Pilot study of feasibility of a randomised controlled trial of asthma risk with paracetamol versus ibuprofen use in infancy

Judith Riley, Anna Hunt, Alice McDouall, Steve Waqanivavalagi, Irene Braithwaite, Mark Weatherall, Thorsten Stanley, Richard Beasley, Edwin A Mitchell, Stuart R Dalziel

ABSTRACT

AIM: To undertake a randomised controlled trial (RCT) of paracetamol versus ibuprofen use during infancy to determine if paracetamol is associated with an increased risk of developing asthma, the preferred method of recruitment needs to be determined. We assessed three different recruitment domains to determine the likely enrolment rates of newborn infants into a three-year or six-year RCT of paracetamol versus ibuprofen and the development of asthma symptoms. The proposed RCT would require 1,806 participants.

METHODS: A questionnaire was administered to a convenience sample of Auckland and Wellington based parents/guardians within three different recruitment domains: antenatal classes, postnatal wards and six-week well-child visits at primary healthcare centres.

RESULTS: Over a twelve-week period 19/586 (3.2%), 196/861 (22.8%), and 0/110 (0%) questionnaires were completed by parents/guardians of newborn infants in antenatal, postnatal and primary healthcare domains. In the postnatal recruitment domain, the likelihood of newborn infants being enrolled in the proposed RCT was rated 'very likely', 'likely' and 'neutral' by 15 (8%, CI 4–12%), 65 (33%, CI 26–40%) and 64 (33%, CI 25–39%) of respondents for a RCT of three years duration; and by 5 (3%, CI 1–5%), 37 (19%, CI 14–25%) and 59 (30%, CI 24–36%) of respondents respectively for a RCT of six years duration.

CONCLUSIONS: Postnatal wards are expected to be the most successful recruitment domain for the proposed RCT, likely a reflection of the face-to-face direct recruitment by researchers. It appears feasible to recruit into the proposed RCT using three large New Zealand tertiary hospitals.

Paracetamol (acetaminophen) use may be a risk factor both for the development of asthma and an increase in the severity of established asthma.[1–8] Epidemiological associations between asthma and paracetamol exposure have been described in the intrauterine environment,[9–14] infancy,[3] later childhood[4] and adult life.[1,2,6] These associations may be confounded by indications such as respiratory tract infections, which are associated with an increased risk of asthma[7,15] and a common reason for parents/guardians to use paracetamol in children.[7,15] Paracetamol reduces circulating and airway glutathione levels, thereby potentiating increased oxidant-induced inflammation, either directly or by enhancing TH_2 cell polarisation,[16–20] hence leading to asthma.

Randomised controlled trials (RCTs) to investigate the association between paracetamol use and asthma are required in order to prove or disprove causality. There is one published RCT[21] and one completed RCT published since the completion of this pilot study,[22] comparing the effect of paracetamol versus ibuprofen use for fever and asthma outcomes in children with asthma. The former found that children with asthma

had a decreased risk of out-patient asthma treatment when given ibuprofen compared to paracetamol, over a four-week period.[21] In contrast, the latter study, a 48-week trial in which asthmatic children, aged from one to five years, were randomised to receive either paracetamol or ibuprofen administered per parental/guardian decision, for fever and analgesia, found no difference in asthma exacerbation rates, asthma control days or albuterol use between the paracetamol and ibuprofen groups.[22] There are no RCTs assessing long-term risk of asthma in children who are naïve to paracetamol or ibuprofen in early infancy.

In order to complete a RCT assessing the long-term risk of asthma in children who are naïve to paracetamol in early infancy, a number of key feasibility questions need to be answered; firstly, the suitability and acceptability of possible comparators and secondly, if recruitment into a RCT is achievable. Previously, we approached parents/guardians of infants admitted into hospital with bronchiolitis to determine the acceptability of placebo, ibuprofen or 'restricted' paracetamol (in accordance with World Health Organization recommendations[23]) as comparators. This feasibility study established the non-acceptability of placebo and a clear preference for ibuprofen to be the comparator in future RCTs.[24]

Consequently we plan to undertake a RCT of paracetamol versus ibuprofen to be used (as required) exclusively from birth for fever and/or analgesia in order to determine if paracetamol use is associated with increased risk of asthma and atopic outcomes in childhood. In order to demonstrate a 25% reduction in risk of wheezing at age three years in those exposed to ibuprofen, 1,806 infants would need to be enrolled. The aim of this pilot study is to identify the most suitable recruitment domain for the proposed RCT from among antenatal classes, postnatal hospital wards or primary health care providers of the 'six-week well-child visit'.

