THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Steve Cunningham, et al, for the Bronchiolitis of Infancy Discharge Study (BIDS) group. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *Lancet* 2015; **386:** 1041–48.

Oxygen saturation targets in infants with bronchiolitis (BIDS); a double-blind, randomized, equivalence trial

Cunningham et al

Supplementary Data

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Additional methods data

Centres recruiting

Recruitment was in five centres in season one (Aberdeen, Dundee, Edinburgh, Glasgow and Kilmarnock) with three additional centres added in season two (Bristol, Exeter, Truro). The distribution of standard and modified oximeters was similar within centres and between seasons.

Method for imputing missing data:

Missing data: If a date of cough resolution was known, it was used. If it was known that the cough resolved, but the precise date was unknown, a random value was chosen between the date that the cough was last known to be present and the date of the follow up when it was found that the cough had stopped. The random value was chosen from infants in the same treatment group whose cough stopped in a similar time frame. If it was known that the cough had not resolved by 6 months, the date of cough was predicted by taking a random value from a uniform distribution capped from 180 days to 200 days (upper cap based on the observations by M. Shields[1]). If it was known that the cough had not stopped by the last follow up done, but the infant was not followed to 6 months, then a random value was chosen from a uniform distribution with the lower cap was pegged to the last known follow up time (i.e. 7, 14, 28 days) instead of 180 days. This process was repeated 100 times, and the analysis done on each dataset. The mean values for the estimate of the median, and the estimates of the CI limits were used. If 100 repetitions did not produce a stable estimate, then this number was to be increased, but this was not necessary.

Limits of Equivalence

There is no published evidence to support the limit of equivalence for cough resolution. We therefore sampled the expert opinion of Ten Consultant Paediatricians who contribute to the General Paediatric Service at the Royal Hospital for Sick Children, Edinburgh (and who provide clinical management of infants with bronchiolitis). They were provided with information on the mean time to cough resolution (from Plint et al[2]) and asked, in open-ended unbiased manner (no prompts) to provide their expert opinion on the ranges around this value. A variance of +/- two days was thus identified. The same equivalence limit of two days in either direction was used for time back to normal. For time to return to satisfactory feeding we used a typical infant feed interval of four hours as equivalence.

Figure A1 Adjusted algorithm for modified oximetry (true versus altered)

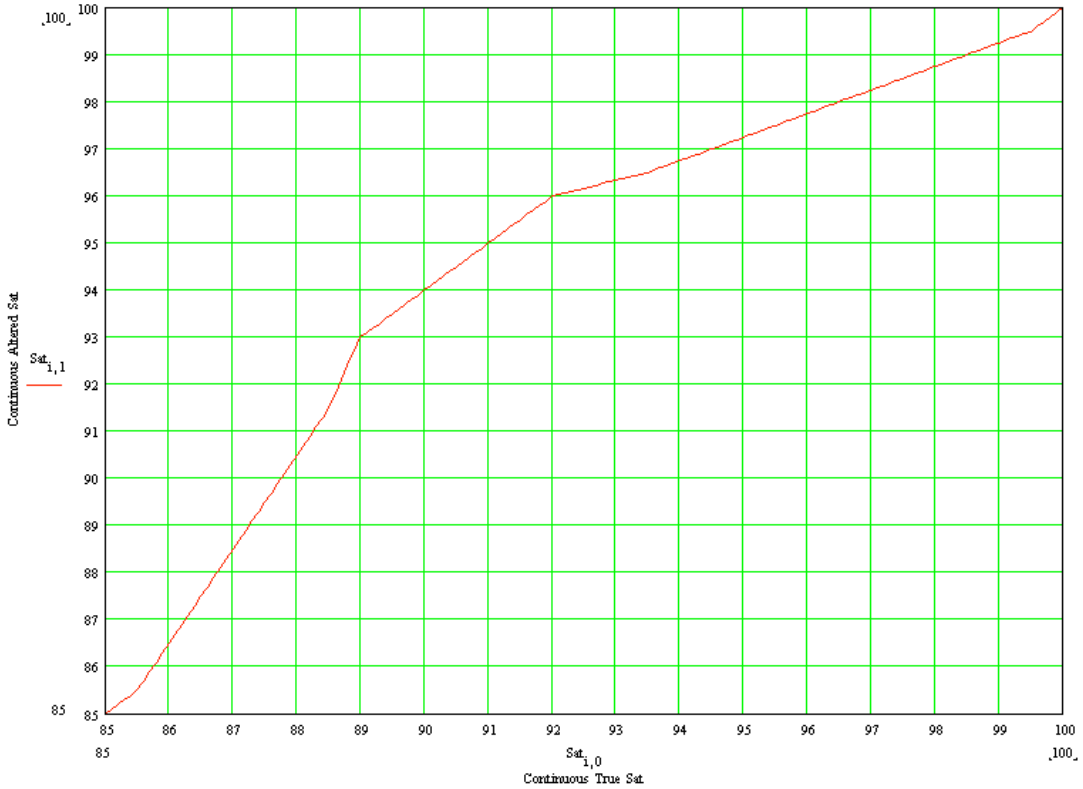

Table A1

Table of primary outcome results for per protocol population

	Standard group	Modified group	Median difference
Time to resolution cough (days)	15·0 (10·0 to 43.0); n=297	16·0 (10·0 to 44·0); n=279	0·0 (–1 to 2)

Table A2

Time to resolution of cough by subgroup analysis demonstrated no notable differences with wide confidence intervals

