

# Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation

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## Scientific summary

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# Scientific summary

## Objectives

Acute respiratory infection is commonly associated with low blood oxygen levels (hypoxaemia). Treatment includes the use of supplemental oxygen to regain normal blood oxygen levels (normoxaemia) until recovery has taken place. The ability to detect hypoxaemia has increased with the introduction of pulse saturation oximetry, but this has also created uncertainty about the clinical impact of incremental differences in oxygen saturation measurements. Recommendations for target oxygen saturation below which oxygen is supplemented vary by condition, age and health-care setting: 90% in developing nations; 90–94% in developed nations. There are no randomised trials of target oxygen saturation targets in acute respiratory infection. Bronchiolitis is a common acute viral lower respiratory tract infection of infants, and the different recommended target oxygen saturations for this condition represent an exemplar of the need for evidence: the American Academy of Pediatrics recommends  $\geq 90\%$ ; the Scottish Intercollegiate Guidelines Network recommends  $\geq 94\%$ . There is no evidence to support either recommendation.

Our hypothesis was that infants with acute bronchiolitis would have equivalent clinical outcomes whether they were managed to maintain target oxygen saturation of  $\geq 90\%$  or  $\geq 94\%$ .

The primary outcome was time to resolution of cough, which we considered would be equivalent with a maximal variance of 2 days either way.

Central to the study aims was also the need to demonstrate safety and clinical comparability through secondary outcomes: time to back to normal, time to back to adequate feeding, hospital-based parameters, parental anxiety and parental loss of activity. The cost-effectiveness of the intervention was also investigated.

## Methods

This was a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial conducted in the UK (eight sites).

Infants were eligible for the trial if they were  $> 6$  weeks and  $\leq 12$  months of age (corrected for prematurity), and presented to a participating hospital emergency department (ED)/acute assessment area (AAA) with a clinical diagnosis of bronchiolitis made by acute receiving medical staff, and required admission to hospital for supportive care.

Infants were excluded if they (1) were born preterm ( $< 37$  weeks) and had received oxygen therapy in the previous 4 weeks, (2) had haemodynamically significant congenital heart disease, (3) had cystic fibrosis or known interstitial lung disease or (4) had documented immune function defect.

## Intervention

The intervention was randomisation to an oxygen saturation monitor used to target oxygen saturation supplementation (Masimo Corporation Limited, CA, USA); all other care provided was as usual. Infants were allocated 1 : 1 to trial intervention.

Following consent and randomisation in an EE/AAA, infants were allocated to one of two groups for their inpatient stay:

- Standard care: standard oximeters measured and displayed oxygen saturation as usual.
- Modified care: modified oximeters measured oxygen saturation as usual but displayed an altered percentage. The display for measured values of 85–100% oxygen saturation was altered so that at measured 90% oxygen saturation the monitor would display 94%; values above and below this point were smoothed.

Infants could be eligible for discharge once oral feeding was re-established and continuously monitored oxygen saturation was displayed as  $\geq 94\%$  in room air for a minimum of 4 hours including a period of sleep.

All clinicians caring for infants, parents and the study staff involved in day-to-day trial management and outcome assessment remained blinded to study allocation.

## Main outcome measures

The primary outcome was time to no cough. Airway inflammation may be induced by hypoxia, exacerbating duration of symptoms, of which cough is the sign most readily recognisable by parents. Cough duration was ascertained by standardised telephone contact with the primary caregiver at 7, 14 and 28 days and at 6 months. An estimate of 544 participants, rounded to 600 for dropouts and non-compliance, was made by assuming that there would be no difference between the treatment groups, with a common standard deviation of 8.3 days. Equivalence limits of 2 days either way were considered clinically appropriate.

We also looked for equivalence of time of parental perspective of back to normal (2-day variance), time to re-establish adequate feeding (4-hour variance) and measurement of oxygen saturation at 28-day visit in season 1 only (1% variance).

We looked for differences in interventions for the time to fit for discharge and actual discharge, health-care reattendance (primary care, ED, readmission), change in parental anxiety score, time to return to work/usual activity for parents, family and societal costs, health-care costs, and heart rate and respiratory rate at discharge. Data were collected onto case report forms by study staff at admission, at discharge, at 7, 14 and 28 days and at 6 months.

