UNIVERSITY OF BIRMINGHAM | COLLEGE OF MEDICAL AND DENTAL SCIENCES

An evaluation of tools via patient-reported outcome measures to assess the acceptability of existing oral liquid medicines within a paediatric inpatient population.

P.Mistry, J.Hodson, H.Stirling, C.Callens, H.K.Batchelor

Presenter: Punam Mistry

8th Conference of the European Paediatric Formulation Initiative
20-22 September 2016 Lisbon, Portugal

Introduction

- Palatability of liquid medicines is a recognised challenge within the paediatric population
- **Acceptability**: “The overall ability of the patient and its caregiver to use the medicine as intended”
- Patient needs must be met when medicines are designed
- Patient acceptability of a medicinal product is likely to have a significant impact on adherence and consequently, on its safety and efficacy.
- Currently no guidance of how ‘acceptability’ should be measured in an age-appropriate paediatric setting

Study Aims

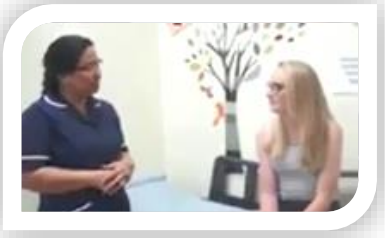
- To investigate the suitability of tools for assessment of acceptability for existing oral liquid medicines
- To compare patient-reported outcome measures (PROMs) with researcher observations
- To obtain data on the suitability of these tools for use in children
- To assess whether a simple cut-off scale value reflects overall medicine acceptability

Study Design

ACCEPT: NRES Research Ethics Committee **(15/LO/1253)**

Child takes medicine within NHS site

Researcher observes child's behaviours



Child completes 2 questionnaires
- 5-point facial hedonic scale
- 10cm VAS

Negative face hedonic score
VAS score >5

Researcher conducts questionnaire to identify cause for medicine dislike

UNIVERSITY OF BIRMINGHAM

Assessment tools

PRO

1. 5-point facial hedonic scale

2. 10cm VAS + anchor phrases

0 _____ 10

I really liked it — I didn't like it at all

3. Structured questionnaire, if:

→ Negative faces on hedonic scale
→ VAS score >5

Researcher Observations

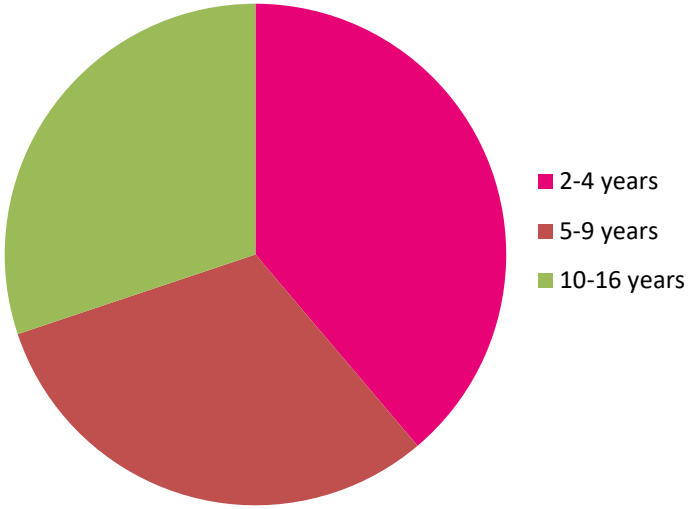
Facial Expressions
Brow bulge
Eyes squeezed / shut
Nose wrinkled
Pursed lips

Behaviours (prior/during/post) administration
Refusal
Cries/ screams
Physical restraint
Voices resistance/ digust
Vomits/ spits out medicine