Methods

This pilot study was conducted in two New Zealand urban areas: Wellington and Auckland. Eligible participants were parents/guardians of yet-to-be-born or newborn infants, who attended antenatal classes, or were parents/guardians on a postnatal ward or parents/guardians of infants who attended a six-week well-child visit during the period 10 November 2014 to 28 February 2015 inclusive. Ethical approval was obtained from the New Zealand Southern Health and Disability Ethics Committee (HDEC 14/STH/83).

Following written informed consent, parents/guardians completed a two-part questionnaire: Part one collected demographic information of one parent and the infant; including family history of asthma, eczema and atopy. Part two investigated the likelihood of parents/guardians enrolling their infant into a proposed RCT (See Online Supplement).

Procedures

Antenatal domain: Study information was sent electronically to identified antenatal class coordinators in each centre where at least one class was scheduled to occur during the study period. In Wellington, permission was sought for study investigators to attend classes to promote the study and to recruit participants. Study investigators attended eight classes and spoke briefly to the whole class, answered any questions and then approached potential participants individually during break-time or after the class. Those who expressed interest, accepted a participant information sheet (PIS) and provided their contact details were followed up within three weeks. In Auckland, printed PISs and an introduction letter were provided to class coordinators who then handed these out to potential parents/guardians in 17 classes, mainly during discussions of postnatal infant care. Potential parents/guardians were invited to contact study investigators by phone or email for further information regarding participation.

Postnatal domain: Study investigators approached in-patient postnatal families in Wellington Regional Hospital (Wellington) and Middlemore Hospital (Auckland) during the hours of 9am to 4pm Monday to Friday over seven and eight weeks respectively. In Auckland, recruitment also occurred over two weekends. Potential parents/guardians were individually approached and offered study information; those deemed unsuitable

by clinical staff were not. Numbers deemed unsuitable or who declined either the initial offer of information, or to participate, were recorded.

Six-week visit domain: Two Wellington-based primary health care providers gave out a letter containing study information to families who had a six-week well-child visit scheduled during the study period. Potential parents/guardians were invited to contact study investigators by phone or email for further information regarding participation.

Sample size and study power

As this was a pilot study to inform recruitment strategies for the proposed RCT, a formal sample size and power calculation was not undertaken prior to the study. We attempted to approach at least 100 possible parents/guardians in each domain as this was considered to give a sufficient comparison. We aimed to recruit 50 people from each of the three domains in both centres, giving a total of 300 completed questionnaires.

Statistical analysis

Primary outcome was the proportion of infants where parents/guardians indicated they would be 'very likely' or 'likely' to enroll their infant in the proposed RCT from each of the three domains studied. 95% confidence intervals were calculated using McCallum Layton Confidence Interval Calculator for Proportions.[25] Secondary outcomes were the proportion of these infants, where parents/guardians indicated they would likely enroll the infant into the proposed RCT: i) whose mother has current asthma; and ii) with any first degree family member (mother, father or sibling) with current asthma. Parental/guardian concerns about convenience, study length and their child's health were estimated from the answers given in the questionnaire.

Post hoc analysis was undertaken to determine the number of infant births required, and likely feasibility, to recruit the appropriate sample size (n=1,806) for the proposed RCT from the postnatal wards, over a two and three year recruitment window, for the following three potential recruitment scenarios: 'Best', recruiting all who indicated they were 'very likely' and 'likely' to participate in the proposed RCT; 'Intermediate', recruiting all who indicated they were 'very likely' and 50% who indicated they were 'likely' to participate in the proposed RCT; and 'Worst', only recruiting those who indicated they were 'very likely' to participate in the proposed RCT. The proposed RCT was determined feasible if the number of infant births required per year was less than the total births reported for Wellington, Middlemore and Auckland City Hospitals for 2013 (the anticipated sites for the proposed RCT). Enhanced recruitment for each scenario was further explored for the following strategies; 1) 25% of those who indicated they were 'neutral' participating in the proposed RCT, 2) recruitment occurring in the weekends and 3) recruitment occurring in the Satellite Birthing Units associated with the three hospitals.