We estimated the incremental cost and effectiveness of the 90% compared with the 94% oxygen saturation discharge procedure in terms of health, social care and societal costs as well as the clinical and quality-of-life outcome measures. The economic analysis also took into consideration the seasonality of the disease and the economic impact of this with regard to the availability of ward space/beds during peak hospital times.

All analyses were intention to treat (ITT). The primary outcome was the number of days until resolution of cough from randomisation, estimating the median difference and the 95% confidence intervals (CIs) for the difference. The primary outcome was considered firmly concluded only with a per protocol analysis in agreement. Missing values for the primary outcome (and time back to normal) were imputed where it was known that the cough had resolved, but not the precise date. Uniform distributions enabled estimates of

time to no cough in those still coughing, with follow-up < 6 months or not resolved by 6 months with 100 repetitions. Sensitivity analysis on complete-case analysis was also done.

Cox proportional hazards regression was used to estimate the treatment effect for times to (1) fit for discharge, (2) actual discharge, (3) no supplemental oxygen, (4) readmission to hospital. Binary logistic regression reported as adjusted odds ratios and Poisson regression and analysis of covariance models were used to test differences in health-care reattendances and parental anxiety at days 7, 14 and 28 and at 6 months. Mean differences were used for heart rate and respiratory rate at discharge.

The economic evaluation examined whether or not the modified arm was cost-effective compared with the standard arm. Measurements of costs to the NHS and social care were combined with the primary outcome to create a cost-effectiveness analysis. The seasonality of the disease was also considered by taking into account opportunity costs of hospital bed displacement during peak winter seasons. The economic evaluation used the mean time to cough resolution by area under the curve. The resource use is from the perspective of the NHS and personal social services, with unit costs based on 2012/13 values. Missing data are handled through multiple imputation.

## Results

The trial opened to recruitment in two winter seasons: season 1 (3 October 2011 to 30 March 2012) and season 2 (1 October 2012 to 29 March 2013). Season 1 was a quieter respiratory syncytial virus (RSV) season than expected, so three additional sites were opened for season 2. The trial completed recruitment on schedule and to target on 29 March 2013.

In total, 1643 infants were screened for eligibility; of these, 451 were ineligible (317 were under 6 weeks of age). Of the 1192 eligible infants, the parents of 722 were approached for consent and 615 infants were randomised, 308 to standard care and 307 to modified care. A total of 584 infants (95%) reached the end of the study at 6 months.

Baseline characteristics were similar between groups, with a mean age of 21 weeks in both groups. In the modified care group there were more preterm infants (16.15% vs. 10.1%) and fewer males (54.1% vs. 60.4%). There were fewer RSV-positive infants in the standard care group (69.8%) than in the modified care group (76.3%). Length of illness and measures of heart rate, respiratory rate, oxygen saturation, previous health contacts and household smokers were otherwise similar.

The primary outcome was equivalent. Time to resolution of cough was 15 days in both standard and modified care groups. The median difference was 1 day (benefit to modified) with the 95% CI of the difference -1 day to 2 days. Both the complete-case analysis of the ITT population and the per protocol analysis demonstrated a median difference of 0 days with 95% CI of the difference -1 day to 2 days.

Oxygen saturation measured at 28 days was also equivalent, with a mean difference of 0.11% (95% CI -0.35% to 0.57%), well within the prespecified 1% variance.

Time to re-establish adequate feeding was sooner (median 19.5 hours) in the modified care group than in the standard care group (24.1 hours). The median difference was 2.7 hours (95% CI -0.3 hours to 7.0 hours). This falls outside the prespecified equivalence limits of  $\pm 4.0$  hours; therefore, we cannot infer equivalence. The 95% CI overlaps zero, so we cannot conclude that there is a difference either. A post-hoc analysis gave a hazard ratio of 1.22 (95% CI 1.04 to 1.44;  $p$ -value = 0.015) with a survival curve indicating that any difference between the groups was in the time period following the median time to return adequate feeding. Thus, we have not proved equivalence. If any difference does exist, it goes in favour of the modified care group.

