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**RANDOMIZED CONTROLLED TRIAL OF ASTHMA RISK WITH PARACETAMOL USE IN
INFANCY – A FEASIBILITY STUDY**

Condensed Title:

ASTHMA WITH PARACETAMOL IN INFANCY – FEASIBILITY STUDY

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ABSTRACT

Background: There is non-experimental evidence that paracetamol (acetaminophen) use may increase the risk of developing asthma. However numerous methodological issues need to be resolved before undertaking a randomized controlled trial to investigate this hypothesis.

Objective: To establish the feasibility of a randomized controlled trial of liberal paracetamol as usually given by parents/guardians versus a comparator (restricted paracetamol in accordance with WHO guidelines, ibuprofen or placebo), and childhood asthma risk.

Methods: Questionnaires were completed by parents/guardians of infants admitted to Wellington Hospital with bronchiolitis to assess views about comparator treatments. Subsequently infants of parents/ guardians who provided informed consent were randomized to restricted or liberal paracetamol use for 3 months with paracetamol use recorded.

Results: Of 120 eligible participants, 72(60%) parents/guardians completed the questionnaire. Ibuprofen, restricted paracetamol and placebo were acceptable to 42(58%), 29(40%) and 9(12%) parents/guardians respectively. 36(30%) infants were randomized to restricted or liberal paracetamol. Paracetamol use was greater for the liberal versus restricted group for reported [Hodges-Lehmann estimator of difference 0.94 mg/kg/day (95% CI 0.2 to 3.52), $P=0.02$] and measured use [Hodges-Lehmann estimator of difference 2.11 mg/kg/day (95% CI 0.9 to 4.18), $P=0.004$]. The median reported and measured use of paracetamol was 2.0-fold and 3.5-fold greater in the liberal versus restricted group.

Conclusions and Clinical Relevance: Although separation in paracetamol dosing is likely to be achieved with a liberal versus restricted paracetamol regime, ibuprofen is the preferred comparator treatment in the proposed RCT of paracetamol use and risk of asthma in childhood.

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KEY WORDS:

asthma; acetaminophen; paracetamol; infants; bronchiolitis; feasibility; comparator arm

ABBREVIATIONS

RCT: Randomized Controlled Trial; WHO: World Health Organization

INTRODUCTION

The reasons for the increase in the worldwide prevalence of asthma in the past 50 years and the large variations in prevalence between different countries are unknown [1-3]. This has led to the investigation of novel risk factors in the pathogenesis of asthma and its severity. One such risk factor is paracetamol (acetaminophen), for which there is substantial observational evidence that its use may be a risk factor for the development of asthma and also an increase in its severity once established [4-7]. An association between asthma and exposure to paracetamol has been shown in the intrauterine environment [8-13], infancy [14], later childhood [15] and adult life [16-19]. Biologically plausible mechanisms for these associations include paracetamol use depleting circulating and airway glutathione levels leading to increased oxidant-induced inflammation with direct or indirect enhancement of Th2 cell polarization [20-25], and neurogenic inflammation of the airways through stimulation of the transient receptor potential ankyrin-1 (TRPA-1) cation channel, which mediates a non-eosinophilic inflammatory response [26].

One published randomized controlled trial (RCT) has investigated the effect of paracetamol use for fever and asthma outcomes in childhood [27, 28]. This study randomly assigned over 80,000 children aged between 6 months and 12 years of age to either paracetamol or one of two doses of ibuprofen for treatment of a febrile illness [27]. The asthma outcomes paper [28] is a secondary analysis of a sub-group of 1,879 children who were on some form of asthma treatment. The outcomes for this secondary analysis were hospitalization for asthma or an outpatient visit for asthma. The sub-group analysis, which was not apparently pre-specified in the primary study, found an association between paracetamol use and attendance as an outpatient for asthma. There were 32/632 (5.1%) randomized to paracetamol and 37/1247 (2.6%) randomized to ibuprofen, who attended outpatients due to asthma, resulting in a relative risk, paracetamol compared to ibuprofen, of 1.71 (95% CI 1.07 to 2.71, $P=0.027$). It is difficult to rule out the possibility that this association is a result of multiple statistical testing in a post-hoc sub-group analysis. As this study did not have a placebo arm it was not possible to determine whether the difference was due to a harmful effect of paracetamol, or a protective effect of ibuprofen.