Results

The flow of parents/guardians through the study is shown in Figure 1. Overall, 1,557 possible parents/guardians were identified over the study duration. 584 parents/guardians were approached via intermediaries (coordinators of antenatal classes and of six-week checks) to complete the study questionnaire. 456 parents/guardians were approached in person by the researchers. Questionnaires were only completed by parents/guardians who had been approached face-to-face by researchers. In the antenatal domain, of the eligible 586 parents/guardians, 112 were approached face-to-face, of whom 19 (17%) completed the study questionnaire. In the postnatal wards, of the 861 parents/guardians, 344 were approached face-to-face, of whom 196 (57%) completed the study questionnaire. None of the parents/guardians (0/110) who received a letter at the time of their infants' six-week well-child check responded and none were seen face-to-face by the research team.

Figure 1:

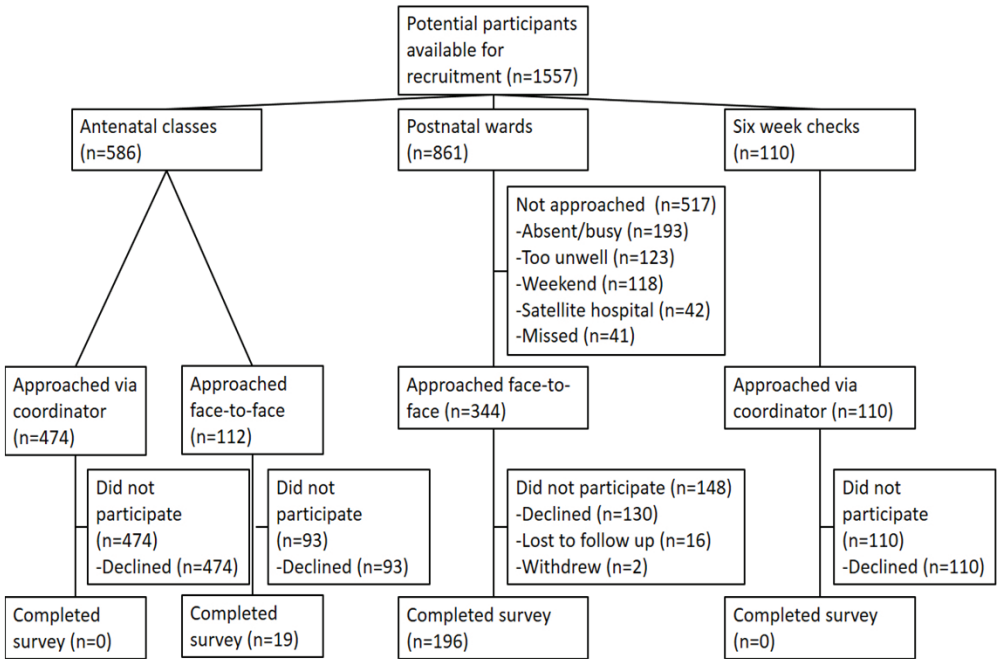

Table 1: Characteristics of study participants who completed the questionnaire.†

	Wellington antenatal n=19	**Wellington postnatal n=102**	**Auckland postnatal n=94**
Parent‡ mean age (SD), years	33±3	33±6	30±7
Median number of siblings of infant (range)	0 (0–1)	0 (0–8)	1(0–6)
Parent‡ gender female	13 (68)	66 (65)	34 (36)
Parent‡ ethnicity			
European	16 (84)	73 (72)	21 (22)
Māori	2 (12)	8 (8)	11 (12)
Pacific	1 (5)	3 (3)	35 (37)
Asian	0 (0)	15 (15)	22 (23)
Other	0 (0)	3 (3)	5 (5)
History of asthma			
Mother of infant	3 (16)	25 (25)	4 (4)
Father of infant	8 (42)	19 (19)	6 (6)
Any sibling of infant	0 (0)	10 (10)	4 (4)
History of eczema			
Mother of infant	6 (32)	34 (33)	6 (6)
Father of infant	5 (26)	15 (15)	2 (2)
Any sibling of infant	0 (0)	2 (2)	4 (4)
History of hayfever			
Mother of infant	5 (26)	33 (32)	6 (6)
Father of infant	8 (42)	37 (36)	5 (5)
Any sibling of infant	0 (0)	4 (4)	3 (3)

†Data are n (%) unless indicated.
‡'Parent' refers to the parent/guardian who answered the questionnaire.

Table 2: Total number of live births required in all participating sites according to possible recruitment strategies and likelihood of enrolment into the proposed three-year RCT.