Parents considered that their child had returned to normal after a median of 12.0 days in the standard care group and 11.0 days in the modified care group. The median difference was 1.0 day (95% CI 0.0 days to 3.0 days). This falls outside the prespecified equivalence limits of  $\pm 2.0$  days; therefore, we cannot infer equivalence. The 95% CI just touches zero, so there is some evidence that there was a small difference in favour of the modified care group. A post-hoc analysis gave a hazard ratio of 1.19 (95% CI 1.00 to 1.41;  $p$ -value = 0.043), providing some evidence that the infants in the modified care group returned to normal faster than those in the standard care group, and the survival curve indicates that any difference between the groups was in the time period following the median time to return to normal. Thus, we have not proved equivalence. If any difference does exist, it is in favour of the modified care group. The benefit to the modified care group was not expected and is modest overall.

As may have been expected, infants in the modified care group (median 30.2 hours) were fit for discharge sooner than those in the standard care group (median 44.2 hours), with a hazard ratio estimate of 1.46 (95% CI 1.23 to 1.73;  $p$ -value < 0.001), and were discharged sooner too (modified care 40.9 hours, standard care 50.9 hours; hazard ratio 1.28, 95% CI 1.06 to 1.50;  $p$ -value < 0.003). Oxygen supplementation was required by fewer infants (55.6%) and for a much shorter duration (median 5.7 hours) in the modified care group than in the standard care group (73.1% of infants and medication duration of 27.6 hours) with a hazard ratio of 1.37 (95% CI 1.12 to 1.68;  $p$ -value < 0.002).

Overall, safety concerns arising from adverse event reporting were no greater in the modified care group than in the standard care group. Two deaths, both in the standard care group, were unrelated to the study intervention. There were slightly more high-dependency unit admissions in the modified care group (13 admissions in 12 infants) than in the standard care group (eight readmissions in eight infants), but this was within clinical variability of the condition. At time of discharge, heart rate (hazard ratio -1.16;  $p$ -value = 0.37) and respiratory rate (hazard ratio 0.09;  $p$ -value = 0.88) were very similar between groups. There were similar numbers of readmissions within the first 7 days, with eight readmissions in six infants in the standard care group and five readmissions for five infants in the modified care group; however, by 28 days the number of readmissions was higher in the standard care group (26 readmissions in 23 infants) than in the modified care group (12 admissions in 12 infants). There were no significant differences in reattendance at health-care facilities at any time point after discharge between the groups. Overall, there were 35 serious adverse events (SAEs) in 32 infants in the standard care group and 25 SAEs in 24 infants in the modified care group.

Parental anxiety scores were not significantly different at follow-up. Contrary to expectation, primary carers lost less time to usual activities in the modified care group than in the standard care group at all time points; this was most marked up to 14 days (standard care 62.3 hours lost compared with modified care 45.0 hours lost).

The economic analysis shows that the modified therapy dominates the standard therapy when using conventional economic evaluation cost-effectiveness criteria. The economic analysis reveals that total NHS costs are £290 lower in the modified arm, a non-significant difference. The difference in favour of the modified arm further increases when patient costs are included within a societal perspective. The economic analysis shows little uncertainty regarding the likelihood of the modified protocol being cost saving compared with the standard protocol; however, there is greater uncertainty regarding any improvement on reduction in days to cough resolution. The modified protocol is the dominant option, with a likelihood of being cost-effective of 91.5%, even when society is willing to pay zero for the health improvements.

## Conclusions

This study identifies that it is as clinically effective to manage acute viral bronchiolitis in infants to a modified target oxygen saturation of  $\geq 90\%$  as a standard target oxygen saturation target of  $\geq 94\%$ . The study found no safety concerns associated with the use of the lower modified oxygen saturation target, and there was no additional burden on primary care or families from earlier discharge. Infants under 6 weeks of age will require a personalised approach to safe oxygen saturation at discharge.

## Recommendations for research

The trial results raise the following questions:

- Is 90% an appropriate lower threshold for oxygen saturation in the management of acute respiratory infection in children?
- How clinically effective and cost-effective is community-based supplemental oxygen provision at home for infants with acute bronchiolitis who have been discharged from hospitals that have adopted a target oxygen saturation of 90%?
- How clinically effective and cost-effective is continuous or intermittent oxygen saturation monitoring in improving outcomes in children with acute bronchiolitis managed to a target oxygen saturation of 90%?
- What are safe oxygen saturation targets for the management of infants with acute bronchiolitis in primary care and emergency department discharge?

## Trial registration

This trial is registered as ISRCTN28405428.

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