7.0	63%
Genetic SPA	1	3.0	5.2	0%
Teva UK Ltd	9	4.5	8.6	86%

This checklist was used and all items are provided within the manuscript: Evaluation of patient reported outcome measurements as a reliable tool to measure acceptability of the taste of paediatric medicines

	Item No	Recommendation	Appears in manuscript (line number)
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	34-35
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2 – Abstract
Introduction		6	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	115-123
Objectives	3	State specific objectives, including any prespecified hypotheses	139-142
Methods			
Study design	4	Present key elements of study design early in the paper	145-150
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up,	167-180
		and data collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants.	168-171
		Describe methods of follow-up	
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and	
		control selection. Give the rationale for the choice of cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed	n/a
		Case-control study-For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give	183-208
		diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	172-174; 183-208
measurement		Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	211-212
Study size	10	Explain how the study size was arrived at	216-218
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings	193-196; 219-232

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		were chosen and why	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for confounding	220-222; 215-232
		(b) Describe any methods used to examine subgroups and interactions	240-241
		(c) Explain how missing data were addressed	227-228
		() Colored at the 16 and include method have been to fully more and a damaged	222.224
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(<u>e</u>) Describe any sensitivity analyses	284-290
		(a) Conor study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	

Results			Appears in manuscript	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	250-259	
		(b) Give reasons for non-participation at each stage	250-259	
		(c) Consider use of a flow diagram	n/a	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	237-239	
		(b) Indicate number of participants with missing data for each variable of interest	250-259	
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	n/a	
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	250-259	
		Case-control study-Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study-Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95%	261-364	
		confidence interval). Make clear which confounders were adjusted for and why they were included		
		(b) Report category boundaries when continuous variables were categorized	301-313	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a	
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses	343-364	
Discussion				
Key results	18	Summarise key results with reference to study objectives	366-422	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both	56-69	
		direction and magnitude of any potential bias		
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results	425-438	
		from similar studies, and other relevant evidence		
Generalisability	21	Discuss the generalisability (external validity) of the study results	433-438	
Other informati	on			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	90-95	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluation of patient reported outcome measurements as a reliable tool to measure acceptability of the taste of paediatric medicines in an inpatient paediatric population

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Journal:	BMJ Open
Manuscript ID	bmjopen-2018-021961.R2
Article Type:	Research
Date Submitted by the Author:	02-May-2018
Complete List of Authors:	Mistry, Punam; University of Birmingham, School of Pharmacy Stirling, Heather; University Hospitals Coventry and Warwickshire NHS Trust, Paediatrics Callens, Claire; NIHR Clinical Research Network:West Midlands – Young Person's Steering Group (YPSG), CRN: Children Hodson, James; Queen Elizabeth Hospital Birmingham, Institute of Translational Medicine Batchelor, Hannah; University of Birmingham, School of Pharmacy
Primary Subject Heading :	Paediatrics
Secondary Subject Heading:	Patient-centred medicine, Pharmacology and therapeutics
Keywords:	THERAPEUTICS, PAEDIATRICS, palatability, ORAL MEDICINE



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15	(Smart Paediatric Drug Development – UK, accelerating paediatric formulation development
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Abstract

Objective: To evaluate the age-appropriateness and suitability of patient reported outcome measures to assess the acceptability of the taste of oral liquid medicines in children.

Design and setting: An observational mixed methods study involving children aged 2-16 years old taking oral liquid medicine in paediatric inpatient wards across the West Midlands (UK). Assessment tools included: patient-reported scores on the taste of medicines via a 5-point facial hedonic scale; a visual analogue scale (VAS); a question, "Did you think the medicine tasted OK?" and researcher observations of facial expressions and behaviours immediately before, during and after administration.

Results: 611 children participated. The percent unable to complete the scales were 7% (n=46) for the VAS; 2% (n=15) for the hedonic scale and 1% (n=7) for the question about taste. Significant correlations (Spearman's rho) were observed between the patient reported outcome measures: 0.80 and 0.78 for the taste question and hedonic and VAS respectively and 0.84 for the hedonic and VAS. Researcher observations demonstrated the ability of the patient to take the medicine as intended but did not provide sensitive measures of taste. 5% of administrations were not taken as intended by the children. Medicines known to have poor taste (clarithromycin and prednisolone) showed mean hedonic and VAS scores of \geq 3.5 and >65mm respectively.

Conclusions: Patient reported outcome measures correlate with each other and are a useful means to assess the taste (and acceptability) of medicines. Hedonic scales are better understood by children and should be the first choice tool in the assessment of medicines taste.

Key words: medicines, taste, acceptability, age-appropriate, hedonic scale, paediatric medicine,

patient-reported outcome measures, VAS

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2	Strengths and limitations of this study
3 4	Strengths and initiations of this study
5	• This is the first study to compare methodologies to assess the acceptability of taste of liquid
7 8	medicines in a large UK based paediatric population aged 2-16 years
9 10	• The sample size in this study provided large data sets of six key medicines, which provides a
11 12	representative comparison for newly developed products
13 14	• This study was conducted within an inpatient environment and the acceptance of taste of
15 16	medicines in a domiciliary environment may differ
17 18	The study design captured the most relevant aspects of acceptability of taste whilst
19 20	minimising the burden to participants, it was not possible to measure every aspect.
21 22	Suggestions for future research include measurement of: impact of the devices used to
23 24 25	administer medicines; use of alternative hedonic scales (e.g. those with 2-9 faces);
25 26 27	alternative anchor phrases; an endpoint of neutral and not positive within a hedonic scale;
28 29	further exploration of medicines that tasted OK as well as those with a reported negative
30 31	taste.
32 33	taste. What is already known about this subject?
34 35	What is already known about this subject?
36 37	New medicines for children must be demonstrated to be acceptable to a paediatric
38 39 40	population
41 42	Measurement of acceptability of the taste of medicines is complex and a wide range of
43 44	methods have been used previously, making comparison between studies complex.
45 46	• There is a need for age-appropriate reproducible and reliable methods to measure the
47 48	acceptability of medicines
49 50	
51 52	What this study adds
53 54 55	Patient reported outcome measures offer a pragmatic means to assess the taste of
55 56 57	medicines in children aged from 2-16 years
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- 5-point hedonic scales were better understood compared to visual analogue scales in children aged 2-16 years
- Although 41% of medicines were reported to have unacceptable taste only 5% were so bad that they could not be taken as intended

Funding Statement

This work was conducted as part of the SPaeDD-UK project (Smart Paediatric Drug Development – UK, a project co-funded by Innovate UK and the contributing companies of AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Juniper Pharmaceuticals and Pfizer. (http://www.paediatricscienceuk.com).

Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Data sharing statement

Additional data is available in the Supplementary files. The full data set is held by the corresponding author, please email with any requests for extra data.

Authorship contributions

Punam Mistry contributed to the acquisition, analysis and interpretation of the data.

Heather Stirling contributed to the design, acquisition, analysis and interpretation of the data and

revising the manuscript following reviewers' comments.

Claire Callens contributed to the design of the study and acquisition of the data

James Hodson contributed to the design, statistical analysis and interpretation of the data and

revising the manuscript following reviewers' comments.

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2	Hannah Batchelor contributed to the design, acquisition, analysis and interpretation of the data and
3 4	
5	revising the manuscript following reviewers' comments. She is the corresponding author for this
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Measurement of acceptability of paediatric medicines is important for two major reasons: (i) poor acceptability is likely to be associated with poor compliance and therefore suboptimal therapy; (ii) regulatory guidelines dictate that paediatric medicines' acceptability should be assessed (preferably in children) [1]. Patient acceptability has been defined as, "an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised)" [1]. A major barrier in the assessment of acceptability and subsequent interpretation of results is the lack of guidance on how an acceptability test should be conducted and the criteria used to determine acceptability in children [2]. It is unlikely that a single acceptability test will be valid for all medicines, due to the need to consider the benefit:risk balance on an individual basis.

Taste was previously identified as the biggest barrier in adherence and compliance in a paediatric population [3]. Previous techniques to evaluate acceptability focussed on taste and were based on methodology adapted from sensory analysis undertaken in the food industry. A variety of scales have been used to measure the acceptability of medicines, yet it remains unclear whether any of the scales is better for a particular purpose with regard to validity, reliability, feasibility, and preference [4, 5]. Patient reported measures of taste offer a pragmatic means to collect data on products. However, there is often concern about the reliability of these measures, particularly in a paediatric population [6]. Sensory analysis is commonly used to show a preference for one product over another, but this is not always relevant to medicines as often there is no alternative available. In addition, it can be rationalized that the therapeutic benefits of medicines outweigh the negative taste. It is complex to distinguish between acceptability and likeability of a medicine's taste, yet this difference may be critical for appropriate interpretation of resulting data.

The validity of any new method relies on how well it compares to other measures [7]. The development of a reliable method to assess the taste of medicines requires comparison of a variety of tools. This study compares a range of methods to assess the taste of medicines within a large

paediatric inpatient population. Independent researcher observations are also compared to the selfreported data. The results of this study will be used to propose a suitable method that can be used for future taste assessments.

2. Materials and Methods

Three patient-reported outcome (PRO) measures were compared to each other, and to researcher observations of medicines administration in an observational mixed methods study.

2.1. Patient and Public Involvement

Bespoke PRO tools were developed for this study based on previous methodologies and in consultation with the National Institute for Health Research (NIHR) Children Specialty's Young Person's Advisory Group (West Midlands) [8]. The young people (aged 11-18 years) reviewed the tools and provided feedback that the tools were age-appropriate. The same young people provided feedback on the trial materials including information sheets and how to minimise the burden to participants during the conduct of the study. The results are available to participants as a poster summary from the corresponding author's personal webpage (www.hannahbatchelor.com); this poster was also reviewed by the young person's group.

2.2. Patient reported outcome measures used

The hedonic scale selected was a genderless image where the mouth was the only expressive facial feature (see Figure 1(a)). The images were yellow to ensure they stood out from the background paper. They were obtained from S-cool the revision website (http://www.s-cool.co.uk/gcse/food-technology/systems-and-control/revise-it/sensory-evaluation (accessed December 2015)). Children and young people preferred simple faces and felt that this would be most appropriate for the youngest age group [8]; anchor phrases were not included on the hedonic scale to keep this tool basic. The visual analogue scale (VAS) included anchor phrases selected by the young persons'

group as the most clear and relevant [8], these were used at the extreme ends of the continuous scale.

The direction of change was from positive to negative, which corresponds to the extensive data on hedonic scales used for pain assessment in children [9]. Previous studies in adult studies of foods showed no difference based on structural variations that read from positive to negative or vice versa [10].

The third PRO was a question, 'Did you think the medicine tasted OK?' with the response options of: yes, no, not sure.

2.3. Participants and Setting

Paediatric inpatients aged between 2 to 16 years taking any oral liquid medicine as part of their medical care were recruited using convenience sampling, from inpatient wards at 11 sites across the West Midlands. Informed consent was obtained from the parent or legal guardian of the participating child and for children over 12 years of age assent was also required. The study was conducted between December 2015- April 2016. Ethical approval was granted by London Surrey borders ethical committee (REC reference: 15/LO/1253; IRAS project ID: 179684).

Demographic information was obtained on participant's age and whether this was their first dose of the medicine under evaluation. The medicine name; brand; manufacturer; concentration (strength); dose administered and product batch number was recorded.

Each participant was observed by a researcher as they took their medicine. Some medicines were provided to the patient as an oral liquid following extemporaneous preparation within the clinical setting, for example, dispersion of prednisolone tablets immediately prior to dosing. Depending on the capability of the child, the medicines were either self-administered, or administered by nursing staff and/or parents. Participants were asked not to mix the medicine with any other food product, as this might influence the participant's responses.

2.4. Patient-reported outcome tools

Participants were asked to complete (a) 5-point facial hedonic scale and (b) 10cm VAS (Figures 1(a) and (b)) immediately after administration of their medicine; both scales were provided on separate paper documents in a randomized order. Children were free to ask for support in completing the questionnaires from parents, nursing staff or the researcher present. The cognitive function of children was not assessed and age may not always predict a child's ability to complete the questionnaire, therefore all children were free to ask for support if requried. Both reporting documents included a third PRO (Figure 1 (c)) as a question, 'Did you think the medicine tasted OK?' with the response options of: yes, no, not sure. The purpose behind this question was to endorse the reliability of the participant's reporting from both scale-based questionnaires.

Figure 1

The data from the scales (Figure 1 (a) and (b)) were transformed into numbers for subsequent statistical analysis. Hedonic expressions were converted to scores of 1 to 5 with 1 being the most positive expression and 5 the most negative. VAS scores were reported as measurements from the extreme left hand side of the scale in mm; this provided scores of 0-100 mm (although scale was written as 0-10 cm).

2.5. Researcher Observations

A facial expression and behavioural scale to capture researcher observations was a 12-point tick chart designed in-house (Figure 2), based on an existing scale used to measure behavioural distress in children undergoing medical procedures [11], the Procedural Behavior Rating Scale (PBRS). The PBRS was developed specifically for infants and children with cancer, who were undergoing bone marrow aspirations or lumbar punctures. It contained 13 behavioural codes including: cry, cling, pain verbal, flail, stall, scream, refuse position, restrain, emotional support, muscular rigidity and requests termination [11]. The in-house tool was based on this scale plus other scales used to measure

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behavioural distress in children [12]. The facial expressions included on the scale were derived from previous studies that assessed food-liking in children based on their facial expressions; typically negative tastes are associated with eyes squeezing, brow bulge, nose wrinkle and pursed lips [13]. *Figure 2*

A series of nine short films or still pictures of children were made available to researchers participating in the study to assess the inter-rater agreement in the facial expressions displayed.

2.6. Statistical analysis

A sample size was not fixed for this study at the outset as there was no appropriate power calculation. Advice from a statistician was to ensure we had sufficient numbers (<50) paired data to ensure that selectivity and sensitivity of the methods could be demonstrated. Initially, the mean age of participants that were unable to understand the assessments were compared to those who could using Mann-Whitney tests. The same approach was also used to compare the scores for patients receiving their first dose, relative to those who had previously received the medicine. Age was then divided into categories, and the proportions of participants scoring in the extreme categories for the scales were compared using Fisher's exact tests. Spearman's correlation coefficients were used to assess the degree of correlation between the assessments for the cohort as a whole, and within each of the age categories. In this analysis, the "Did you think the medicine tasted OK?" question was treated as an ordinal scale, with the response of Don't Know being between Yes and No. Where responses were not recorded for all criteria, the outcome was calculated based on those that were available

The assessments were then dichotomised, and compared using McNemar's tests to assess for marginal homogeneity in the 2x2 tables, and Kappa to assess agreement. The three assessments were then combined into a composite score, which was compared with reported behaviours using

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Kendall's tau correlation coefficients. All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), and p<0.05 deemed to be indicative of statistical significance throughout.

3. Results and discussion

Data were available for 628 administrations to 611 children aged between 2-16 years. The median participant age was 6 years. Further details on the distribution of the participant ages can be found in supplementary material 1.

To ease analysis of data, the population for this study was stratified by age into three groups: 2-4 years (n=237); 5-9 years (n=227) and 10-16 years (n=147).

The medicine was administered as the first dose in 162 cases. There was no evidence of a significant difference in the hedonic or VAS scores between those receiving their first dose of a medicine, compared to those who had previous administrations (p=0.336, 0.909 respectively). For all subsequent analysis the data was pooled for those receiving their first and subsequent doses of medicine.

3.1. Completeness of patient-reported assessment scales

The assessment scales were not completed by all of the study participants. The VAS had the lowest completion rate, where 46 (7%) were not completed due to lack of understanding by the child, compared to 15 (2%) for the hedonic scale. There were 7 (1%) cases where the child did not understand the question, "Did you think the medicine taste OK?". The range and mean age of those unable to complete the scales were 2-5 years with a mean of 2.4 years for the hedonic; 2-6 years with a mean of 3.1 years for the VAS and 2-3 years with a mean of 2.3 years for the taste question. In each case, participants unable understand the assessment methods were significantly younger than the remainder of the cohort (p<0.001 each assessment). The cognitive function of children was not

assessed within this study and there was an assumption of cognitive normal for age for all participants.

3.2. Distribution of responses to patient-reported assessment scales

In the patient reported scales (VAS and hedonic), the responses tended to be biased towards the extreme responses, with 56% of responses being in the highest or lowest categories for hedonic score (Figure 3a) and, 55% within 1cm from either end of the scale in the VAS (Figure 3b).

Figure 3

The use of the extreme ends of the scales was greater in the younger populations (p<0.001) (data is shown in Supplementary material 2). For those that completed the hedonic scale, 64% of those aged 2-4 years used the extreme ends of the scale compared to 60% of those aged 5-9; 35% of those aged 10-16 years. A similar trend was observed in the VAS data where 66% of those aged 2-4 years were within 10mm of either end of the scale compared to 60% of 5-9 year olds and 39% of 10-16 year olds.

3.3. Reliability of assessment, "Did you think the medicine tasted OK?"

The question, "Did you think the medicine tasted OK?" was asked to participants on two occasions for each medicine administration; once following the hedonic and once following the VAS (which were presented in a randomized order). In the 600 cases where participants responded to both questions, the same response was given in 569 (95%) of cases, giving a Kappa statistic of 0.91. In cases where the answers were not consistent, the median age of the respondents was 5 years (mean age = 6.3 years). For subsequent analysis, the two versions of this question were merged, with discrepancies resolved by taking the most positive response given by the participant.

3.4. Correlation between patient reported outcome measures

Significant correlations were observed between the hedonic scale score, VAS and "Did you think the medicines tasted OK?" question (all p<0.001 Table 1), with the strongest correlation observed between the hedonic and VAS scores (Spearman's rho=0.84). The weakest correlations were consistently observed in the youngest patients (age 2-4 years), implying that this group of patients had the lowest consistency in scores given across the different assessments. However, despite this, the consistency between the scores was still reasonable, with correlation coefficients ranging from

0.68- 0.77.

The assessments were dichotomised, to identify those responses that classified a medicine as tasting acceptable. For the hedonic scale, this was defined as a neutral to positive response (the leftmost three faces of Figure 1a). For the "*Did you think the medicine tasted OK?*" question, grouping the "yes" and "not sure" responses was considered most appropriate, as the overall purpose is the assessment of acceptability of taste of a medicine; the response "no" is clearly aligned to an unacceptable taste, making other responses acceptable. The level of agreement between the resulting dichotomised scores was high (90%), with a Kappa statistic of 0.782, and no indication of bias (McNemar's test: p=0.519).

Correlation of the hedonic scale to the "tastes OK" question is simple; however interpretation of the VAS is more complex. The VAS had anchor phrases at either end to maintain the continuous scale, so it was not obvious where neutral or positive was ranked on the scale. Initially, an arbitrary cut-off of <50mm in the VAS was used to define acceptability, which gave reasonable agreement with both the dichotomised hedonic (88%) and "tastes OK" (86%) measures. However, McNemar's test indicted significant bias in both cases (p<0.001), with a tendency for the VAS score of 0-50mm to underestimate the number of tastes-acceptable responses, compared to the hedonic and "tastes OK" assessments. As a result, alternative VAS cut-offs were explored, with 0-70mm selected to approximately match the cut-off on the hedonic scale where the neutral face becomes the negative.

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Using 70mm rather than 50mm in the VAS marginally increased the agreement with both the dichotomised hedonic and "tastes OK" measures to 91% but, more importantly, eliminated the previously observed bias (McNemar's test p=1.000, 0.683 respectively). All subsequent analysis used the cut-off of >70mm as a measure of unacceptable taste.

3.5. Associations with researcher observations and patient reported outcome measures

One patient did not have a record of facial expression/behaviours, hence they were excluded, and the analysis was based on n=620 cases. Associations between facial expressions and behaviours (listed in Figure 2) were linked to cases where the medicines were reported to have an unacceptable taste, based on a composite outcome (Table 2). This was defined using the criteria defined previously. Where responses were not recorded for all criteria, the outcome was calculated based on those that were available. In total, 255/620 (41%) of assessments identified the taste of medicines to be unacceptable. The associations between this outcome, and the various facial expressions and behaviours that were recorded were then assessed.

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Table 2 shows the incidence of the facial expression or behaviour as a fraction of the total population. The behaviours are listed in order of Kendall's tau correlation coefficients, with those behaviours most strongly associated with unacceptable taste having the highest value of tau. Based on this metric, voicing disgust was the behaviour most strongly associated with negative taste. Of the 105 patients that voiced disgust, 95 (90%) reported the taste of the medicine to be negative. This rate was almost three-fold higher than the 160/515 (31%) who reported negative taste after not voicing disgust. Ordering the data in this way puts 'vomits' in last place, despite the fact that 100% of patients who vomited found the taste of their medicine to be unacceptable. Since so few children vomited (n=7), the proportion of the total number of children who identified the taste as unacceptable and also displayed this behaviour (i.e. the sensitivity) was low, at 3%. Hence, although a vomiting child is almost certain to find the taste unacceptable, using this behaviour in isolation as a predictor of negative taste would miss the vast majority of patients who reported taste to be negative

Inter-rater agreement assessed via the use of short films and images were mixed; prevalent expressions were detected in >95% of cases, whereas some mild expressions were only detected in 40-50% of those viewing the images.

3.6. Analysis of medicine-specific taste assessment

Fifty-seven different drugs were observed in this study and the six most commonly administered were paracetamol, ibuprofen, prednisolone, co-amoxiclav, amoxicillin and clarithromycin, which made up 76% (n=477) of the total data set.

Comparisons were made across the six most commonly prescribed drugs. Table 3 ranks these drugs in order of taste, and reports the means scores on the hedonic scale and VAS, as well as the proportion of patients answering "no" to the, "Did you think the medicine tasted OK?" question.

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The drugs can be divided into three groups based on this data: clarithromycin and prednisolone were found to be the worst tasting; amoxicillin and co-amoxiclav were mid-range, and ibuprofen and paracetamol were the best tasting medicines. The effect of brand was also investigated and the data is presented in Supplementary material 3.

In addition to reports of taste, the proportion of children who refused, vomited or spat out the medicines, was calculated and classified as unable to "use a medicinal product as intended". In total, this occurred in 33/620 (5%) administrations, which are reported for the six most commonly used drugs in Table 4.

Clarithromycin was the most commonly not taken as intended and was also the drug most frequently identified as having unacceptable taste, based on the previously defined composite outcome. However, there was insufficient data to suggest that the taste of the medicine was directly related to the ability to take the medicine as intended. Children may vomit due to their underlying illness rather than as a direct result of the taste of their medicine.

4. Discussion

Few studies have categorised acceptability of the taste of medicines. The results within this study agree with previous reports, where a neutral to positive hedonic response indicates acceptable taste [14-17]; Sjovall et al (1984) compared two brands of penicillin and reported that the acceptable taste mean hedonic score was within the neutral to positive range and an unacceptable taste was in the negative range [18]. Children were free to ask for support in completing the PRO measured and we did not collect data on how many received help in this aspect; it would be of value to consider how many, particularly in the youngest age group received support. Many of the children aged 2-5 years were able to provide reliable data on the taste of medicines demonstrating that the scales and questions used within this study are suitable for very young participants.

4.1. Interpretation of facial expressions and behaviours

Voicing disgust was the behaviour most strongly associated with unacceptable taste whilst, perhaps counterintuitively, vomiting was the behaviour least strongly correlated with unacceptable taste. Despite the fact that 100% of patients who vomited found the taste of their medicine to be unacceptable, only a small number of patients vomited (n=7). As a result, whilst vomiting was a highly specific predictor of unacceptable taste, it had very low sensitivity. A similar pattern was also observed for the other facial expressions and behaviours, with sensitivity ranging from 10%-51%, and specificity from 84%-99%. This can be interpreted as indicating that, whilst it was uncommon to observe these facial expressions and behaviours in patients who found the taste of the medicine acceptable, displaying facial expressions and behaviours was not a strong indicator of unacceptability.

The behaviours used to inform the researcher observations were not always clearly defined; for example the use of physical restraint was not explicitly stated and further work is required to better understand what physical restraint may be considered acceptable.

The explicit definition of an acceptable medicine being "an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised)" (Kozarewicz, 2014), includes the patient/caregiver's ability to access the medicine and comply with packaging requirements and for this study to demonstrate that the medicine was swallowed without incident. In total, 33/620 (5%) of medicines were spat out or vomited, and therefore unacceptable within this in patient population. This demonstrates that, although some of the behaviour and expressions observed may link more strongly to a negative taste, they do not automatically mean that the medicine was unacceptable.

In future studies, observations should ensure that the medicine was taken as intended; this may require a simple tool to ensure that the dose was completely swallowed without spitting out or

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vomiting. There is no need to include additional observations, as these were not strongly correlated to patient reported outcomes on the taste of medicines.

4.2. Medicine-specific taste assessment

Our results correlate well with other reports in the literature on the taste of medicines. Both paracetamol and ibuprofen have previously been reported to demonstrate acceptable taste (mid-range in a 5 point hedonic scale) in paediatric populations [19, 20]. Co-amoxiclav and amoxicillin were reported to have acceptable taste to 57-67% of children within this study, which is consistent with previous literature, which has reported co-amoxiclav to be preferred to other antibiotics in terms of taste, including amoxicillin [21-27]. Previous work suggested that 60% of children accepted amoxicillin without problems and 63% of children liked the taste of co-amoxiclav [27]. Prednisolone and clarithromycin were the least liked medicines, again consistent with published data, with results showing predominantly negative scores in hedonic scales or the equivalent of >70mm in a VAS [28-30, 23, 31, 32, 3]. This study identified differences in acceptance of certain brands of medicines; however, there was insufficient sample numbers to undertake a detailed analysis of the impact of brand on taste and acceptance. A future study that explored brand preference would be of value to patients and those purchasing commonly used medicines.

Using our criteria, the proportion of patients classifying taste as acceptable for the most liked of the frequently prescribed medicines (ibuprofen and paracetamol) was over 70%; the proportion classifying taste as acceptable for the least liked medicines (prednisolone and clarithromycin) was less than 30%. This study provides some standardised values for medicines used within a UK population, the thresholds reported here provide guidance for future medicines development where in addition to taste scores the overall risk-benefit of the medicine will need to be considered.

4.3. Recommended tools to assess acceptability

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This study has correlated three simple patient reported measures of medicines taste acceptability. It has also provided comparative data from existing medicines. Regulations mandate that all new medicines need to be demonstrated to be acceptable to children [1]. This study provides pragmatic and reliable tools to conduct this assessment. Furthermore, comparison of the results from a new medicine using these tools can be directly compared to existing medicines to support evidence of acceptance.

5. Conclusions

This study has generated data on the taste of medicines commonly used in paediatric populations aged 2-16 years. The results of this study suggest that patient reported outcome measures are a reliable and valid assessment of the taste of children's medicines, for children aged from 2-16 years. These assessment tools offer a mechanism to evaluate the taste of other medicines (either novel products and formulations or medicines used orally in an off-label or unlicensed manner) to generate comparative data on the taste of medicines.

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The data from this study coupled with previous literature on the taste of medicines provides evidence to suggest criteria to demonstrate acceptability of taste of medicines.

Our results suggest that criteria to demonstrate acceptability of taste are: a mean VAS score of <70mm; a mean hedonic score of \leq 3 (neutral or positive face) and a non-negative response to the "Tastes OK?" question. Pragmatically, there is no need to use all methods. As the hedonic scale was understood across the widest age range, this should be the first choice method going forwards. It would be prudent to ensure that any new product exceeds these scores to demonstrate that it is likely to have acceptable taste in practice.

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Figure Legends

Figure 1. Scales used within PRO tools completed by paediatric participants immediately after administration of their medicine. (a) Hedonic scale; (b) Anchored visual analogue scale (VAS); (c) direct question on taste.

Figure 2. Researcher observation sheet completed by the researcher prior to, during and post medicine administration.

Figure 3. Hedonic and VAS score distribution

Table headings

 Table 1. Spearman's rho correlation values between patient-reported outcome measures.

	"Tastes OK" vs. Hedonic	"Tastes OK" vs. VAS	Hedonic vs. VAS
Overall	0.80	0.78	0.84
Age (Years)			
2-4	0.77	0.68	0.76
5-9	0.83	0.85	0.90
10-16	0.80	0.81	0.86

Table 2. Relationship between facial expression or a behaviour and a patient report of an unacceptable tasting medicine

	Cases Wher				
	Reported as unac				
Behaviour	Not Displayed	Displayed	Tau	Sens.	Spec.
Voices disgust	160/515 (31%)	95/105 (90%)	0.45	37%	97%

Eyes squeezed	131/460 (28%)	124/160 (78%)	0.44	49%	90
Nose Wrinkle	125/433 (29%)	130/187 (70%)	0.38	51%	84
Voices resistance	184/539 (34%)	71/81 (88%)	0.37	28%	97
Refusal	192/551 (35%)	63/69 (91%)	0.36	25%	98
Pursed Lips	168/505 (33%)	87/115 (76%)	0.33	34%	92
Cries/Screams	201/559 (36%)	54/61 (89%)	0.32	21%	98
Brow bulge	149/463 (32%)	106/157 (68%)	0.31	42%	86
Physical restraint	219/579 (38%)	36/41 (88%)	0.25	14%	99
Cries	216/573 (38%)	39/47 (83%)	0.24	15%	98
Spits out	229/590 (39%)	26/30 (87%)	0.21	10%	99
Vomits	248/613 (40%)	7/7 (100%)	0.13	3%	100

Table 3. Patient reported taste scores by medicine

	Hedonic Score		VAS Score		Tastes OK?	Composite Outcome
Drug	Mean	% unacceptable	Mean (mm)	% unacceptable	(% "No")	% unacceptable
Clarithromycin (n=26)	3.5	62%	70	58%	65%	77%
Prednisolone (n=86)	3.6	58%	68	54%	61%	70%
Amoxicillin (n=30)	2.7	37%	37	23%	33%	43%
Co-Amoxiclav (n=50)	2.5	30%	39	24%	29%	33%
Paracetamol (n=193)	2.4	22%	37	21%	21%	29%
Ibuprofen (n=92)	2.1	14%	27	12%	12%	20%

Table 4. Percentage unable to take medicine as intended

Medicine	% spat out/vomited the medicine	Composite Outcome % unacceptable
Clarithromycin (n= 26)	23%	77%
Amoxicillin (n=30)	13%	43%
Prednisolone (n= 86)	9%	70%
Co-amoxiclav (n= 50)	6%	33%
lbuprofen (n= 92)	2%	20%
Paracetamol (n= 193)	1%	29%

2	Defense
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Figure 1. Scales used within PRO tools completed by paediatric participants immediately after administration of their medicine. (a) Hedonic scale; (b) Anchored visual analogue scale (VAS); (c) direct question on taste.

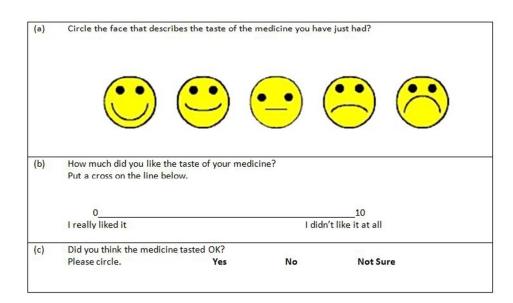


Figure 1. Scales used within PRO tools completed by paediatric participants immediately after administration of their medicine. (a) Hedonic scale; (b) Anchored visual analogue scale (VAS); (c) direct question on taste.

67x53mm (300 x 300 DPI)

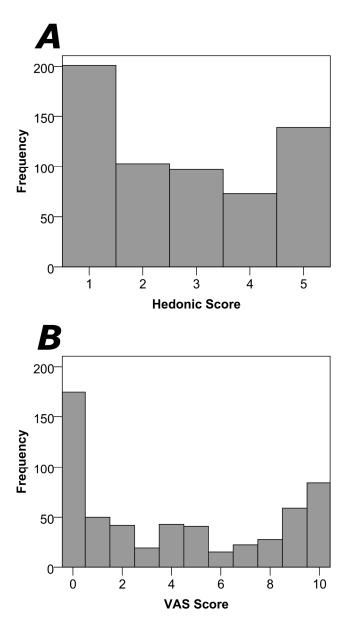
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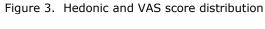
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Expression		Tick if observed prior to administration		Tick if observed during administration	
Eyes squeezed shut or towar	ds shut				
Brow bulge/lower (frown)					
Nose wrinkle					
Pursed lips					
Behaviours observed					
		if observed prior to ninistration	Tick if observed during administration		
Child refuses medicine	0				=unacceptable
Child cries/screams					=unacceptable
Child requires physical restraint					=unacceptable
Child voices resistance					=unacceptable
	imn	t if observed nediately after ninistration			
Child voices disgust					=unacceptable
Child vomits					=unacceptable
Child spits out medicine					=unacceptable
Child cries					=unacceptable

Figure 2. Researcher observation sheet completed by the researcher prior to, during and post medicine administration.

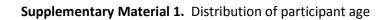
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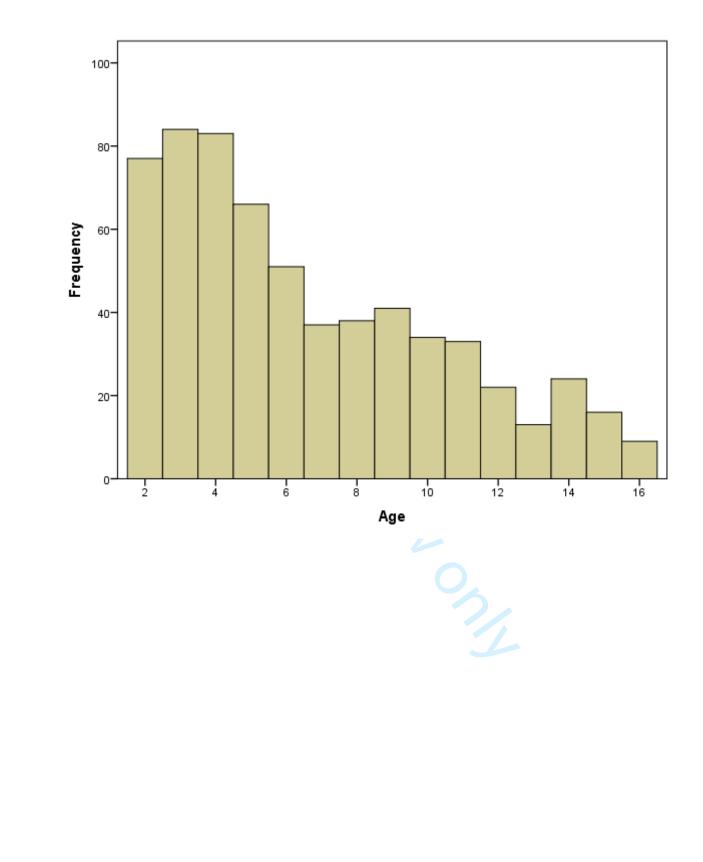


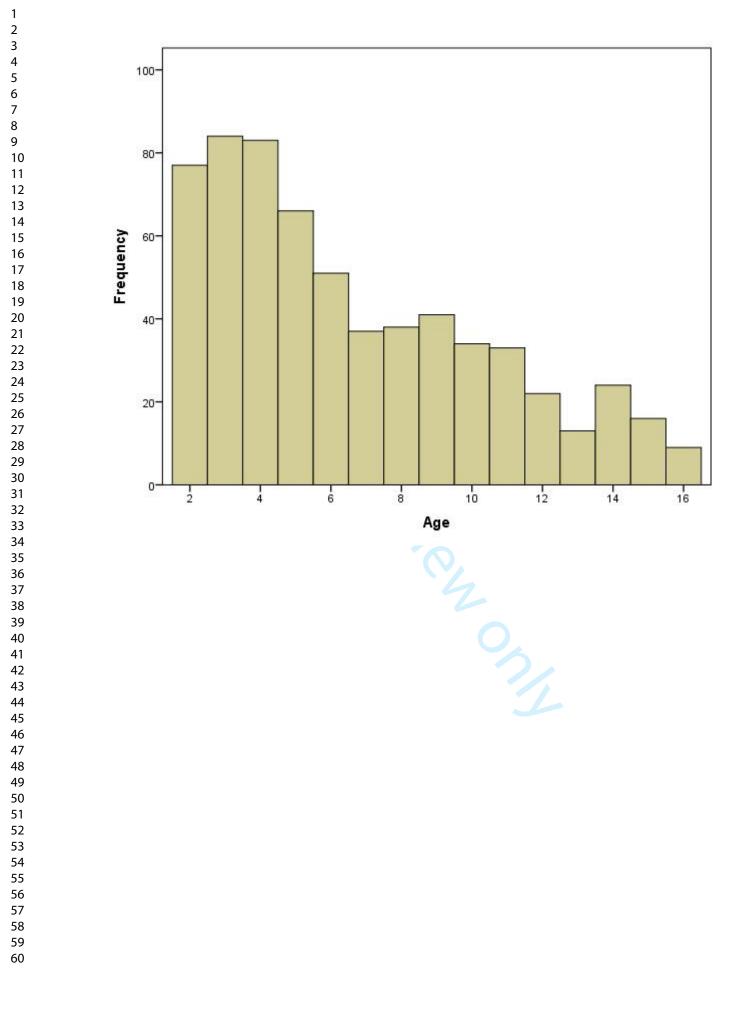


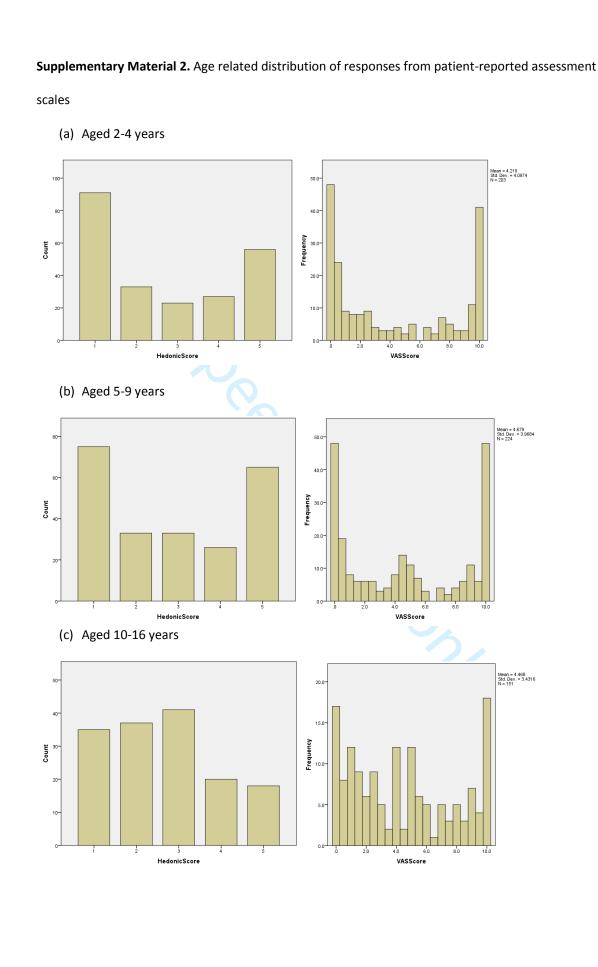
168x300mm (300 x 300 DPI)

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Supplementary material 3. Table of taste scores for the six most commonly administered drugs by

brand

		Mean	Mean	Tastes
		Hedonic	VAS	ОК
Drug/Manufacturer	Ν	Score	Score	(% "No")
Amoxicillin			-	-
Athlone Laboratories	21	2.8	4.4	33%
Clamo	2	5.0	0.3	100%
Kent Pharmaceuticals	2	1.0	1.3	0%
Medreich PLC	1	3.0	10.0	100%
PL Holder	4	2.0	1.3	0%
Clarithromycin				
Abbott	11	3.7	7.4	82%
Klaricid	1	5.0	9.9	100%
MA Holder	1	2.0	4.2	0%
Sandoz Ltd.	13	3.4	6.7	54%
Co Amoxiclav				
Medreich PLC	1	3.0	5.0	0%
Rosemont Pharmaceutical Ltd	1	2.0	2.4	0%
Sandoz Ltd.	48	2.5	4.0	30%
Ibuprofen				
Fenpaed	9	2.1	3.4	22%
MA Holder	1	5.0	5.2	0%
McNeil Products	1	5.0	10.0	100%
Pinewood	78	2.0	2.5	10%
Reckitt Benckiser Healthcare	3	2.3	3.7	0%
Paracetamol				
Bristol Laboratories	1	3.0	4.0	100%
MA Holder	38	1.9	2.4	3%
McNeil Products	6	2.3	2.5	17%
Pinewood	113	2.6	4.3	28%
Rosemont Pharmaceutical Ltd	35	2.4	3.0	17%
Prednisolone				
Actavis	12	3.1	4.7	42%
Amdipharm	64	3.6	7.0	63%
Genetic SPA	1	3.0	5.2	0%
Teva UK Ltd	9	4.5	8.6	86%

This checklist was used and all items are provided within the manuscript: Evaluation of patient reported outcome measurements as a reliable tool to measure acceptability of the taste of paediatric medicines

	Item No	Recommendation	Appears in manuscript (line number)
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	34-35
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2 – Abstract
Introduction		6	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	115-123
Objectives	3	State specific objectives, including any prespecified hypotheses	139-142
Methods			
Study design	4	Present key elements of study design early in the paper	145-150
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up,	167-180
		and data collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants.	168-171
		Describe methods of follow-up	
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and	
		control selection. Give the rationale for the choice of cases and controls	
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed	n/a
		Case-control study-For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give	183-208
		diagnostic criteria, if applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement).	172-174; 183-208
measurement		Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	211-212
Study size	10	Explain how the study size was arrived at	216-218
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings	193-196; 219-232

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		were chosen and why	
Statistical methods	12	(<i>a</i>) Describe all statistical methods, including those used to control for confounding	220-222; 215-232
		(b) Describe any methods used to examine subgroups and interactions	240-241
		(c) Explain how missing data were addressed	227-228
		() Colored at the 16 and include method have been to fully more and a damaged	222.224
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(<u>e</u>) Describe any sensitivity analyses	284-290
		(a) Conor study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	

Results			Appears in manuscript
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	250-259
		(b) Give reasons for non-participation at each stage	250-259
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	237-239
		(b) Indicate number of participants with missing data for each variable of interest	250-259
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	250-259
		Case-control study-Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study-Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95%	261-364
		confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	301-313
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses	343-364
Discussion			
Key results	18	Summarise key results with reference to study objectives	366-422
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both	56-69
		direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results	425-438
		from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	433-438
Other informati	on		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	90-95

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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