Subgroup analyses:	Standard (median, IQR, n)	Modified (median, IQR, n)	Median Difference	Upper and Lower 95% CI	All (median, IQR, n)
Time to cough resolution: smoking household (days)	15.0 (10.0, 35.0) n=129	13.0 (9.0, 34.0) n=125	1.0	-2,3	14.0 (10.0,35.0)
non-smoking household (days)	15.5 (10.0, 47.0) n=166	16.0 (10.0, 44.0) n=168	0	-2,2	16.0 (10.0,45.0)
Time to cough resolution: onset illness ≤3 days (days)	13.0 (10.0, 32.0) n=143	14.0 (10.0, 33.0) n=134	0	-2,2	14.0 (10.0,32.0)
≥ 4 days (days)	18.0 (10.0, 48.0) n=153	16.0 (9.9, 44.0) n=157	1.0	-1,3	17.0 (10.0,47.0)
Time to cough resolution: antibiotics yes	12.0 (9.0,65.0) n=57	15.0 (10.0,43.0) n=52	0	-4,5	13.0 (10.0,55.0)
Antibiotics no	16.0 (10.0,39.0) n=239	15.0 (9.0,40.0) n=241	1	-1,2	15.5 (10.0,39.5)

Table A3 : Adverse Events (AE are reported on ITT allocation)

(a) Adverse Events: Number of events by severity

Parameter	Category	Standard pulse oximeter (N=308)	Modified pulse oximeter (N=307)
Number of AEs	Overall	89	84
Number of respiratory AEs by severity	Mild	28	25
	Moderate	17	20
	Severe	7	9
Number of gastrointestinal AEs by severity	Mild	7	8
	Moderate	0	5
	Severe	0	0
Number of other AEs by severity	Mild	19	12
	Moderate	8	2
	Severe	2	0

(b) Adverse Events by category (>3 events). Each SAE had a corresponding AE.

	Standard	Modified
Total Events (number of infants)	89 (87)	84 (81)
Increased chesty/bronchiolitis	25 (25)	23 (23)
Cough	16 (15)	21 (20)
Wheeze	4 (4)	3 (3)
Pyrexia	5 (5)	2 (2)
Ear Infection	8 (8)	3 (3)
Decreased feeding	4 (4)	4 (4)
Diarrhoea and/or vomiting	4 (4)	10 (9)
Eye Infection	3 (2)	3 (3)
Eczema/rash/dry skin	4 (4)	1 (1)
Other Respiratory	7 (7)	8 (8)
Other	9 (9)	6 (6)

Table A4 Additional Therapies in Hospital

	Standard	Modified	All
Need for supplemental oxygen	223 (73.1%) n=305	169 (55.6%) n=304	392 (64.4%) n=609
Use of nasogastric tube feeding	141 (46.2%) n=305	125 (41.3) n=303	266 (43.8) n=608
Use of intravenous fluids	29 (9.5%) n= 305	28 (9.2%) n= 304	57 (9.4%) n=609
Use of antibiotics	44 (14.4%) n=305	39 (12.8%) n=304	83 (13.6%) n=609
Use of Salbutamol	25 (8.2%) n=305	21 (6.9%) n=304	46 (7.6%) n=609

Table A5 Parent Anxiety Scores

	Standard (median, iqr)	Modified (median, iqr)	All (median, iqr)	Mean Difference (95% CI)	p
Anxiety Score at admission	7 (4,10) n=298	7 (4,11) n=298	7 (4,11) n=596		
Anxiety Score 7 days	4 (2,8) n=266	4 (2,7) n=265	4 (2,7) n=531	-0.18 (-0.75,0.39)	0.53
Anxiety Score 14 days	3 (1,6) n=256	3 (1,5) n=252	3 (1,5) n=508	0.00 (-0.57,+0.56)	0.99
Anxiety Score 28 days	3 (1,7) n=259	3 (1,6) n=252	3 (1,6) n=511	-0.27 (-0.88,0.34)	0.39

Table A6 Lead carer loss of hours to usual activities

	Standard	Modified	All
Lead carer (=mother)	288 (95.4%) n=304	283 (93.4%) n=303	571 (94.4%) n=607
Lead carer hours missed days 0-7 days (median, iqr)	58.3 (25.1, 96.5) n=304	44.8 (24.6, 72.0) n=302	49.3 (24.8, 85.5) n=606
Lead carer hours missed days 0-14 days (median, iqr)	62.3 (25.7, 97.3) n=304	45.0 (25.3, 72.7) n=303	50.9 (25.6, 85.5) n=607
Lead carer hours missed days 0-28 days (median, iqr)	63.4 (27.5, 101.2) n=304	47.3 (25.7, 76.4) n=303	53.4 (26.3, 89.3) n=607

Table A7 Number (%) of infant return to childcare

	Standard	Modified	All
Attending childcare at time of randomisation	58 (19.1%) n=303	41 (13.6%) n=301	99 (16.4%) n=604
Well enough to attend childcare from 0 -7 days	24 (48.0%) n=50	18 (52.9%) n =34	42 (50.0%) n=84
Well enough to attend childcare from 7 -14 days	28 (54.9%) n=51	22 (62.9%) n =35	50 (58.1%) n =86
Well enough to attend childcare from 14 -28 days	35 (68.6%) n =51	19 (57.6%) n =33	54 (64.3%) n = 84

The Bronchiolitis of Infancy Discharge Study (BIDS) Group

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Database programming and data management

Ronald Harkness, Samantha Thomas, Allan Walker.

References

1. Shields MD, Thavagnanam S. The difficult coughing child: prolonged acute cough in children. *Cough* 2013; **9**(1): 11.
2. Plint AC, Johnson DW, Patel H, et al. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 2009; **360**(20): 2079-89.