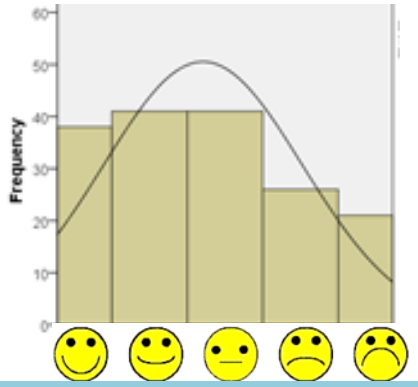
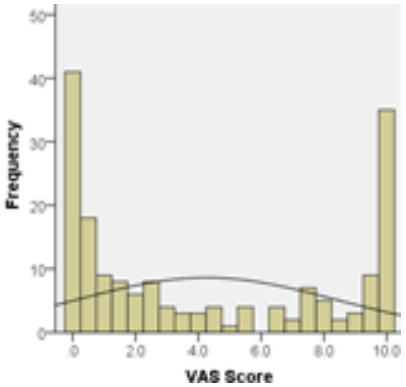
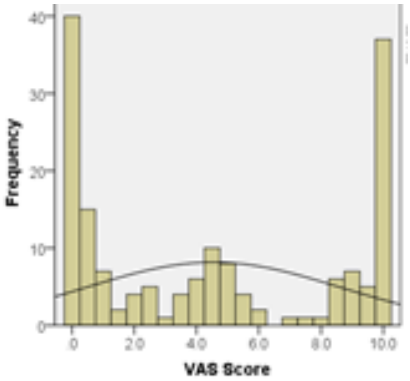
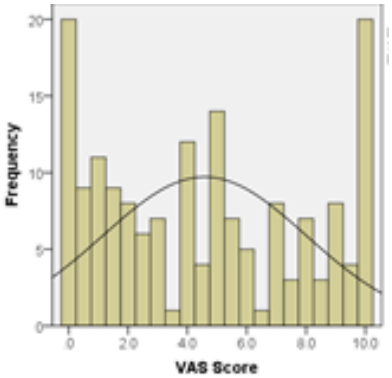
UNIVERSITY OF BIRMINGHAM

Demographics

- **611** participants aged 2-16 years
- Population was stratified by age range:
  - 2-4 years (n=237)
  - 5-9 years (n=227)
  - 10-16 years (n=157)
- Data sets were available in 628 drugs
- Participation from 14 NHS sites
- 57 unique medicines assessed
- The most commonly seen drugs were Paracetamol, Ibuprofen, Prednisolone, Co Amoxiclav, Amoxicillin and Clarithromycin, which made up 76% (n=477) of the total



Distribution of responses

2-4 years	5-9 years	10-16 years
Hedonic scale		
		
VAS		
		

Results – Hedonic scale

- 2.4% did not understand this scale
  - 11/77 of those aged 2; 3/84 of those aged 3; 1/55 of those aged 5
  - Correlation to Did it taste OK?

Did it taste OK?						Overall agreement %
No	0	2.3	11.4	**27.5**	**58.8**	86
Yes	**57.7**	**26.3**	**12.7**	1.2	2.1	97
Not Sure	**14.0**	**15.5**	**43.7**	15.5	11.3	74

Results – Visual Analogue Scale

- 7.6% did not understand this scale
  - 22/77 of those aged 2; 14/84 of those aged 3; 4/83 of those aged 4; 5/66 of those aged 5; 2/51 of those aged 6
  - Correlation to Did it taste OK?

	VAS Score											
Did it taste OK?	0	1	2	3	4	5	6	7	8	9	10	Overall Agreement %
No	2	0	1	0	2	6	1	6	9	17	54	**95**
Yes	42	17	14	7	8	6	2	1	1	0	2	**94**
Not Sure	3	10	2	2	12	24	21	12	5	3	5	**72**