A robust RCT is required to directly investigate whether paracetamol increases the risk of asthma in childhood. The number of participants needed for a such a trial could be reduced by recruiting those who are at higher risk of developing asthma in future life. One such group is infants who are admitted to hospital with bronchiolitis, who have a 40% risk of subsequent childhood asthma, defined as the symptom of wheeze occurring in the last 12 months, by the age of 3 years [29]. A two-arm study with a total sample size of 1,126 is needed to detect a 20% risk-reduction in asthma (from 40% to 32%), with 80% power and a type I error rate of 5%. Assuming a 20% drop-out rate this would require recruitment of 1,350 infants. New Zealand is an ideal country to undertake such a study due to the high rates of administration of paracetamol in infancy and childhood [14, 15], and the high prevalence of childhood asthma [30,31]. However, before undertaking such a large multi-center RCT it would be necessary to undertake a study of its feasibility.

The study reported in this paper addresses three key feasibility issues for such a RCT:

1. The proportion of parents or guardians who would be likely to enroll their child in a proposed large RCT, with randomized assignment to liberal paracetamol use (as parents/guardians would normally give it to their child) and comparator regime such as placebo, ibuprofen, or restricted paracetamol use (use of paracetamol only in accordance with WHO guidelines: i.e. only if the infant's temperature was $\geq 38.5^{\circ}\text{C}$ or in the setting of marked pain or other discomfort). [32]
2. The preference of parents or guardians for the comparator treatments.
3. The magnitude of the difference in paracetamol administration achieved for a liberal versus restricted paracetamol regime.

METHODS

Participants and Study design

This feasibility study was conducted in two parts at Wellington Regional Hospital, New Zealand. Ethical permission was obtained from the New Zealand Southern Health and Disability Ethics Committee. Eligible participants for Module One were the parents/guardians of infants aged between 6 and 24 months and admitted with bronchiolitis, between 29 April 2013 and 27 September 2013. Eligible participants for Module Two were the infants themselves along with the parents or guardians who had completed Module One. In the absence of an international standardized diagnosis of bronchiolitis [33, 34] the clinical diagnosis used was tachypnea, defined as a respiratory rate $\geq 50/\text{min}$ if 6 to 12 months of age or $\geq 40/\text{min}$ if between 13 and 24 months, in association with wheeze or crackles [35]. Where possible randomization occurred within 24 hours of hospital admission, however any participants admitted over weekends or public holidays were randomised the next working day. Potential participants were not considered for Module Two if the infant had a known sensitivity to paracetamol, history of liver disease, the parents or guardians were unwilling to limit the use of paracetamol during the trial period, were unable to be followed up by

telephone, or for any other reason which, at the investigator's discretion, was believed to present a safety risk or impact the feasibility of the study or the study results.

Module One

After written informed consent procedures Module One participants completed a questionnaire designed to explore parental or guardian attitudes towards participating in the proposed RCT for up to two and a half years, and towards each of the possible comparator arms. They were also asked if they would be interested in enrolling their infant into the feasibility study RCT for 3 months with an equal, 50%, chance of allocation to the liberal or restricted paracetamol administration group.

Module Two

The feasibility study RCT was designed to estimate the difference in paracetamol administration between infants randomized to liberal or restricted paracetamol regimens, for the treatment of symptoms during both admission and for 3 months after discharge. The 3-month follow-up period was selected to enable recruitment and follow-up of a cohort of infants from a full bronchiolitis season within the one year period defined by the feasibility study.

Procedures

Module One

Study investigators identified potential study participants each week-day morning from children admitted to the Pediatric Inpatient Service at Wellington Regional Hospital. The parents or guardians of potential participants were approached by a study clinician and given an information sheet for Module One. Following written informed consent procedures, a study clinician completed the questionnaire with each participant. Six parents or guardians of potential participants who had been discharged home were contacted by telephone, and agreed to receive study information. Two of these subsequently consented verbally prior to completion of the questionnaire over the telephone; one was visited at home where written

consent was obtained prior to completion of the questionnaire; and three participants returned self-completed copies of consent and questionnaire.