Recruitment strategy	Best recruitment†	Intermediate recruitment‡	Worst recruitment§
Base case			
Number of births required in participating hospitals	19,437	32,736	103,664
-Annual number of births in participating hospitals if two years of recruitment	9,719	16,368	***51,832***
-Annual number of births in participating hospitals if three years of recruitment	6,479	10,912	***34,555***
¶Enhanced recruitment - 25% of neutrals enroll			
Number of births required in participating hospitals	16,198	24,488	50,160
-Annual number of births in participating hospitals if two years of recruitment	8,099	12,244	***25,080***
-Annual number of births in participating hospitals if three years of recruitment	5,399	8,163	***16,720***
¶Enhanced recruitment - recruitment in weekends*			
Number of births required in participating hospitals	14,473	24,375	77,187
-Annual number of births in participating hospitals if two years of recruitment	7,236	12,187	***38,594***
-Annual number of births in participating hospitals if three years of recruitment	4,824	8,125	***25,729***
¶Enhanced recruitment - recruitment from satellite hospitals*			
Number of births required in participating hospitals	17,322	29,174	92,385
-Annual number of births in participating hospitals if two years of recruitment	8,661	14,587	***46,192***
-Annual number of births in participating hospitals if three years of recruitment	5,774	9,725	***30,795***
¶Enhanced recruitment - all three strategies			
Number of births required in participating hospitals	11,055	16,714	34,236
-Annual number of births in participating hospitals if two years of recruitment	5,528	8,357	***17,118***
-Annual number of births in participating hospitals if three years of recruitment	3,685	5,571	11,412

In 2013 there were 16,555 births in Wellington, Middlemore and Auckland City Hospitals (Data from Capital Coast, Counties Manukau and Auckland District Health Boards annual reports). The proposed paracetamol-ibuprofen randomised controlled trial is deemed feasible if the required number of births per year for the various recruitment scenarios is less than, or equal to, 16,555 (indicated in black). The proposed paracetamol-ibuprofen randomised controlled trial is deemed not feasible if the required number of births per year for the various recruitment scenarios is greater than 16,555 (indicated in bold black italic).

†Best recruitment: where all the "very likely" responders and all the "likely" responders enrol their infants.

‡Intermediate recruitment: where all the "very likely" responders and 50% of the "likely" responders enrol their infants.

§Worst recruitment: where only the "very likely" responders enrol their infants.

¶ Recruitment of additional participants occurs at same rate as base rate.

Table 3: Total number of live births required in all participating sites according to possible recruitment strategies and likelihood of enrolment into the proposed six-year RCT.

Recruitment strategy	Best recruitment†	Intermediate recruitment‡	Worst recruitment§
Base case			
Number of births required in participating hospitals	37,023	66,169	310,993
-Annual number of births in participating hospitals if two years of recruitment	18,512	33,084	***155,497***
-Annual number of births in participating hospitals if three years of recruitment	12,341	***22,056***	***103,664***
¶Enhanced recruitment - 25% of neutrals enroll			
Number of births required in participating hospitals	27,400	40,653	78,732
-Annual number of births in participating hospitals if two years of recruitment	13,700	***20,326***	***39,366***
-Annual number of births in participating hospitals if three years of recruitment	9,133	13,551	***26,244***
¶Enhanced recruitment - recruitment in weekends*			
Number of births required in participating hospitals	27,567	49,269	231,562
-Annual number of births in participating hospitals if two years of recruitment	13,783	***24,634***	***115,781***
-Annual number of births in participating hospitals if three years of recruitment	9,189	16,423	***77,187***
¶Enhanced recruitment - recruitment from satellite hospitals*			
Number of births required in participating hospitals	32,995	58,969	277,155
-Annual number of births in participating hospitals if two years of recruitment	16,497	***29,485***	***138,577***
-Annual number of births in participating hospitals if three years of recruitment	10,998	***19,656***	***92,385***
¶Enhanced recruitment - all three strategies			
Number of births required in participating hospitals	18,702	27,747	53,738
-Annual number of births in participating hospitals if two years of recruitment	9,351	13,874	***26,869***
-Annual number of births in participating hospitals if three years of recruitment	6,234	9,249	***17,913***

In 2013 there were 16,555 births in Wellington, Middlemore and Auckland City Hospitals (Data from Capital Coast, Counties Manukau and Auckland District Health Boards annual reports). The proposed paracetamol-ibuprofen randomised controlled trial is deemed feasible if the required number of births per year for the various recruitment scenarios is less than, or equal to, 16,555 (indicated in black). The proposed paracetamol-ibuprofen randomised controlled trial is deemed not feasible if the required number of births per year for the various recruitment scenarios is greater than 16,555 (indicated in bold black italic).