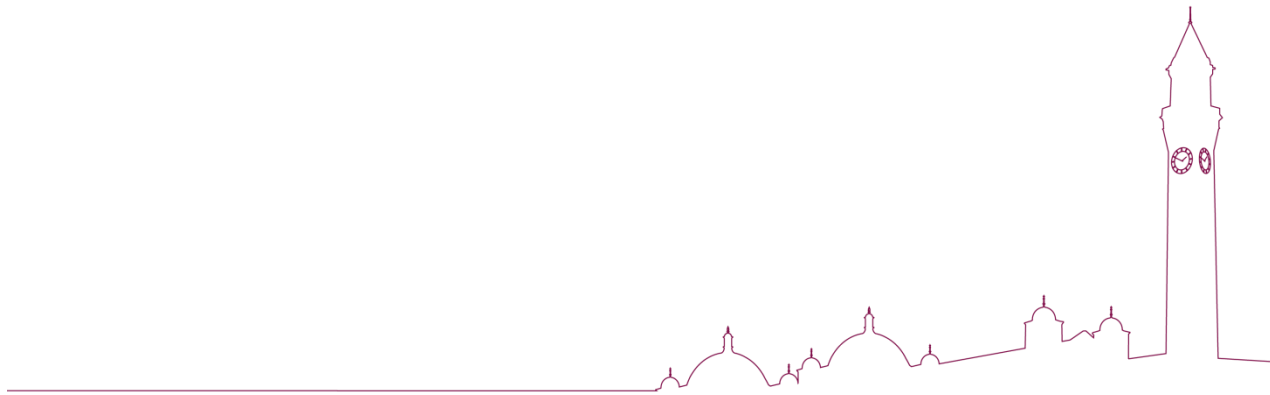
Results – Facial Expressions/ Behaviours

- Used in all populations
  - Correlation to Did it taste OK?
    - 96% agreement: stated that it tasted OK but showed non-acceptance
  - Correlation to hedonic
    - 85% agreement: scored from positive to neutral but showed non-acceptance
  - Correlation to VAS
    - 72% agreement: scored from positive to neutral but showed non-acceptance

Facial Expressions
Brow bulge
Eyes squeezed / shut
Nose wrinkled
Pursed lips

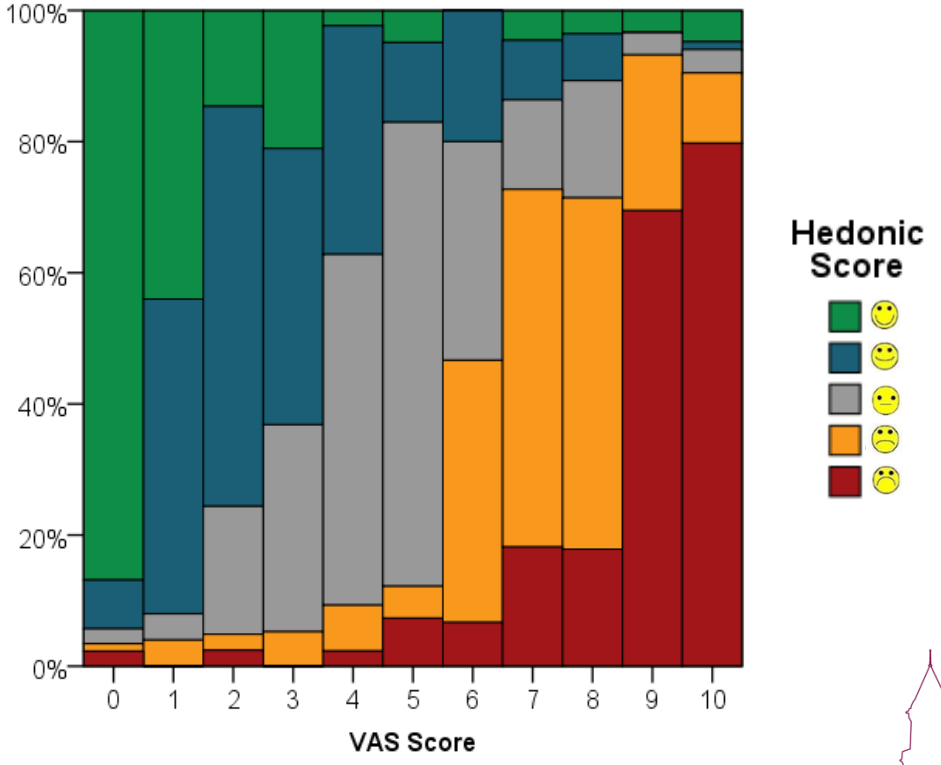
Behaviours (prior/during/post) administration
Refusal
Cries/ screams
Physical restraint
Voices resistance/ digust
Vomits/ spits out medicine