Responses regarding potential participation in the proposed RCT were recorded on a Likert scale (1: 'very likely' to 5: 'very unlikely'). Parental attitudes towards the possible comparator groups of placebo, ibuprofen, or restricted paracetamol, were also recorded on a Likert scale (1: 'very acceptable' to 5: 'totally unacceptable').

Module Two: Feasibility RCT

Participants who expressed interest in the feasibility RCT were given an information sheet and an opportunity to discuss what the study entailed. Following written informed consent, infants were randomized with equal probability by a computer-generated randomization sequence, by the study statistician, to one of two treatment strategies for 3 months: liberal or restricted paracetamol administration. The study statistician placed the randomization codes in sealed, sequentially numbered envelopes which were opened only at time of randomization. The liberal paracetamol group was advised to administer paracetamol whenever the parent or guardian (or nursing staff or doctors during the inpatient stay), considered it necessary to relieve fever or discomfort, within current safe medication dosing guidelines [36]. The restricted paracetamol group was asked to administer paracetamol only if the infant's temperature was $\geq 38.5^{\circ}\text{C}$ or in the setting of marked pain or other discomfort in accordance with World Health Organization (WHO) recommendations [32].

The 3-month follow-up period started immediately after randomization during the infant's hospital inpatients stay. Parents/guardians in both groups were given a study diary to record the date, time, dose and reason for all paracetamol administrations, as well as any 'over-the-counter' medications which contained paracetamol, or ibuprofen. Paracetamol dosage for each child was calculated according to their weight (15mg/kg/dose) and this dose, along with the maximum daily dose (four doses in 24 hours), was written on each bottle and on the front

of each study diary. 200ml of paracetamol (120mg/5ml) was initially dispensed to all parents or guardians with arrangements made for further paracetamol to be supplied by the researchers as required. Participants in the restricted paracetamol group received instruction on accurate temperature measurement for their child and were supplied with a digital thermometer (*Protec Digital Thermometer*, distributed by Protec Solutions Limited, Wellington, New Zealand) for axillary temperature measurements. Restricted group participants were asked to record the child's temperature before giving paracetamol and to avoid giving it if the WHO criteria were not met.

Scheduled telephone follow-up with the parents or guardians occurred one week after study enrolment and monthly thereafter for 3 months. The information collected at follow-up included adverse events, illness, use of study and other medications. At 3 months all study diaries and remaining study paracetamol were collected during a home visit.

Analysis of data from the study diaries included calculation of the amount (mg) of paracetamol reported administered to each child. Paracetamol administration was also calculated by comparing the weight dispensed with returned bottles of paracetamol (measured use). Discrepancies in measured volumes compared to diary data were reviewed and accounted for where possible. Occasions when parents or guardians in the restricted paracetamol group gave paracetamol to their infants outside of the WHO criteria were recorded.

Statistical analysis

Module One

The proportion of children whose parents/guardians who agreed to complete Module One and Module Two respectively was calculated by the total number of those enrolled out of the total number of eligible admissions, with appropriate binomial confidence intervals for a

proportion. In a similar way the relative acceptability of the comparator treatments is estimated from the answers given by the parents/guardians in the questionnaire.

Module Two

The main outcomes were reported and measured paracetamol administration expressed as mg/kg/day. The pre-specified analysis plan was to use a t-test to estimate the difference in paracetamol administered between the liberal and restricted paracetamol administration regimes. In the event the distribution of the paracetamol administration variables did not meet normality assumptions and we chose to estimate the difference between the randomized groups by a Wilcoxon test with a Hodges-Lehmann estimator of the difference in dose with appropriate confidence intervals. Simple data descriptions are also shown for the total reported and measured administration but these are not used for analysis purposes.

SAS version 9.3 was used.

Sample size

For Module One we aimed to recruit at least 50 children so that the confidence interval for estimating a proportion would be at most $\pm 15\%$. We then planned to randomize at least 25 participants to each treatment strategy in Module Two as this gives reasonable precision for estimation of the standard deviation of actual paracetamol use and an estimation of the difference between the two regimes.