†Best recruitment: where all the "very likely" responders and all the "likely" responders enrol their infants.

‡Intermediate recruitment: where all the "very likely" responders and 50% of the "likely" responders enrol their infants.

§Worst recruitment: where only the "very likely" responders enrol their infants.

¶ Recruitment of additional participants occurs at same rate as base rate.

Parent/guardian characteristics are shown in Table 1. Of the 215 parents/guardians who completed the questionnaire, 113 (53%) were female, with the cohort having a mean age of 32 years (SD six years) and having a median of 0 other children (range 0–8). European parents/guardians were more common in Wellington, while Pacific Island peoples were more common in Auckland. A history of personal/partner or sibling atopic disease was more common in parents/guardians recruited from Wellington.

Given the relative success of enrolment into the study by face-to-face recruitment with researchers while on the postnatal wards, we only report recruitment into the proposed RCT in this domain. Participation in a proposed RCT of three years duration was rated 'very likely', 'likely' and 'neutral' by 15 (8%, CI 4–12%), 65 (33%, CI 26–40%) and 64 (33%, CI 25–39%) of postnatal parents/guardians respectively. Participation in a proposed RCT of six years duration was rated 'very likely', 'likely' and 'neutral' by 5 (3%, CI 1–5%), 37 (19%, CI 14–25%) and 59 (30%, CI 24–36%) of postnatal parents/guardians respectively.

The proposed three-year RCT is deemed feasible for 'Best' and 'Intermediate' recruitment scenarios over a two- or three-year recruitment period from the postnatal wards of the three proposed recruitment domains (Table 2). Furthermore, the proposed three-year RCT is deemed feasible for 'Worst' recruitment scenario over a three-year recruitment period from the postnatal wards of the three proposed recruitment sites with enhanced recruitment strategies.

The proposed six-year RCT is deemed feasible only for the 'Best' recruitment scenario over a three-year period from the postnatal wards and may become feasible over two years with addition of enhanced recruitment strategies (Table 3). The proposed six-year RCT is deemed infeasible with the worst recruitment scenario regardless of any enhanced recruitment strategies.

Potential barriers to participation

Parental/guardian concerns regarding convenience, study length and their child's health on possible participation are shown in Table 3. Overall, the 52 parents/guardians who rated possible participation as 'unlikely' or 'very unlikely' had greater levels of being 'concerned' or 'very concerned' in terms of convenience study

Table 4: Potential barriers to participation in a randomised controlled trial of three years duration.

	Participation N (%) 'Likely' and 'Very likely' (n=80)	**Participation N (%) 'Neutral' (n=64)**	**Participation N (%)'Unlikely' and 'Very unlikely' (n=52)**
Convenience			
'Very inconvenient'/'Inconvenient'	8 (10)	13 (20)	26 (50)
'Neutral'	26 (33)	35 (55)	17 (33)
'No trouble'	46 (58)	16 (25)	9 (17)
Study length			
'Very concerned'/'Concerned'	11 (14)	27 (42)	28 (54)
'Neutral'	28 (35)	20 (31)	11 (21)
'No trouble'	41 (52)	17 (27)	13 (25)
Your child's health			
'Very concerned'/'Concerned'	26 (33)	32 (50)	40 (77)
'Neutral'	27 (34)	25 (39)	8 (15)
'Not concerned'	27 (34)	7 (11)	4 (8)

length, and the effect on their child's health of participation in the study compared with the other parents/guardians ($p<0.01$ for all three comparisons). Of the 80 parents/guardians who rated possible participation as 'likely' or 'very likely', 26 (33%) were 'concerned' or 'very concerned' about the effect on their child's health of participation in the proposed RCT. Narrative responses identified 17 (9%) parents/guardians wanting the choice of medication, 10 (5%) unwilling to use ibuprofen for a child under three years of age, seven (4%) likely to travel overseas within three years and six (4%) who stated a need for more information about both medications.

Secondary outcomes

Twenty-four (12%) postnatal parents/guardians had at least one first-degree relative with current asthma. Of these families, 17 (71%) and 14 (58%) responded 'likely' or 'very likely' to participate in the proposed RCT of three years and six years duration respectively. Current maternal asthma was reported in 14 (7%) parents/guardians. Of these, 11 (79%) and eight (57%) responded 'likely' or 'very likely' to participate in the proposed RCT of three years and six years duration respectively.

Discussion

This pilot study showed that the most successful recruitment domain for the proposed paracetamol-ibuprofen RCT is likely to be the postnatal wards. As the study progressed it became obvious that this recruitment strategy was superior to recruitment from antenatal classes or six-week checks, answering the primary objective of the study. Eighty (23%) of the 344 parents/guardians who were approached face-to-face in the postnatal wards indicated that they were 'very likely' or 'likely' to enroll their newborn infant into the proposed RCT of three years duration.

The comparatively high number of questionnaires answered in the postnatal wards is most likely due to accessibility of investigators, face-to-face recruiting and the ability to allow parents/guardians to answer questions and make decisions regarding participation over time. In contrast, antenatal recruiting was often limited to a single-class period for multiple parents-to-be, and the six-week well-child visit was dependent on new parents/guardians acting on written information given to them. For the proposed RCT, concentrating recruitment resources at a few postnatal locations appears to be the most efficient recruitment strategy. The postnatal domain also allows access to a population sample with broader demographics compared to antenatal classes, which tend to attract first-time parents and those in higher socio-economic groups.[26,27]

Previously researchers in New Zealand have enrolled infants from both the antenatal and postnatal environments in large numbers for either long-term observational studies[28] or short-term interventional studies in selected at-risk or pathological populations.[29] To our knowledge, recruitment of large numbers of newborn infants from the general population into a long-term interventional study in New Zealand has not occurred. Given that the arrival of a newborn infant is a time of increased stress, it is very possible that recruitment into a long-term interventional study would not be successful. Thus this current study provides important information regarding the feasibility of undertaking the proposed RCT. Furthermore, the findings are generalisable to others who may be planning large long-term interventional studies in New Zealand infants from birth.

Accurate prediction of the real enrolment rate into RCTs is problematic. When assessing the feasibility of the proposed RCT we calculated recruitment from the 80 of the 861 potential parents/guardians identified on the postnatal wards, who indicated that they would 'very likely' or 'likely' enroll their newborn infants into the proposed RCT. These results are not generalisable to the antenatal or six-week check groups and given the low response rates from these two groups, they were excluded from possible recruitment calculations. Postnatal recruitment rates could be enhanced by strategies to encourage the 'neutral' group (33% of those who completed the questionnaire) to consider enrolling their infants, recruiting from satellite postnatal locations, recruiting outside of regular working hours and providing study information to all parents/guardians in the postnatal ward.

Recruitment of infants with a higher risk of developing asthma, such as those with

a first degree relative with asthma, would increase the power of the proposed RCT. In our current study the potential recruitment rate in this sub-population (12% of population) was higher than the remainder of the sample. However, the percentage of newborn infants meeting this category would make limiting recruitment to this cohort impractical. By enrolling infants into the proposed RCT from a general population, the subsequent results would be broadly generalisable, but reassuringly still provide important information on the sub-population of those with a first-degree relative with asthma.

There are a number of limitations to this study. Firstly, all antenatal classes attended by study investigators were aimed at first-time parents/guardians. Study information was not provided to parents/guardians expecting a second or subsequent child and thus we were unable to explore antenatal recruitment in this population. Secondly, the study sample was a convenience sample and thus at risk of selection bias. However, as recruitment into the proposed RCT is likely to occur predominantly in the same working hours this is unlikely to have a significant effect. Thirdly, the current study is a pilot study and recruitment rates into the proposed RCT may not reflect parents/guardians responses to a questionnaire.

Conclusion

Recruitment into a large (n=1,806) long-term RCT of paracetamol versus ibuprofen is likely to be successful from postnatal wards but not from antenatal clinics and six-week well-child visits. By recruiting from postnatal wards in three large hospitals, the proposed RCT is likely to be feasible at high and intermediate recruitment rates, and at low rates with enhancement of recruitment strategies.

Competing interests:
Ms McDouall reports grants from Capital Coast District Health Board during the conduct of the study.

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Author information:
Judith Riley, Research Nurse, Medical Research Institute of New Zealand, Wellington; Anna Hunt, Research Nurse, Medical Research Institute of New Zealand, Wellington; Alice McDouall, Summer Student, Medical Research Institute of New Zealand, Wellington; Steve Waqanivavalagi, Summer Student, The University of Auckland, Auckland; Irene Braithwaite, Research Fellow, Medical Research Institute of New Zealand, Wellington; Mark Weatherall, Consultant Geriatrician, Capital and Coast District Health Board, Professor of Medicine, University of Otago, Wellington; Thorsten Stanley, Consultant Paediatrician, Capital and Coast District Health Board, Senior Lecturer, University of Otago, Wellington; Richard Beasley, Director, Medical Research Institute of New Zealand, Respiratory Physician, Capital and Coast District Health Board, Wellington; Edwin A Mitchell, Professor, Paediatrics (Child and Youth Health), School of Medicine, The University of Auckland, Auckland; Stuart R Dalziel, Specialist, Liggins Institute, The University of Auckland, Paediatric Emergency Medicine Specialist, Auckland District Health Board, Auckland.

Corresponding author:
Dr Irene Braithwaite, Research Fellow, Medical Research Institute of New Zealand, Wellington.
irene.braithwaite@mrinz.ac.nz

URL:
http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2016/vol-129-no-1443-14-october-2016/7030

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Appendix I: Pilot study questionnaire: infant paracetamol trial

DATE: _____ PARTICIPANT NUMBER: PIP/_____ PARTICIPANT INITIALS:_____

Recruited from: _____

You have received a draft information sheet about a trial where your child would be randomised (allocated by chance), to either paracetamol exclusively for their fevers, aches and illnesses, OR to ibuprofen exclusively, at least until they reach the age of three. The trial may be extended until your child reaches the age of six. You and your child would be followed up three monthly by phone, and have a clinic visit at three years of age and then (if extended), six years of age. The main outcome of the study would be to see if there is any difference in wheezing and allergies of the children in the paracetamol group compared to the ibuprofen group at the end of the study.

We would like to assess the likely enrolment rates into this study by asking you some questions about how likely you would be to enrol in a study like this, and to see whether this might change if your infant were to be enrolled until the ages of five or seven.

Demographics:

Parent / Guardian:

Date of Birth: _____ Gender: _____

Ethnicity: _____, _____, _____

Child (if at ante-natal class, gender should be N/A)

Date of birth (or due date):_____ Gender:_____

Ethnicity: _____, _____, _____

How many older siblings? _____

1. **Family history of asthma / eczema / hayfever? (Family history to be obtained relative to child, not parent / guardian). Circle response(s).**

- Mother: asthma / eczema / hayfever / unknown/none
  Age of asthma onset: _____ Resolution: Yes / No
- Father: asthma / eczema / hayfever / unknown/none
  Age of asthma onset: _____ Resolution: Yes / No
- Sibling 1: asthma / eczema / hayfever / unknown/none
  Age now: _____ Age of asthma onset: _____
- Sibling 2: asthma / eczema / hayfever / unknown/none
  Age now: _____ Age of asthma onset: _____
- Sibling 3: asthma / eczema / hayfever / unknown/none
  Age now: _____Age of asthma onset: _____
- Other siblings? Detail re asthma history: _____
  _____
  _____

2. **How likely is it that you would enrol your child into a study as described in the information sheet provided to you for a period of THREE years?**

1	2	3	4	5
Very likely	*Likely*	*Neutral*	*Unlikely*	*Very unlikely*

If 'unlikely' or 'very unlikely', what would be your main reason(s) for NOT participating?

_____
_____
_____

3. **Please rate how you feel about the following aspects of the study as described in the information sheet provided to you:**

- **Convenience of participating in a study like this**

1	2	3	4
Very inconvenient	*Inconvenient*	*Neutral*	*No trouble*

- **Study length**

1	2	3	4
Very concerned	*Concerned*	*Neutral*	*Not concerned*

- **Your child's health**

1	2	3	4
Very concerned	*Concerned*	*Neutral*	*Not concerned*

4. How likely is it that you would enrol your child into a study as described in the information sheet provided to you for a period of SIX years?

1	2	3	4	5
Very likely	*Likely*	*Neutral*	*Unlikely*	*Very unlikely*

If 'unlikely' or 'very unlikely', what would be your main reason(s) for NOT participating?

_____

_____

_____

Thank you for taking the time to complete this questionnaire.

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