UNIVERSITY OF BIRMINGHAM



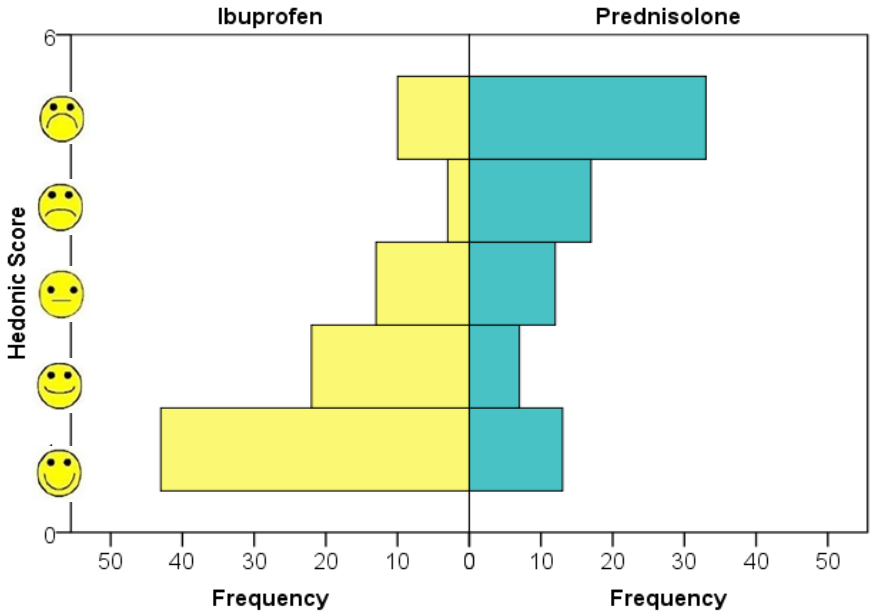
Completeness and Consistency

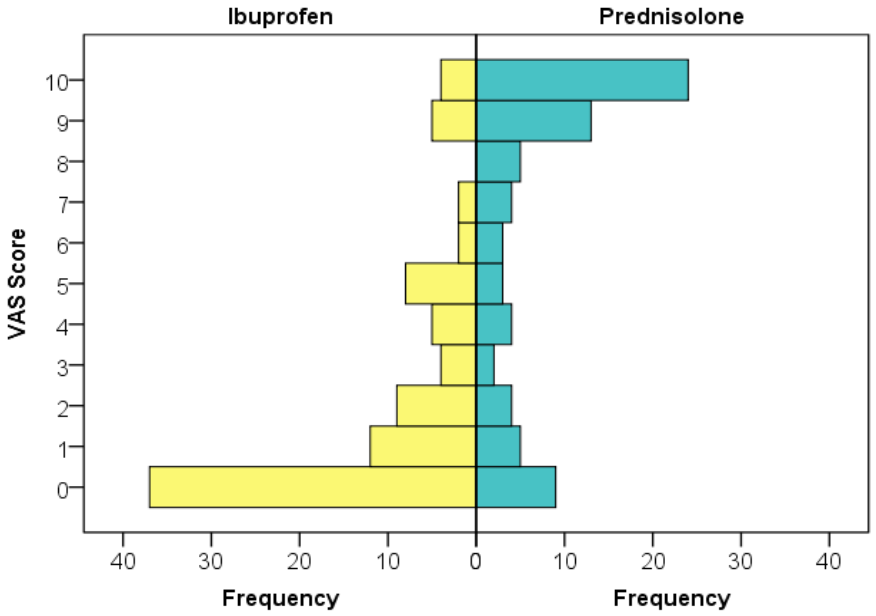
- Significant correlation observed between all 3 assessments ($p<0.001$) with the strongest correlation between the hedonic and VAS scores (Rho=0.84)
- Weakest correlation in younger patients (2-4 years), however the correlation coefficients were still reasonable ranging from 0.68 to 0.77



PRO and response reliability

Ibuprofen typically considered to be an acceptable medicine
Prednisolone typically considered to be unacceptable due to taste