RESULTS

Module One

There were 120 potential participants admitted to the pediatric inpatient ward during the 5 months of the study recruitment period and 72/120 (60%, 95% CI 51 to 69) completed Module One; 36/72 (50%, 95% CI 39 to 62) who participated in Module One then participated in Module Two (Figure 1). 36/120 (30%, 95% CI 22 to 39) of potential

participants enrolled in the feasibility RCT. Characteristics of participants are shown in Table 1.

Participation in the proposed large RCT was rated 'very likely' in 15 (12.5%) of the potential participants and a further 25 (20.8%) responded 'likely' to participate. Concerns raised included possible development of health concerns in their child, inconvenience, length of the study, complexities of raising several small children, having twins, illness in the family, being in paid employment, and coordinating childcare arrangements with research requirements.

Placebo was the least acceptable comparator treatment as 52 (72%) respondents rated this option as 'totally unacceptable' or 'unacceptable'. The main concerns ('concerned' or 'very concerned') with placebo related to safety due to the lack of an effective treatment being available, particularly in the management of pain (66/72, 92%), febrile convulsions (53/72, 74%) and fever (44/72, 61%). Ibuprofen and restricted paracetamol were rated as either 'very acceptable' or 'acceptable' by 42/72 (58%) and 29/72 (40%) respondents respectively. The main concerns with both active treatments related to safety and effectiveness.

Module Two – Feasibility RCT

Of the 36 parents/guardians who gave informed consent for their infants to participate in Module Two, one was lost to follow-up following randomization, one withdrew after one month, and two withdrew after two months in the study (Figure 1). Data was available for analysis in 17 and 18 infants randomized to the liberal and restricted groups respectively. Paracetamol use was greater for the liberal versus restricted group for both reported [Hodges-Lehmann estimator of location difference 0.89 mg/kg/day (95% CI 0.15 to 3.53), $P=0.02$], and measured use [Hodges-Lehmann estimator of location difference 2.11 mg/kg/day (95% CI 0.90 to 4.18), $P=0.004$]. The median reported total use of paracetamol was 2.0-fold greater in the liberal versus restricted group (1,066 mg versus 538 mg) and 3.5-fold higher for measured paracetamol use (1,709 mg versus 488 mg).

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Parents/guardians in the restricted paracetamol group adhered to the administration guidelines on 71/84 (84.5%) of the occasions that paracetamol was given. For the 13 occasions on which paracetamol was given outside the restriction criteria the reasons stated were fever, grizzling, or teething. There were 12 occasions reported by parents/guardians in the restricted paracetamol group when they would have given paracetamol if not for the study requirements. Parents/guardians in the liberal paracetamol group reported the following reasons, in order of frequency for paracetamol administration: fever, teething, grizzling, pain, or unwell. Three participants in the restricted group and one in the liberal group received no paracetamol use.

The median measured use of paracetamol was greater than reported use in the liberal (1,709 mg versus 1,066 mg) but not the restricted (488 mg versus 538 mg) groups.

Eight participants reported paracetamol use at least two-fold greater than measured paracetamol use, primarily due to paracetamol administered from other sources such as in hospital, at home, or in a child day-care facility. For 17 participants reported use was substantially less than measured use and explained by parents/guardians by doses administered not being recorded, paracetamol being administered to siblings, and spillage. At least one dose of ibuprofen was used in 3/17 (18%) and 5/18 (28%) of the liberal and restricted groups.

Hospital attendances, adverse events and serious adverse events

No serious adverse events were reported. There were two reports of administration of a dose of paracetamol <4 hours after the previous dose, and one report of five doses being given in a 24 hour period. There were 11 hospital admissions during the feasibility RCT, nine due to bronchiolitis and two due to pneumonia. Five admissions were from children randomized to the liberal paracetamol group and six from the restricted group.

DISCUSSION

This feasibility study has clarified key issues for planning a robust RCT to directly investigate whether paracetamol increases the risk of asthma symptoms in childhood. It suggests that about one-third of eligible infants admitted to hospital with bronchiolitis would be likely to participate in an RCT of liberal paracetamol use and childhood asthma risk. Ibuprofen is the preferred comparator regime, although restricted paracetamol use is a feasible option with separation in paracetamol dosing from liberal paracetamol use likely to be achieved.

Methodological issues

The approach of recruiting parents/guardians and infants admitted to hospital with bronchiolitis highlighted three things: i) two-thirds of the eligible participants agreed to participate in the questionnaire, ii) one third consented to randomization of infants to either liberal or restricted paracetamol use for 3 months; and iii) a strong representation of Maori and Pacific infants recruited. There is a potential advantage recruiting Maori and Pacific children who have a higher rate of asthma diagnosis, reported asthma symptoms and hospitalizations compared with New Zealand European children [31, 37, 38] yet are under-represented in RCTs [39]. Recruiting in-hospital, particularly for a questionnaire, yielded a very good response rate in this population.

Retention of infants in the 3-month study was very high, with only one of 36 infants being withdrawn (lost to follow-up after initial recruitment). However, arranging home visits was problematic with some participants' final interview conducted via telephone, and the diary and paracetamol bottle collected by courier. The retention of infants in a longer term study is likely to be more difficult to maintain over a longer period of time, with ongoing medication documentation and a final outpatient visit requiring study procedures. For the proposed RCT consideration could be given to using a mobile phone messaging system for reminders for appointments. In support of this approach, we noted that all participants had access to a

mobile phone. Consideration could also be given to web-based or smart-phone follow-up questionnaires that can be accessed and filled in by participants at their own convenience.

Parents/guardians encountered difficulties with documentation of paracetamol use. Reports included difficulties at night while managing an unwell child, having additional children sick simultaneously, and different preferences of other adults caring for the child. Also reported were retrospective diary entries, either from memory or copied from notes, and data being forgotten. The most successful Study Diaries were those kept with the paracetamol bottle using the simple expedient of a rubber band! Some participants suggested electronic data capture for the proposed RCT. However, another option would be not to record or measure paracetamol use in the proposed RCT, an approach which would have major practical advantages, but weaken the study in the event that restricted paracetamol use was the comparator. In particular the uncertainty would remain whether separation in paracetamol dosing occurred throughout the study period. Serial serum paracetamol levels would not be helpful in the context of as-needed medication over a three year period and would be most unlikely to be acceptable to infants (or parents).

A related methodological consideration is the medication reconciliation process, in which discrepancies were noted between the reported and measured paracetamol use. This primarily related to the liberal rather than the restricted paracetamol group.

Parents/guardians reported administered doses of paracetamol not recorded in the diary, doses not from the study medication bottle recorded in the diary, and paracetamol dispensed to other children (for example siblings) from the study bottle.

Further, we note the use of ibuprofen in some of the infants in the liberal and restricted paracetamol groups. This contamination, which would reduce the ability to discern a difference between the randomized treatments should a difference exist, is likely to be a practical problem in a study of longer duration.

A final issue to consider is the preferred approach of following children until the age of 5 years of age, when asthma can be more reliably diagnosed rather than 2-3 years as in the proposed RCT. This would extend the follow-up period for participants and potentially further stretch retention rates.

Designing a main trial

With regard to future planning, the approach of recruiting from a population of infants admitted to hospital with bronchiolitis resulted in a third of them participating. An alternative design includes recruiting infants from the community who are skin prick test positive to common allergens, and/or have a family history of asthma, eczema or hayfever, groups which are also associated with an increased risk of subsequent childhood asthma [39, 40, 41]. A related study design is to recruit mothers early during pregnancy [39], which would also provide the opportunity to investigate the effect of restricted versus liberal paracetamol use in utero and/or in infancy, on risk of asthma in childhood.

Placebo would not be an option in an RCT as a comparator treatment as it was unacceptable to around three-quarters of parents/guardians, mainly due to safety concerns about the lack of treatment being available for a sick child with pain or fever. Ibuprofen was the preferred comparator being acceptable to around 60%, compared with restricted paracetamol which was acceptable to around 40%. Therefore both ibuprofen and restricted paracetamol are potential comparators for an RCT depending on other considerations.