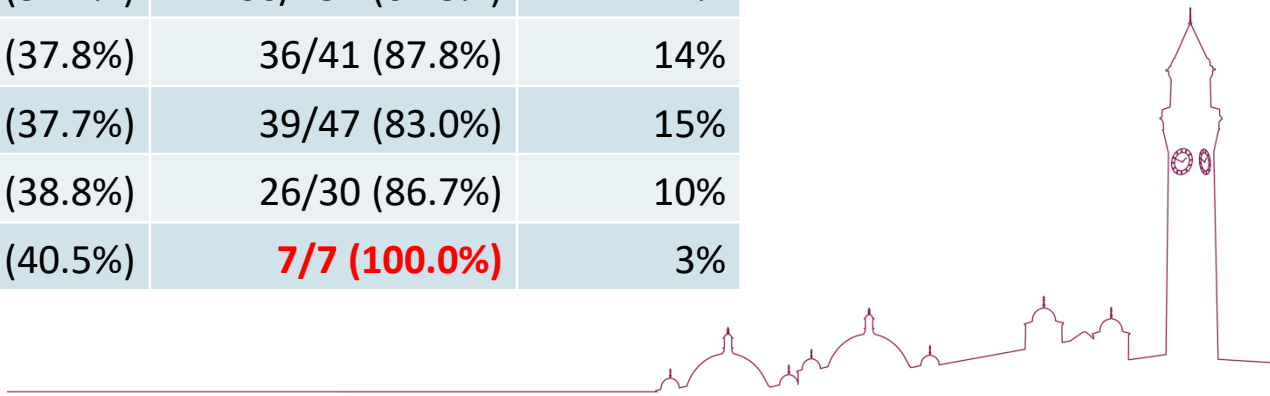
Researcher observations vs. PRO

	Cases Where Taste was Unacceptable if Behaviour was:		
Behaviour	Not Displayed	Displayed	Sensitivity
Voices disgust	160/515 (31.1%)	95/105 (90.5%)	37%
Eyes squeezed	131/460 (28.5%)	124/160 (77.5%)	49%
Nose Wrinkle	125/433 (28.9%)	130/187 (69.5%)	51%
Voices resistance	184/539 (34.1%)	71/81 (87.7%)	28%
Refusal	192/551 (34.8%)	63/69 (91.3%)	25%
Pursed Lips	168/505 (33.3%)	87/115 (75.7%)	34%
Cries/Screams	201/559 (36.0%)	54/61 (88.5%)	21%
Brow bulge	149/463 (32.2%)	106/157 (67.5%)	42%
Physical restraint	219/579 (37.8%)	36/41 (87.8%)	14%
Cries	216/573 (37.7%)	39/47 (83.0%)	15%
Spits out	229/590 (38.8%)	26/30 (86.7%)	10%
Vomits	248/613 (40.5%)	**7/7 (100.0%)**	3%

Associations between behaviours and unacceptable taste

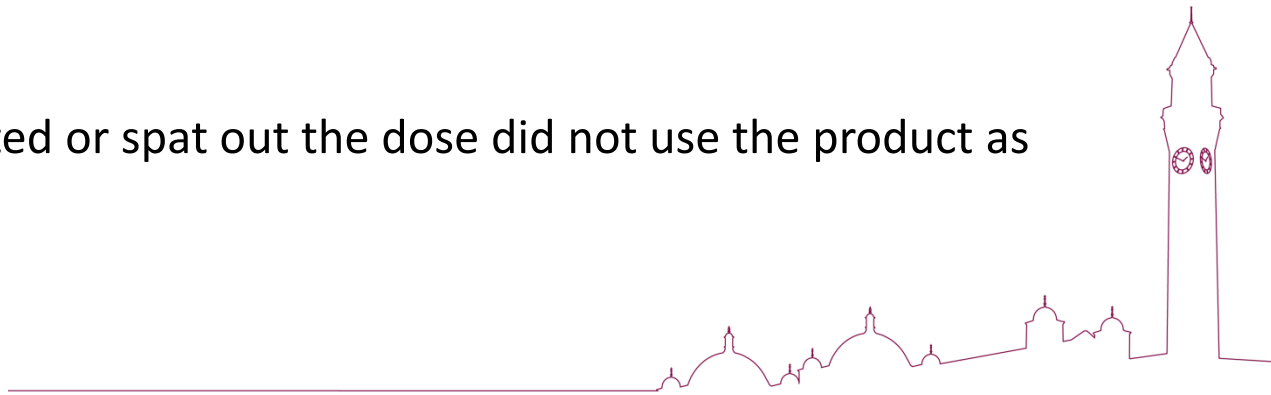
All of the behaviours were significantly associated with unacceptable taste, with $p<0.001$ for all factors except "vomits" ($p=0.007$)

UNIVERSITY OF BIRMINGHAM



Did the patient “use the medicinal product as intended (or authorised)”
= current regulatory definition of acceptability

- Prior to administration of the medicine
  - 1% of patients voiced resistance
  - 3% cried
  - 2% required physical restraint
- Following administration of the medicine
  - 0.8% voiced disgust
  - 1.8% vomited
  - 0.3% spat the dose out
  - 0.3% cried
- Only those that vomited or spat out the dose did not use the product as intended

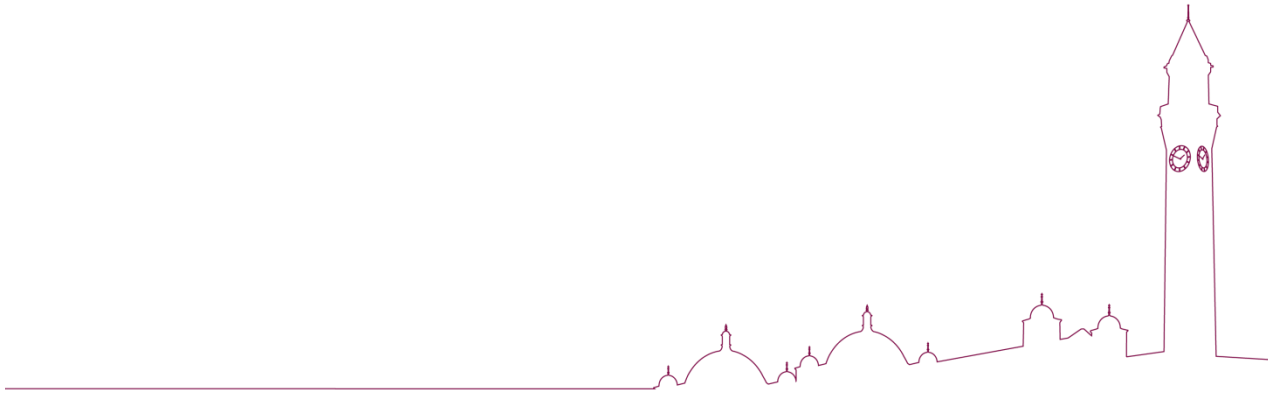


So what was the acceptability in the ACCEPT study?

Tool Used	% of doses acceptable
Hedonic scale	67.1
VAS	62.3
Did it taste OK? (Y/N/Not sure)	67.1
Researcher observations	86.9
Was the product taken as intended	97.9

The method used influences the acceptability rating of the product….

UNIVERSITY OF BIRMINGHAM



Acceptability.....

- In considering whether a medicine is acceptable it is essential to think about the definition used

- Is ***the ability to use as intended*** sufficient?

- What is the real measure of acceptability in administration of medicines to children?
- And what tool should we use to evaluate this?

UNIVERSITY OF BIRMINGHAM

Conclusions

- This is the first study to evaluate tools used in determining medicines acceptability in children and current data suggests that simple PROM measures are effective
- VAS and hedonic scales provided the best correlation with one another
- Hedonic scales are better suited to the youngest children
- There is considerable debate on the methodological aspects of effective testing of medicines involving children, whereby global regulatory guidance is needed to define “acceptability” within this population
- Further studies are needed to generate knowledge towards standardised methodology for acceptability testing

Acknowledgments

This work was conducted as part of the SPaeDD-UK project (Smart Paediatric Drug Development – UK, accelerating paediatric formulation development)which is co-funded by Innovate UK and industrial partners: Astra Zeneca, BMS, GlaxoSmithKline, Juniper and Pfizer.

http://www.paediatricscienceuk.com

The authors would like to thank all participants and hospitals for their participation in this study.

Thank you for listening!