The main issue with the use of ibuprofen is the difficulty in determining, if in fact it was demonstrated that ibuprofen reduced the risk of asthma compared with paracetamol, whether the effect was due to an increased risk with paracetamol or reduced risk with ibuprofen. This difficulty was present in the only RCT to date of paracetamol and asthma risk in children, in which children receiving ibuprofen were less likely to have an outpatient visit for an exacerbation of wheeze during a 4 week period [28]. The Acetaminophen Versus

Ibuprofen in Children with Asthma (AVICA) study currently underway in the United States similarly seeks to assess asthma exacerbation rates in a cohort of preschool children already diagnosed with persistent asthma on standardized asthma therapy who have been randomized to receive paracetamol or ibuprofen on an as needed basis for fevers and pain [43].

In contrast, an RCT of ibuprofen exposure compared with paracetamol exposure in infancy would extend these findings by determining if there was a difference in the risk of developing asthma at age 3 years, instead of exacerbation risk in children with already established asthma. While this may still not answer the question of whether one comparator arm is detrimental or the other is protective, any significant difference in asthma risk between the two groups is a useful clinical finding that will guide clinical practice, particularly in infants at high risk of developing asthma.

We identified that the liberal regime resulted in a 2.0 to 3.5-fold greater use of paracetamol, depending on whether reported or measured use of paracetamol was assessed. From this we infer that restricted paracetamol is a viable comparator arm in the proposed RCT to determine whether paracetamol increased the risk of developing asthma in childhood.

We intended to enroll 50 infants into Module Two and this could not be achieved in a single winter season, with 36 participants randomized, and this may have been due to New Zealand experiencing the warmest winter since 1870 [42]. To enable sufficient power to determine a 20% reduction in risk, 10 centers with a population the size of Wellington Hospital catchment would need to recruit over 3 years to ensure that the required 1,028 infants were randomized.

Conclusion

This study has shown that the proposed RCT to directly investigate whether paracetamol increases the risk of asthma symptoms in childhood is feasible if ibuprofen and/or restricted paracetamol, but not placebo, is used as a comparator treatment to liberal paracetamol treatment. Consideration would need to be given to not recording or measuring medication use, to reduce the burden on parents and guardians over the prolonged study period, and improve the generalizability of the study findings. We propose that this feasibility study provides the basis for future RCTs, undertaken in response to calls for RCTs of paracetamol use and risk of asthma in children [4,14,15,25,44-46].

Role of the funding source

The funding sources had no involvement in the study design; in the collection, analysis, and interpretation of data; in manuscript preparation; or in the decision to submit for publication. JR, IB, PS, RC, AH, VB, SP, MW, RB had full access to the raw data. The corresponding author had full access to the study data and final responsibility in submitting the manuscript for publication.

Conflicts of Interest:

RB has received consultancy fees from GlaxoSmithKline (GSK; manufacturer of paracetamol) in his role as a member of the New Zealand GSK Advisory Board, and as a member of a GSK Research Adjudication Committee, and has received reimbursement for attending symposia and fees for speaking. The Medical Research Institute of New Zealand received a research grant for an unrelated study from GSK. There are no other conflicts of interest to declare.

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Table 1: Characteristics of study participants

	Mean (Standard deviation)
Child's age (months)	12.9 (5.2)
Main Parent's age (years)	30.5 (1.0)
	N (%)
Child's gender female	31 (42.5)
Main Parent's gender female	62 (84.9)
Ethnicity	
NZ European	30 (41.1)
Maori	25 (34.2)
Pacific	15 (20.6)
Other	3 (4.1)
First admission with bronchiolitis	51 (29.9)

Table 2: Outcome variables for feasibility RCT

Variable	Mean (Standard deviation)	Median (Inter-quartile range)	Hodges-Lehmann difference (95% CI)	P
<i>Reported paracetamol (mg/kg/day)</i>				
Liberal N=17	3.06 (3.12)	1.53 (0.78 to 4.64)	0.94 (0.20 to 3.52)	0.02
Restricted N=18	0.87 (0.76)	0.74 (0.35 to 1.12)		
<i>Measured paracetamol (mg/kg/day)</i>				
Liberal N=17	3.13 (2.68)	2.68 (1.50 to 5.28)	2.11 (0.90 to 4.18)	0.004
Restricted N=18	0.89 (0.76)	0.84		

		(0.35 to 1.12)
<i>Reported total paracetamol (mg)</i>		
Liberal N=17	2749 (3078)	1066 (547 to 4243)
Restricted N=18	653 (557)	538 (211 to 907)
<i>Measured total paracetamol (mg)</i>		
Liberal N=17	2771 (2443)	1709 (1178 to 4800)
Restricted N=18	594 (591)	488 (0 to 960)

FIGURE LEGENDS

Figure 1: Figure showing the flow of participants in the study

Figure 2: Box-plots of reported and measured paracetamol by randomized groups in the feasibility RCT

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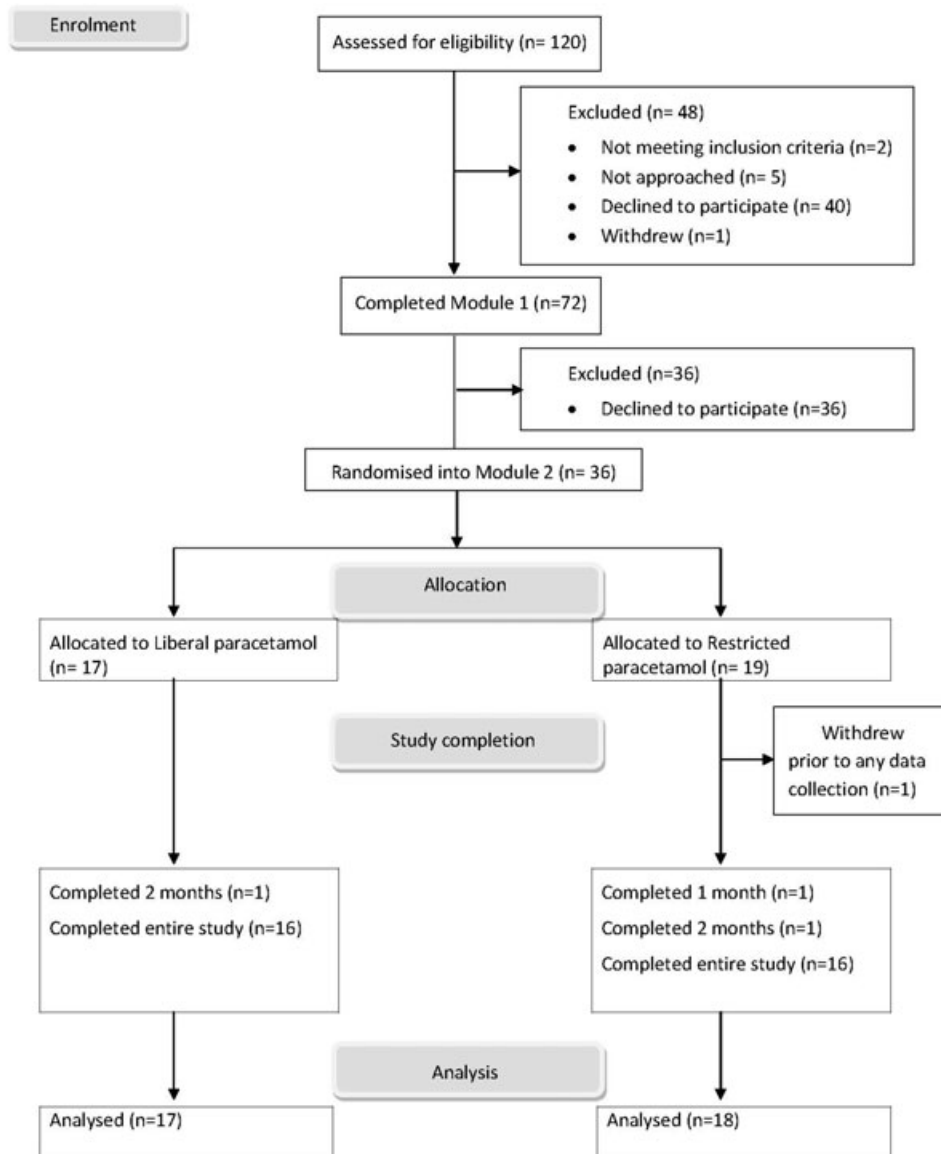
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Figure 1

Flow diagram



Paracetamol Bronchiolitis Feasibility Study, Flow Diagram

Figure 2:

