Trial Title: Paracetamol or Ibuprofen in the Primary Prevention of Asthma in Tamariki

Short title: PIPPA Tamariki

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There are no conflicts of interest to declare.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.
TABLE OF CONTENTS

1. KEY TRIAL CONTACTS........................................................................................................... 7
2. SYNOPSIS .............................................................................................................................. 8
3. ABBREVIATIONS.................................................................................................................. 11
4. BACKGROUND AND RATIONALE...................................................................................... 13
5. OBJECTIVES AND OUTCOME MEASURES........................................................................ 17
6. TRIAL DESIGN.................................................................................................................... 21
7. PARTICIPANT IDENTIFICATION ......................................................................................... 21
   7.1. Trial Participants .............................................................................................................. 21
   7.2. Inclusion Criteria ........................................................................................................... 21
   7.3. Exclusion Criteria ......................................................................................................... 22
8. TRIAL PROCEDURES .......................................................................................................... 22
   8.1. Recruitment ................................................................................................................... 22
       Antenatal identification of potential participants................................................................. 22
       Post-natal identification of potential participants: ........................................................... 22
   8.2. Screening and Eligibility Assessment ............................................................................ 23
   8.3. Informed Consent .......................................................................................................... 23
   8.4. Randomisation ............................................................................................................. 24
   8.5. Baseline Assessments ................................................................................................... 24
   8.6. Subsequent Assessments ............................................................................................. 25
   8.7. Data linkage ................................................................................................................ 25
   8.8. Discontinuation/Withdrawal of Participants from Trial Treatment ............................. 26
   8.9. Definition of End of Trial ........................................................................................... 26
9. STUDY MEDICATION ......................................................................................................... 27
   9.1. Study Medication Description ....................................................................................... 27
   9.2. Instructions for parents/caregivers .............................................................................. 27
   9.3. Adherence with Trial Treatment .................................................................................. 27
   9.4. Other children under 10 years in the household ........................................................... 28
   9.5. Post-trial Treatment .................................................................................................... 28
10. SAFETY REPORTING ....................................................................................................... 28
    10.1. Definitions .................................................................................................................. 29
    10.2. Causality .................................................................................................................... 30
    10.3. Surveillance for Serious Adverse Events of Special Interest ...................................... 30
    10.4. Data Collection for SAESIs / SARs .......................................................................... 30
    10.5. Reporting Procedures for Deaths ............................................................................. 31
21. APPENDIX D: 1 MONTH, 3 MONTH, 6 MONTH AND 9 MONTH QUESTIONNAIRE ...................... 57
22. APPENDIX E: 1 YEAR QUESTIONNAIRE ............................................................................. 65
23. APPENDIX F: 3 AND 6 YEAR QUESTIONNAIRE ................................................................. 80
24. APPENDIX X: AMENDMENT HISTORY ............................................................................. 92
1. KEY TRIAL CONTACTS

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2. SYNOPSIS

<table>
<thead>
<tr>
<th>Trial Title</th>
<th>Paracetamol or Ibuprofen in Primary Prevention of Asthma in Tamariki</th>
</tr>
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<tbody>
<tr>
<td>Short title</td>
<td>PIPPA Tamariki</td>
</tr>
<tr>
<td>Clinical Phase</td>
<td>Phase IV</td>
</tr>
<tr>
<td>Ethics Registration</td>
<td>New Zealand Health and Disability Ethics Committee (Northern A): Number to be updated</td>
</tr>
<tr>
<td>Trial Design</td>
<td>Open label, two-arm, parallel group, randomised controlled trial with 1:1 allocation</td>
</tr>
<tr>
<td>Trial Participants</td>
<td>Infants</td>
</tr>
<tr>
<td>Planned Sample Size</td>
<td>3,922</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>12 months (birth to 12 months of age)</td>
</tr>
<tr>
<td>Follow up duration</td>
<td>72 months (6 years)</td>
</tr>
<tr>
<td>Planned Trial Period</td>
<td>Birth to age 72 months (6 years)</td>
</tr>
<tr>
<td>Objectives</td>
<td>Outcome Measures</td>
</tr>
<tr>
<td>------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of asthma at age 6 years.</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life increases the risk of:</td>
</tr>
<tr>
<td><strong>1. Hospitalisation for bronchiolitis, viral induced wheeze or asthma in the first year of life.</strong></td>
<td><strong>2. Wheeze at 3 years of age.</strong></td>
</tr>
<tr>
<td><strong>3. Eczema at 3 and 6 years of age.</strong></td>
<td></td>
</tr>
</tbody>
</table>
4. Atopy at 3 and 6 years of age.

| Diagnostic Criteria for Eczema questionnaire (3), when the participant is aged 3 years and 6 years. |

| The proportion of participants whose parent/caregiver answers “yes” to the question “Has your child had wheezing or whistling in the chest in the past 12 months?” using the ISAAC Phase III Core Questionnaire for Asthma for 6 to 7 year olds (1) AND/OR “yes” to the questions “In the last year, has your child had an itchy skin condition – by itchy, we mean scratching or rubbing the skin?” and IF YES “Has this skin condition ever affected the skin creases in the past - by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?” using the United Kingdom Diagnostic Criteria for Eczema questionnaire (3) AND/OR “yes” to the questions “In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?” and IF YES “In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?” using the ISAAC Phase III Core Questionnaire for Rhinitis for 6 to 7 year olds (1), when the participant is aged 3 years and 6 years. |

5. Hospital admissions with bronchiolitis, wheeze or asthma in the first 6 years of life.

| Proportion of participants hospitalised with bronchiolitis, viral induced wheeze or asthma by 6 years of age using ICD-10 (2) and querying the Ministry of Health ‘National Non-Admitted Patient Collection’ and ‘National Minimum Dataset’. |
Study Medications

1. Paracetamol (acetaminophen)
2. Ibuprofen

Formulation, Dose, Route of Administration

“Doses will be calculated in accordance with the New Zealand Formulary for Children (4).

Paracetamol oral suspension (120 mg/5 mL, 250 mg/5 mL):
• Child from 1 month of age
  o 15 mg/kg/dose every 4 hours as required;
  o Maximum of 60 mg/kg per day.
• Under 1 month of age, paracetamol may be used (15 mg/kg every 6 hours as required; maximum of 60 mg/kg per day), but ONLY under the advice of a healthcare professional.

Ibuprofen oral suspension (100 mg/5 mL):
• Child 1 to 3 months of age
  o 5 mg/kg every 6 hours as required;
  o Maximum 20 mg/kg per day.
• Child over 3 months of age
  o 10 mg/kg every 6 hours as required;
  o Maximum 30 mg/kg per day.
• Under 1 month of age, ibuprofen may be used (5 mg/kg every 6 hours as required; maximum 20 mg/kg per day), but ONLY under the advice of a healthcare professional.

3. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>Accident Compensation Corporation</td>
</tr>
<tr>
<td>ANZCTR</td>
<td>Australian and New Zealand Clinical Trials Registry</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse reaction</td>
</tr>
<tr>
<td>BW</td>
<td>Birth Weight</td>
</tr>
<tr>
<td>CARM</td>
<td>Centre for Adverse Reactions and Monitoring</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DHB</td>
<td>District Health Board</td>
</tr>
<tr>
<td>DSMC</td>
<td>Data and Safety Monitoring Committee</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GINA</td>
<td>Global Initiative for Asthma</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
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</tr>
<tr>
<td>HDEC</td>
<td>Health and Disability Ethics Committee</td>
</tr>
<tr>
<td>HIPAA</td>
<td>United States Health Insurance Portability and Accountability Act 1996</td>
</tr>
<tr>
<td>HOME</td>
<td>Harmonising Outcome Measures for Eczema</td>
</tr>
<tr>
<td>HRC</td>
<td>Health Research Council of New Zealand</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Related Health Problems 10th Revision</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon gamma</td>
</tr>
<tr>
<td>IL-2</td>
<td>Interleukin-2</td>
</tr>
<tr>
<td>ISAAC</td>
<td>International Study of Asthma and Allergies in Childhood</td>
</tr>
<tr>
<td>LMC</td>
<td>Lead Maternity Carer</td>
</tr>
<tr>
<td>Medsafe</td>
<td>New Zealand Medicines and Medical Devices Safety Authority</td>
</tr>
<tr>
<td>mg/kg</td>
<td>Milligrams per kilogram of body weight</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NHI</td>
<td>National Health Index (number)</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PIS</td>
<td>Participant Information Sheet</td>
</tr>
<tr>
<td>POEM</td>
<td>Patient-Oriented Eczema Measure</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>REDCap</td>
<td>Research Electronic Data Capture</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SAG</td>
<td>Scientific Advisory Group</td>
</tr>
<tr>
<td>SAESI</td>
<td>Serious Adverse Event of Special Interest</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>Th1</td>
<td>Type 1 T helper cells</td>
</tr>
<tr>
<td>Th2</td>
<td>Type 2 T helper cells</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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4. BACKGROUND AND RATIONALE

Asthma: a major public health burden requiring primary prevention

Asthma is one of the most common diseases in the world and represents a major global public health burden (4). In New Zealand (NZ) prevalence rates for asthma during childhood, and for severe asthma, are amongst the highest in the world (5–7). One-in-seven children, and one-in-nine adults, receive treatment for asthma (8,9). Childhood asthma is the major determinant of subsequent asthma during adulthood. Māori children have a particularly high prevalence, with a relative risk (RR) of 1.54 for “medicated asthma” prevalence compared with NZ European children (8). Annually, over 3,500 children and over 4,600 adults in NZ are admitted to hospital with asthma exacerbations (8). Asthma is the commonest reason for hospital admission during childhood (8). For adults, asthma is the leading cause for males, and the third leading cause for females, of years lost to disability (6). The economic costs of asthma to NZ are considerable (6).

Over the last two decades, research efforts and public health measures have largely been directed at improving the assessment and management of asthma (10) resulting in a 42% reduction in age-standardised asthma death rates worldwide between 1990 and 2013 (11). However, as a chronic illness with no known cure, such strategies will always have a ceiling effect. Furthermore, the burden of asthma will continue to be driven by its increasing prevalence, the reasons for which are poorly understood (4,12,13). Therefore, there is an urgent need to develop alternative primary preventive strategies to reduce the prevalence of asthma worldwide.

It is reasonable to suggest that asthma prevention is possible, as standardised international epidemiological studies have shown that some populations have low asthma symptom prevalence (5,7). Genetics, environment (both in-utero and ex-utero), diet, infections and medications have all been identified to play a role in the development of childhood asthma (14). To date, randomised controlled trials (RCTs) looking at primary prevention of asthma have focused on dietary modification, probiotics, breastfeeding and multifactorial avoidance of environmental triggers, such as exposure to tobacco smoke, house dust mite and other allergens (14). Unfortunately, none of the primary prevention strategies that have undergone scrutiny in RCTs have provided sufficient evidence to lead to widespread public health implementation. This has led to the investigation of novel risk factors that might have a role in the pathogenesis of asthma.

Paracetamol as a novel risk factor for the development of asthma

One novel risk factor that might have a role in the development and severity of asthma is the use of paracetamol (15,16). Paracetamol is now the most commonly prescribed medicine in children (17), and there is a temporal association between the increased use of paracetamol over the past 50 years and the rise in asthma prevalence worldwide (12,13). Biological plausibility of this association is supported by a number of potential mechanisms. The main mechanism suggested is that paracetamol may reduce the concentrations of the antioxidant glutathione in the lung, leading to oxidant-induced airway inflammation (18–20). Lower levels of glutathione may also produce a shift away from Type 1 T helper cells (Th1) towards Type 2 T helper cells (Th2) cytokine production, which increases the phenotypic expression of atopic diseases like asthma (21). Finally, another possible mechanism could be related to its antipyretic effect: by reducing fever, paracetamol may reduce the cytokine storm that takes place as a part of the febrile response, mainly the production of Interferon gamma (IFN-γ) and Interleukin-2 (IL-2), which have predominant Th1 profiles (22).
Epidemiological evidence of the association between paracetamol exposure and asthma

In 2000 concern was raised about the safety of paracetamol as a result of the findings of a case–control study by Shaheen et al. (23) which suggested that frequent use of paracetamol among adults was associated with asthma, and among those who already had asthma, with more severe disease. This concern has led to more than a decade of observational research with epidemiological associations described between asthma and paracetamol exposure in the intrauterine environment (24–29), infancy (25,26,29–32), childhood (31,33–35), and adult life (23,36–38). Several systematic reviews and meta-analyses have been published in an effort to determine the nature and strength of this association (39–41). In 2009, a meta-analysis by Etminan et al. (39), which included 19 studies comprising 425,140 subjects, confirmed a consistent association between paracetamol use and the risk of asthma. The pooled odds ratio (OR) for all studies, for adults, for children and for almost any other subgroup, was consistently near 1.5, with a narrow 95% confidence interval (CI). In 2011, García-Marcos et al. (40) in an updated comprehensive systematic review and meta-analysis, which now included 41 studies, confirmed pooled ORs of around 1.5. Most recently, a meta-analysis of three longitudinal studies, that included data from 4,226 children, found that paracetamol use in infancy increased the odds of childhood asthma, although this appeared to be confounded by respiratory tract infections (41).

Randomised controlled trials of paracetamol use and asthma development are a high research priority

Nearly all the evidence for the link between paracetamol exposure and asthma is from non-experimental studies. While epidemiological studies have shown associations, associations do not prove causation and may be confounded by indication as a sizeable proportion of paracetamol use in infants is for respiratory tract infections, which themselves are associated with an increased risk of asthma (42,43). The causal relationship between paracetamol and asthma can only be definitively addressed by RCTs. To date, evidence from RCTs is limited to two clinical trials comparing paracetamol versus ibuprofen use and asthma outcomes in children with asthma. The first, a post hoc analysis of the short-term use of paracetamol or ibuprofen for febrile illness reported a two-fold higher risk of unscheduled hospital outpatient visits for asthma in the paracetamol group (44). In contrast, the second study by Sheehan et al. reported that amongst young children (12 to 59 months old) with mild persistent asthma, as-needed use of paracetamol was not associated with a higher incidence of asthma exacerbations or worse asthma control than as-needed use of ibuprofen (45). Both the authors of this study (45) and the associated editorial in the New England Journal of Medicine (46) stressed that this RCT did not address whether paracetamol use can lead to the development of asthma in otherwise healthy children, and they strongly supported the need for a study designed to answer this question. Furthermore, there are no clinical trials assessing the long-term risk of asthma in children who are naïve to paracetamol in early infancy. Given the high burden of asthma, RCTs of the effect of paracetamol on the development of asthma and its severity are a high research priority (15).

A randomised controlled trial of paracetamol use in infancy is needed

We will definitively answer whether paracetamol exposure in infancy is associated with an increased risk of later asthma by conducting the first ever RCT of paracetamol versus ibuprofen, used as required for fever and pain in the first year of life, on asthma prevalence at age six years – Paracetamol and Ibuprofen in Primary Prevention of Asthma in Tamariki (PIPPA Tamariki). The first year of life (12 months) was chosen as the length of the intervention to determine primary prevention of asthma. The epidemiological studies examining the association between paracetamol exposure in infancy and later childhood asthma
have exclusively defined paracetamol exposure in infancy as being within the first 6 or 12 months of life (15,32,39,41).

Measuring the primary outcome at six years of age allows for the clinical uncertainty in the diagnosis of asthma prior to the age of five years to be accounted for (16). Within the first five years of life there is considerable clinical heterogeneity in paediatric presentation of wheeze between bronchiolitis, a predominately wheezy illness due to viral respiratory infections, and reversible airways disease, or asthma, in school-aged children and adults. A number of cohort studies that have followed young children with wheeze show that the vast majority of preschool children who wheeze do not develop asthma in later life (47,48). Indeed, high-quality meta-analysis of the risk of paracetamol in infancy and subsequent childhood asthma have restricted inclusion criteria to only those studies reporting the outcome after five years of age (41).

**Lack of long-term follow-up data on paracetamol and ibuprofen**

Despite the common use of both paracetamol and ibuprofen, there is a paucity of long-term safety data for both medications when used in infancy. The World Health organization (WHO) has highlighted the need for long-term safety data, ranking this research priority in the highest of five priority groups (49).

**Justification for a trial of paracetamol versus ibuprofen, rather than paracetamol versus placebo**

While the use of a placebo group as a comparison arm would allow for easier interpretation of the results of the proposed RCT, this was deemed unacceptable for ethical reasons in that it would not provide infants with analgesia when in pain. In agreement with this approach, our first feasibility study established the non-acceptability of placebo and a clear preference for ibuprofen to be the comparator in future RCT amongst parents of young infants (50). Using ibuprofen as an active control also provides data which is generalisable to standard practice in NZ and internationally (50). As with the Sheehan et al. study, our pragmatic RCT will not be able to exclude the possibility that both paracetamol use and ibuprofen use may be associated with parallel increased risk of asthma. However, as paracetamol and ibuprofen have different mechanisms of action, this possibility is unlikely. Furthermore, even if the use of both medications cause parallel increases in asthma risk, this RCT has been designed to answer the question of which medication (paracetamol or ibuprofen) given to infants with fever or pain, is associated with fewer long-term adverse effects.

**The PIPPA Tamariki study population**

All infants born in the catchment areas of Auckland City, Middlemore and Wellington Hospitals (28% of national birth cohort) will be eligible for enrolment. Infants will be primarily recruited from postnatal wards, as our previous pilot study showed that this was the most successful recruitment domain, with both antenatal classes and primary healthcare domains, alone, unlikely to be successful alternatives (51).

**Description of and justification for the interventions**

Participants will be randomised to oral paracetamol or ibuprofen suspension as required for fever or pain, dosing for each medication is as per the NZ Formulary for Children (52), as follows.

Paracetamol oral suspension (120 mg/5 mL, 250 mg/5 mL):

- Child from 1 month of age
  - 15 mg/kg/dose every 4 hours as required;

*PIPPA Tamariki Protocol Version 1.0, 7 November 2017*

*Page 15 of 92*
• Maximum of 60 mg/kg per day.
• Under 1 month of age, paracetamol may be used (15 mg/kg every 6 hours as required; maximum of 60 mg/kg per day), but ONLY under the advice of a healthcare professional.

Ibuprofen oral suspension (100 mg/5 mL):

• Child 1 to 3 months of age
  o 5 mg/kg every 6 hours as required;
  o Maximum 20 mg/kg per day.
• Child over 3 months of age
  o 10 mg/kg every 6 hours as required;
  o Maximum 30 mg/kg per day.
• Under 1 month of age, ibuprofen may be used (5 mg/kg every 6 hours as required; maximum 20 mg/kg per day), but ONLY under the advice of a healthcare professional.

The intervention will not be double-blinded due to the differing concentrations, minimum dosing intervals and maximum doses per 24 hours of the two interventions. Furthermore, it is common clinical practice to prescribe a second antipyretic or analgesic agent when one alone is assumed to be insufficient, (53) and blinding could potentially place the infant at risk of toxicity.

Research impact

Paracetamol is the most commonly prescribed medication, and over-the-counter medication dispensed, to children in the first year of life, both in NZ and the developed world. The results of the PIPPA Tamariki study will be relevant to all parents and health care providers who see young infants. If the results of the study confirm the strong and consistent epidemiological associations found between paracetamol exposure in infancy and later asthma then we will have provided convincing evidence for a public health intervention that for the first time has the potential to reduce the high prevalence of asthma globally. If the results of the study fail to confirm the epidemiological associations previously found then we will have provided a safety study of the highest quality. Thus, regardless of outcome, the results are expected to be incorporated into all health guidelines that address analgesia and antipyretic use in young infants, including major textbooks, paediatric hospital guidelines, Ministry of Health (MOH) parent advice, and WHO statements. This study will be world leading.
## 5. OBJECTIVES AND OUTCOME MEASURES

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Outcome Measures</th>
<th>Time point</th>
</tr>
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<tbody>
<tr>
<td><strong>Primary Objective</strong>&lt;br&gt;To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of asthma at age 6 years.</td>
<td>The proportion of participants whose parent/caregiver answers “yes” to the question “Has your child had wheezing or whistling in the chest in the past 12 months?” using the ISAAC Phase III Core Questionnaire for Asthma for 6 to 7 year olds. (1)</td>
<td>6 years</td>
</tr>
<tr>
<td><strong>Secondary Objectives</strong>&lt;br&gt;To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of hospital admission with bronchiolitis, viral induced wheeze or asthma in the first year of life.</td>
<td>Proportion of participants hospitalised with bronchiolitis, viral induced wheeze or asthma by 1 year of age using ICD-10 codes (2) and querying the Ministry of Health (MOH) ‘National Non-Admitted Patient Collection’ and ‘National Minimum Dataset’.</td>
<td>1 year*</td>
</tr>
<tr>
<td>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the number of prescriptions for asthma medications in the first year of life.</td>
<td>Proportion of participants completing prescriptions for inhaled corticosteroids (ICS), short acting beta agonists (SABAs), long acting beta agonists (LABAs), or montelukast in the first year of life, by querying the MOH ‘Pharmaceutical Collection’.</td>
<td>1 year*</td>
</tr>
<tr>
<td>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of eczema in the first year of life.</td>
<td>The proportion of participants whose parent/caregiver answers “yes” to the questions “In the last year, has your child had an itchy skin condition – by itchy, we mean scratching or rubbing the skin?” and IF YES “Has this skin condition ever affected the skin creases in the past - by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?” using the UK Diagnostic Criteria for Eczema questionnaire (3)</td>
<td>1 year*</td>
</tr>
<tr>
<td>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of hospitalisation for eczema in the first year of life.</td>
<td>Proportion of participants hospitalised with eczema in the first year of life using ICD-10 codes (54) and querying the MOH ‘National Non-Admitted Patient Collection’ and ‘National Minimum Dataset’.</td>
<td>1 year*</td>
</tr>
<tr>
<td>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of hospitalisation for eczema in the first year of life.</td>
<td>Proportion of participants completing prescriptions for topical steroids in the first year of life.</td>
<td>1 year*</td>
</tr>
</tbody>
</table>
required for fever and pain in the first year of life, increases the number of prescriptions for eczema medications in the first year of life.

<table>
<thead>
<tr>
<th><strong>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the number of prescriptions for eczema medications in the first year of life.</strong></th>
<th><strong>year of life, by querying the Ministry of Health ‘Pharmaceutical Collection’</strong>.</th>
<th><strong>3 years</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of wheeze at 3 years of age.</strong></td>
<td>The proportion of participants whose parent/caregiver answers “yes” to the question “Has your child had wheezing or whistling in the chest in the past 12 months?” using the ISAAC Phase III Core Questionnaire for Asthma for 6 to 7 year olds when the participant is aged 3.</td>
<td><strong>3 years</strong></td>
</tr>
<tr>
<td><strong>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of hospitalisation for viral induced wheeze, bronchiolitis or asthma in the first 3 years of life.</strong></td>
<td>Proportion of participants hospitalised with viral induced wheeze, bronchiolitis or asthma in the first 3 years of life using ICD-10 codes (2) and querying the MOH ‘National Non-Admitted Patient Collection’ and ‘National Minimum Dataset’.</td>
<td><strong>3 years</strong></td>
</tr>
<tr>
<td><strong>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the number of prescriptions for asthma medications in the first 3 years of life.</strong></td>
<td>Proportion of participants completing prescriptions for inhaled ICS, SABA, LABA, montelukast in the first 3 years of life, by querying the MOH ‘Pharmaceutical Collection’.</td>
<td><strong>3 years</strong></td>
</tr>
<tr>
<td><strong>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of eczema at 3 years of age</strong></td>
<td>The proportion of participants whose parent/caregiver answers “yes” to the questions “In the last year, has your child had an itchy skin condition – by itchy, we mean scratching or rubbing the skin?” and IF YES “Has this skin condition ever affected the skin creases in the past - by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?” using the UK Diagnostic Criteria for Eczema questionnaire.</td>
<td><strong>3 years</strong></td>
</tr>
<tr>
<td><strong>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of hospitalisation for eczema in the first 3 years of life.</strong></td>
<td>Proportion of participants hospitalised with eczema in the first 3 years of life using ICD-10 codes(54) and querying the MOH’National Non-Admitted Patient Collection’ and ‘National Minimum Dataset’.</td>
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<td><strong>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of hospitalisation for eczema in the first 3 years of life.</strong></td>
<td>Proportion of participants completing prescriptions for topical steroids in the first 3</td>
<td><strong>3 years</strong></td>
</tr>
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<td>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the number of prescriptions for eczema medications in the first 3 years of life.</td>
<td>years of life by querying the MOH ‘Pharmaceutical Collection’.</td>
<td>3 years</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>The proportion of participants whose parent/caregiver answers “yes” to the question “Has your child had wheezing or whistling in the chest in the past 12 months?” using the ISAAC Phase III Core Questionnaire for Asthma for 6 to 7 year olds, (1) AND/OR “yes” to the questions “In the last year, has your child had an itchy skin condition – by itchy, we mean scratching or rubbing the skin?” and IF YES “Has this skin condition ever affected the skin creases in the past - by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?” using the United Kingdom Diagnostic Criteria for Eczema questionnaire,(3) AND/OR “yes” to the questions “In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?” and IF YES “In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?” using the ISAAC Phase III Core Questionnaire for Rhinitis for 6 to 7 year olds. (1)</td>
<td>3 years</td>
<td></td>
</tr>
<tr>
<td>To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of atopy at 3 years of age.</td>
<td>Proportion of participants completing prescriptions for inhaled ICS, SABA, LABA, montelukast, or monoclonal antibodies for the treatment of asthma in the first 6 years</td>
<td>6 years</td>
</tr>
<tr>
<td>Proportion of participants hospitalised with viral induced wheeze, bronchiolitis or asthma in the first 6 years of life using ICD-10 codes (54) and querying the MOH ‘National Non-Admitted Patient Collection’ and ‘National Minimum Dataset’.</td>
<td>6 years</td>
<td></td>
</tr>
</tbody>
</table>
To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of eczema at 6 years of age.

The proportion of participants whose parent/caregiver answers “yes” to the questions “In the last year, has your child had an itchy skin condition – by itchy, we mean scratching or rubbing the skin?” and IF YES “Has this skin condition ever affected the skin creases in the past - by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?” using the UK Diagnostic Criteria for Eczema questionnaire. (3) 6 years

To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of hospitalisation for eczema in the first 6 years of life.

Proportion of participants hospitalised with eczema in the first 6 years of life using ICD-10 codes(54) and querying the MOH ‘National Non-Admitted Patient Collection’ and ‘National Minimum Dataset’. 6 years

To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the number of prescriptions for eczema medications in the first 6 years of life.

Proportion of participants completing prescriptions for topical steroids in the first 6 years of life by querying the MOH ‘Pharmaceutical Collection’. 6 years

To determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of atopy at 6 years of age.

The proportion of participants whose parent/caregiver answers “yes” to the question “Has your child had wheezing or whistling in the chest in the past 12 months?” using the ISAAC Phase III Core Questionnaire for Asthma for 6 to 7 year olds. (1) AND/OR “yes” to the questions “In the last year, has your child had an itchy skin condition – by itchy, we mean scratching or rubbing the skin?” and IF YES “Has this skin condition ever affected the skin creases in the past - by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?” using the United Kingdom Diagnostic Criteria for Eczema questionnaire. (3) 6 years
AND/OR
“yes” to the questions “In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?” and IF YES “In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?” using the ISAAC Phase III Core Questionnaire for Rhinitis for 6 to 7 year olds. (1)

* If born <37 weeks’ gestation, follow-up based on corrected age

6. TRIAL DESIGN
This is an open-label, two-arm parallel RCT with 1:1 allocation comparing paracetamol treatment versus ibuprofen treatment, as required for fever and pain in the first year of life.

We will enrol 3,922 infants who will be followed up until the age of 6 years, with the schedule and method of contact according to the following table:

<table>
<thead>
<tr>
<th>Age (months)*</th>
<th>Study contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>Informed consent and randomisation, provision of assigned medication</td>
</tr>
<tr>
<td>1</td>
<td>Follow-up reminding parents of study involvement</td>
</tr>
<tr>
<td>3</td>
<td>Follow-up, provision of assigned medication if required</td>
</tr>
<tr>
<td>6</td>
<td>Follow-up, provision of assigned medication if required</td>
</tr>
<tr>
<td>9</td>
<td>Follow-up, provision of assigned medication if required</td>
</tr>
<tr>
<td>12</td>
<td>Follow-up (secondary end-point data collection)</td>
</tr>
<tr>
<td>36</td>
<td>Follow-up (secondary end-point data collection)</td>
</tr>
<tr>
<td>72</td>
<td>Telephone follow-up (primary end-point data collection)</td>
</tr>
</tbody>
</table>

* If born <37 weeks’ gestation, follow-up based on corrected age

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants
3,922 infants.

7.2. Inclusion Criteria
Inclusion criteria:
- Birth within the catchment area of Auckland City, Middlemore or Wellington Hospitals.
- Age <8 weeks (chronological age).

Women may enrol infants from subsequent pregnancies, provided they meet the above inclusion criteria.
7.3. Exclusion Criteria
Infants will not be enrolled if ANY of the following apply:

- Parent is unable to give informed consent for participation in the trial.
- Highly unlikely to remain in NZ for the first 6 years of life.
- Chronic disease associated with limited life expectancy (i.e., less than 6 years).
- Gestational age at birth <32 weeks (very preterm infants are more likely to have a patent ductus arteriosus, which is commonly treated with ibuprofen in the first instance (55,56), and chronic lung disease).
- Previous exposure to paracetamol or ibuprofen since birth.

8. TRIAL PROCEDURES
A schedule of procedures is contained in Appendix A.

8.1. Recruitment

Antenatal identification of potential participants
In the antenatal period, brief information will be available to parents of potential participants. This will be distributed to women who plan to birth within the catchment of Auckland City, Middlemore or Wellington Hospitals through antenatal clinics, general practices and Lead Maternity Carers (LMCs). This brief information will include an invitation to obtain the full Participant Information Sheet (PIS) and the attached Informed Consent Form (ICF), by contacting study personnel via the 0800 number, study email address or by visiting the PIPPA Tamariki Facebook page or Webpage.

In addition to written material handed to pregnant mothers, there will be a PIPPA Tamariki Facebook page and PIPPA Tamariki Web page, which will include a link to the complete PIS/ICF. It will be possible for people to notify a ‘Declaration of Interest’ in the study during pregnancy by contacting study personnel. This will allow early opportunity for parents to have any questions answered, and to indicate interest in enrolling their infant into the study. By visiting the PIPPA Tamariki Facebook page or Webpage it will be possible to select an option to provide contact details and to complete a Maternal Enrolment Questionnaire (Appendix B) on the Webpage.

Post-natal identification of potential participants:
Researchers (research nurses, midwives, doctors, allied health and medical students) will approach families of newborn infants and explain the study to them at a time that is convenient. In hospital, this will be done after ascertaining with the Shift Coordinator of the post-natal ward any families deemed unsuitable for approach. For those who birth at home, it will be up to the parent/guardian to notify the researchers of a convenient time to discuss potential participation. Eligible families will be provided with a PIS/ICF (available in English, Te Reo, Samoan, Fijian, Tongan, Chinese, and Korean) and will have opportunities to discuss the study prior to completing written informed consent. The Language Line telephone interpreting service, or a representative from the Sign Language Interpreters of NZ, will be used when required.
8.2. Screening and Eligibility Assessment

Infants are eligible according to the inclusion and exclusion criteria listed above, and will be screened accordingly by study researchers. Enrolment of the infant and randomisation will occur before the infant is eight weeks of age.

8.3. Informed Consent

Written informed consent will be obtained according to Good Clinical Practice (GCP) guidelines. The informed consent process will involve the researcher giving the parents/guardians the opportunity to read the PIS/ICF, ask questions, and discuss the trial. Although only one parent/guardian is required to sign the consent form, if it is clear that both parents do not agree, the researcher will not enrol the infant. The infant’s parents/guardians will be allowed as much time as wished to consider the information (up to 8 weeks of age), and will be given the opportunity to question the researcher, their General Practitioner (GP), other Primary Health Care provider, or other independent parties to decide whether they will participate in the trial. It will be clearly stated that the parents/guardians of the participant are free to withdraw the participant from the trial at any time, for any reason, without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

Parents/guardians will be asked at enrolment to give prospective informed consent for the study team to use MOH and District Health Board (DHB) databases to track Emergency Department (ED) presentations, hospital admissions, hospital laboratory data (respiratory virus testing results in first year of life), and prescription data based on the participant’s National Health Index (NHI) number. This informed consent will apply to those participants subsequently lost to follow-up and not available to answer follow-up questionnaires.

After the discussion of the trial with the researcher, if the parents/guardians are willing for their infant to participate in the trial, they will be asked to complete, sign, and date the ICF. The researcher will also sign and date the ICF. The researcher will then provide a hard copy of the ICF to the parents/guardians.

Upon completion of the signed ICF by a parent/guardian, the infant is enrolled into the study.

Generally, the ICF would be signed before the infant leaves the hospital. However, if the parents/guardians want more time to consider enrolment following face-to-face discussion with the researcher on the post-natal ward, the researcher would collect the parents’/guardians’ contact details prior to the discharge and follow up via telephone. Subsequent options available to the parents/guardians are:

a) Further telephone discussion with a researcher
b) Posting in their signed ICF after discharge from the hospital (a pre-paid addressed envelope will be provided).
c) Providing evidence of signed informed consent via an electronic ICF after discharge from the hospital.
d) Signing the ICF at a home visit conducted by the researcher.

In the event that there are any other children in the household under the age of 10, parents/guardians will be asked to supply their names, dates of birth and weights to allow prescription of the same study medication to these children, until the index child turns 1 year of age, and to allow ongoing follow-up for potential adverse events (refer to Section 9.5).
8.4. Randomisation

Participants will be randomised with stratification according to maternal asthma status, and multiple birth status, using a computer-generated sequence with randomly permuted block sizes for each site, generated by the study statistician, independent of the researchers and study investigators. Allocation concealment will be by a secure database which contains the randomisation sequence accessible only to the study statistician and independent data manager, utilised just for this role.

Allocation will only be revealed to the researcher once the participating infant is enrolled, and their baseline demographic details and family contact details are entered into the study database.

In the instance of multiple birth, or subsequent birth occurring in the same household, those infants will be allocated to the same intervention (that is the ‘household’ will be randomised to the allocation). In the event of a ‘mixed household’ occurring, where two enrolled households combine, each allocated to a different study medication, subsequent infants enrolled from that mixed household will be allocated to the same study medication as the youngest participant.

This is an ‘open-label’ trial and after randomisation there will be no further concealment of allocation from the parents/guardians.

8.5. Baseline Assessments

Data collection at Enrolment via questionnaire (Appendix B):

- **Maternal demographic and contact details**: name, address, phone number/s, email address(es), social media contacts, date of birth, NHI number, ethnicity, height, weight <14 weeks of pregnancy, DHB of domicile, GP, education level
- **Alternative contacts**: details for two other contacts.
- **Maternal atopic history**: asthma, hayfever, eczema and treatments used
- **Pregnancy details**: Medications, vaccinations, smoking, food allergen exposure, asthma control
- **Paternal demographics and contact details**: name, address, phone number/s, email address, current relationship with mother, smoking
- **Paternal atopic history**: asthma, hayfever, eczema and treatments used
- **Infant demographics**: name/s (if decided); primary caregiver name; address on discharge.
- **Sibling/household members <10 years of age**: For each: date of birth; relationship to index Baby; NHI number; current or last known weight; history of asthma, eczema and hayfever; history of allergy to assigned medication and other medications; history of liver failure; history of kidney failure; history of bleeding, GP details. (Appendix C).

Data collection at Enrolment via clinical record:

- **Birth history**: mode of birth; Apgar at 5 min; resuscitation; birth measurements: weight, head circumference, length; customised birth weight (BW) centile; clinical chorioamnionitis; intrapartum antibiotics; neonatal sepsis and antibiotic use; Neonatal Intensive Care Unit (NICU) or Special Care Baby Unit (SCBU) admission; formula use during primary admission; feed classification at discharge (WHO); neonatal medications during the primary admission (paracetamol, non-steroidal anti-inflammatory use, corticosteroids); neonatal medications on discharge; maternal puerperal sepsis and post-partum antibiotic use.
- **Infant demographics**: NHI; date of birth; place of birth; sex; gestation; birth order, ethnicity
- **Maternal Data**: EDD, parity, number of fetuses,
8.6. Subsequent Assessments
The six subsequent assessments will be conducted by telephone, or may be completed online by parents/caregivers of the enrolled infant. The final 6 year assessment will be conducted by telephone only.

- **Follow-up assessment 1** (at infant age 1 month): confirm name of infant, current weight, current address, GP, and number of people in household and those <10 years of age. For the period from birth to 1 month of age: use of study medication (including number of doses); other medication use; history of wheezy or respiratory illnesses; hospital admissions; adverse reactions (ARs) of index infant and other children <10 years of age who have received study medication. Assess supply of study medication/prescription and recalculate/confirm study medication dose. For siblings/cohabiting other children <10 years of age who receive study medication: supply of study medication/prescription (Appendix D).

- **Follow-up assessment 2** (at infant age 3 months): as for Telephone Assessment number 1, for the period from 1 to 3 months of age.

- **Follow-up assessment 3** (at infant age 6 months): as for Telephone Assessment number 1, for the period from 3 to 6 months of age.

- **Follow-up assessment 4** (at infant age 9 months): as for Telephone Assessment number 1, for the period from 6 to 9 months of age.

- **Follow-up assessment 5** (at infant age 1 year): as for Telephone Assessment number 1, for the period from 9 months to 1 year of age. For the period from birth to 1 year of age: pet exposure, sleeping environment, smoke exposure, health of housing (overcrowding, cold, damp, mould etc.); breast feeding status and use of formula/milk or special diets; current weight; history of wheezy or respiratory illnesses; history of eczema and food allergy; hospital admissions, ethnicity of infant. Record any additional ARs, for infants/children who have received study medication (Appendix D).

- **Follow-up assessment 6** (at child age 3 years): ongoing use of paracetamol or ibuprofen (including number of doses if available); ISAAC Phase III asthma questionnaire (57), history of wheezy or respiratory illnesses; United Kingdom (UK) Diagnostic Criteria for Eczema questionnaire (58); Patient-Oriented Eczema Measure (POEM) (59–62); ISAAC Phase Three rhinitis questionnaire (63); current medication use; hospital admissions; health of housing (overcrowding, heating, cold, damp, mould etc.); smoke exposure; history food allergy in the first 3 years of life (Appendix F), ethnicity of child.

- **Telephone assessment 7** (at child age 6 years; Final assessment): ongoing use of paracetamol or ibuprofen (including number of doses if available); ISAAC Phase III asthma questionnaire (57), history of wheezy or respiratory illnesses; United Kingdom (UK) Diagnostic Criteria for Eczema questionnaire (58); POEM (59–62); ISAAC Phase Three rhinitis questionnaire (63); current medication use; hospital admissions; health of housing (overcrowding, heating, cold, damp, mould etc.); smoke exposure; history food allergy in the first 3 years of life (Appendix F), ethnicity of child.

8.7. Data linkage
A number of study variables will be recorded through data linkage with the following data sets:

**District Health Board (DHB) and the Institute of Environmental Science and Research (ESR) laboratory databases**

- Results of any virology testing for enrolled infants during the 12-month intervention period.

**DHB clinical records**
• Review of medical records for any ‘Serious Adverse Events of Special Interest’ (SAEIs) in enrolled infants during the 12-month intervention period and for household members <10 years of age provided with study medication during the 12-month intervention period.

Ministry of Health Data sets

National Non-Admitted Patient Collection and the National Minimum Dataset
• Hospital presentations for enrolled infants for the duration of the study, and hospital presentations for household members <10 years of age provided with study medication during the 12 month intervention period.

Pharmaceutical Collection
• Prescription use of study medications, asthma medications, antibiotics, oral steroids, topical eczema treatments for enrolled infants for the duration of the study.

The National Immunisation Register
National Immunisation Schedule vaccine doses, and times received, for enrolled infants for the duration of the study.

Ministry of Health

B4 School Check
The data collected in the B4 School Check for the enrolled infants, collected at 4 years of age.

8.8. Discontinuation/Withdrawal of Participants from Trial Treatment
Each participant’s parent/guardian has the right to withdraw their infant from the trial at any time.

In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

• Ineligibility (either arising during the trial, or retrospectively, having been overlooked at screening)
• Significant protocol deviation
• An event which requires discontinuation of the study medication or results in inability to continue to comply with trial procedures
• Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with trial procedures
• Withdrawal of consent

Withdrawal of consent: parents / guardians will be given the option to allow researchers to utilise data collected up to that point, or to have that data excluded from analysis. Data will no longer be collected for any participant after withdrawal of consent. The reason for withdrawal, if given, will be recorded in the withdrawal Case Record Form (CRF).

Lost to follow-up: because parents/guardians will have given prospective informed consent for the study team to use MOH and DHB databases to track ED presentations, hospital admissions and prescription data based on the participant’s NHI number, this information will continue to be collected for participants who are lost to follow-up but have not been withdrawn.

8.9. Definition of End of Trial
The end date of the trial is the completion of the final 6 year telephone follow-up.
9. STUDY MEDICATION

9.1. Study Medication Description
The study medication will be accessed by participants through written prescription. Parents/caregivers may request delivery of study medication if access to a pharmacy is problematic. Dosing for each medication is as per the NZ Formulary for Children (52), and will be in normal formulation in standard therapeutic doses which would otherwise be prescribed in accordance with usual standard of care (52).

Participants will be randomised to one of two treatments for fever and/or pain;

Paracetamol oral suspension (120 mg/5 mL, 250 mg/5 mL):

- Child from 1 month of age
  - 15 mg/kg/dose every 4 hours as required;
  - Maximum of 60 mg/kg per day.
- Under 1 month of age, paracetamol may be used (15 mg/kg every 6 hours as required; maximum of 60 mg/kg per day), but ONLY under the advice of a healthcare professional.

Ibuprofen oral suspension (100 mg/5 mL):

- Child 1 to 3 months of age
  - 5 mg/kg every 6 hours as required;
  - Maximum 20 mg/kg per day.
- Child over 3 months of age
  - 10 mg/kg every 6 hours as required;
  - Maximum 30 mg/kg per day.
- Under 1 month of age, ibuprofen may be used (5 mg/kg every 6 hours as required; maximum 20 mg/kg per day), but ONLY under the advice of a healthcare professional.

Parents/caregivers will be asked to restrict infants to using only the assigned study medication (paracetamol or ibuprofen) for the first 12 months of life.

At each contact point researchers will make sure families have a supply of the study medication, and calculate the appropriate dose for the current weight of the infant and other children <10 years of age in the household. If further study medication is required between phone contacts, this will be sent to families or a prescription faxed to their local pharmacy.

9.2. Instructions for parents/caregivers
Families will receive instructions relating to the safe and appropriate administration and storage of the study medication. This includes contact details for the National Poisons Centre in case of overdose.

9.3. Adherence with Trial Treatment
An 0800 study contact phone line, email address, iPhone and android app, PIPPA Tamariki Website and Facebook private message system will be available for families to request study medication at any time. Doses of assigned study medication will be calculated as described in Section 9.1.
Families will be provided with wallet sized reminder cards concerning the study and the treatment to which their infant has been assigned. Families will be provided with Study Diaries to record number of doses of the study medication given to each participant. Parent/caregivers will have an option of monthly text or email alerts to remind them to enter details of medication administration into their Study Diary. Telephone follow-up conversations in the first 12 months will also be a reminder to families of the study requirements.

Participant’s Primary Health Care providers will be advised of the infant’s participation in the study and their assigned treatment. Electronic alerts will be placed in local hospital records stating that the participant is in the study and the treatment arm to which they have been assigned.

9.4. Other children under 10 years in the household
To assist parents / caregivers with participant adherence to the randomised intervention, an offer to provide the same study medication to other household members <10 years of age will be made. The dosing of study medication will be in accordance with the NZ formulary for children (52).

Respective GPs will be advised that these children are being prescribed study medication for the period that the index infant is receiving study medication.

These other household members <10 years of age provided with study medication will be monitored for SAESI, in accordance with Section 10.

9.5, Post-trial Treatment
The study medication will not be provided or prescribed by researchers beyond the 12-month interventional period of the trial.

10. SAFETY REPORTING
The characteristics of paracetamol and ibuprofen are well understood. Both are widely available to infants and children in the community by prescription and ‘over-the-counter’. Therefore, it is intended only to collect data relating to:

- Adverse reactions to study medication,
- Death,
- Hospitalisation due to events known to be, or putatively associated with, exposure to paracetamol or ibuprofen.

For the purposes of this study, all the above will be referred to as Serious Adverse Events of Special Interest (SAESIs). SAESIs reported by the parent/caregiver, or found on examination of DHB and national datasets, will be recorded on the CRF.

A participant’s Parent/Guardian may voluntarily withhold study medication from the participant due to what they perceive as a safety concern due to the study medication. This will be captured in the electronic Clinical Record Form (eCRF).
### 10.1 Definitions

| Serious Adverse Event of Special Interest (SAESI); known to be, or putatively associated with, exposure to study medication. | • Death  
• Empyema / pleural effusion requiring intervention (diagnostic aspiration or drainage)  
• Probable or confirmed bacterial meningitis  
• Probable or confirmed osteomyelitis  
• Confirmed septicaemia (positive microbiology and a clinical picture consistent with sepsis).  
• Intensive care admission with probable or confirmed varicella, sepsis, bacterial pneumonia or cellulitis  
• Gastrointestinal (GI) bleeding, or haemorrhage, requiring endoscopy or transfusion with blood products  
• Acute liver failure  
• Renal failure  
• Study medication overdose (presentation to an ED with a diagnosis of overdose) |
|---|---|
| Adverse Reaction (AR) | An untoward and unintended response to a Study Medication which is related to any dose administered during the intervention period.  
The phrase "response to a Study Medication" means that a causal relationship between the study medication and an AR is at least a reasonable possibility, i.e., the relationship cannot be ruled out.  
All cases judged by either the reporting medically qualified professional as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions. |
| Serious Adverse Reaction (SAR) | An adverse reaction that results in hospitalisation or death and, in the opinion of the reporting Investigator, is believed with reasonable probability to be due to the use of the study medication, based on the information provided. It is expected that the events that occur will be similar to the SAESIs. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the known information about the study medication. |

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.
10.2. **Causality**
The relationship of each SAESI to the study medication must be determined by the site PI according to the following definitions:

**Related**: The adverse event follows a reasonable temporal sequence from the study medication administration. It cannot reasonably be attributed to any other cause.

**Not Related**: The adverse event is produced by the participant’s clinical state or by other modes of therapy administered to the participant.

**Possibly related**: For each SAESI, the relevant hospital medical record will be reviewed by the Site PI to determine causality, and if necessary parents will be contacted for further information. The causality for all SAESIs will be reviewed yearly by the three site PIs for consistency and agreement between sites. Summary data of these events will be reviewed by the DSMC unless specified otherwise by the DSMC.

10.3. **Surveillance for Serious Adverse Events of Special Interest**
Further information regarding SAESIs will be gathered in the following way.

**Active surveillance**: searching of Wellington, Kidz First and Starship Hospital admission and discharge lists by researchers to determine if any study participant, or household member <10 years of age provided with study medication, has been admitted with an SAESI.

**Active reporting** of SAESIs to Site Investigators by clinicians in the three hospitals will be encouraged.

**Passive surveillance** using NHI numbers and data linkage, (section 8.7) will be undertaken in accordance with study SOPs:

1. All infective admissions to hospital (including all admissions to EDs for longer than 3 hours) on the basis of ICD-10 codes (every admission will be counted);
2. All renal failure admissions to hospital on the basis of ICD-10 codes (only the first admission will be counted);
3. All liver failure admissions to hospital on the basis of ICD-10 codes (only the first admission will be counted);
4. All GI haemorrhage admissions to hospital on the basis of ICD-10 codes (every admission will be counted);
5. All intentional and unintentional overdoses (every admission will be counted);
6. All admissions to hospital with varicella (every admission will be counted);
7. Death.

Passive surveillance summary data will be submitted annually to the DSMC.

10.4. **Data Collection for SAESIs / SARs**
- All SAESIs / SARs will have a CRF completed which will include:
  - Detailed use of study medication in the one month prior to presentation;
  - Length of hospital stay;
• Length of intensive care stay;
• Outcome at one month (discharge from hospital normal function; discharge from hospital likely mild impairment of pre-admission function; discharge from hospital likely moderate/severe impairment of pre-admission function; remains admitted in hospital likely mild impairment of pre-admission function; remains admitted in hospital likely moderate/severe impairment of pre-admission function; death);
• Positive microbiology specimens (including site and organism);
• Initial length of antibiotic treatment;
• Initial length of antiviral treatment;
• Use of N-Acetylcysteine (NAC) for paracetamol overdose;
• Use of renal replacement therapy;
• Patient being considered for renal or liver transplant,
• Event description of admission and clinical course;
• Opinion of local investigator as to relationship of SAE to study intervention.

10.5. Reporting Procedures for Deaths
All deaths must be reported to the Principal Investigator within 72 hours of the researcher(s) becoming aware of the event. The Site Investigator will be responsible for completion of the reporting form. Any additional relevant information will be reported within 40 calendar days of the initial report. Deaths will be reviewed for causality by the three site PIs.

Principal Investigator contact details:

Name: Dr Stuart Dalziel
Children’s Emergency Department,
Auckland District Health Board, New Zealand.
Email: sdalziel@adhb.govt.nz
Phone +64 9 3074949
Mobile +64 21 869 068
Fax +64 9 3757055

10.6. Expectedness
Expectedness will be determined according to the current Data Sheet for both study medications posted on the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) website by both a medically qualified investigator at each site and by the Data and Safety Monitoring Committee (DSMC) at each review period.

10.7. SUSAR Reporting
All SUSARs will be reported by the Principal Investigator to the Centre for Adverse Reactions and Monitoring (CARM). For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Principal Investigator or delegate is first aware of the reaction. Any additional relevant information will be reported within 10 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

The Principal Investigator will be informed of all SUSARs for the study medication throughout the study.
10.8. **Data and Safety Monitoring Committee (DSMC)**

A DSMC will be established, chaired by Associate Professor Philip Pattemore (Department of Paediatrics, University of Otago, and Paediatric Respiratory Physician Christchurch Hospital), who is independent from the study team. A DSMC charter will be prepared, prior to study initiation, focusing on recruitment and safety. Both medications have been widely used for many decades and unexpected adverse events from either intervention are likely to be rare. As all participants will be recruited into the study prior to any measurement of primary outcome, an interim analysis is not planned.

**Reports:** The Data and Safety Monitoring Committee (DSMC) will receive yearly summary reports of all SAEsIs and SARs. Passive surveillance summary data will be submitted annually to the DSMC. These will be masked as to study group allocation in the first instance. Data for SAEsIs / SARs will be reported, using simple descriptive statistics.

11. **STATISTICS**

11.1. **Description of Statistical Methods**

A statistical analysis plan will be developed. In summary, the primary and secondary efficacy analysis will be by intention-to-treat. The primary analysis of the primary outcome variable will be by logistic regression comparing the two randomised groups to allow comparison of the main effect with a sensitivity analysis incorporating the following important variables: parental history of asthma, maternal exposure to paracetamol during pregnancy, number of respiratory infections, smoke exposure, pet exposure, housing, and breast-feeding status.

All members of one family will receive the same study intervention. Twins, and higher order multiple birth infants, will be eligible for enrolment into the study. Although we anticipate that this will be a small proportion of participants as part of the sensitivity analysis we will also use a generalized linear mixed model to account for possible correlation between participants from the same family (household as random effect).

11.2. **Sample Size**

The primary outcome variable is prevalence of wheeze in the last 12 months at age 6 years using the ISAAC Phase III study questionnaire (63). In NZ the ISAAC Phase III study reported the prevalence of wheeze in 6 to 7 year old children in the last 12 months was 22.2% and the estimate from the earlier ISAAC Phase I in the same population was 23.6% (64). An analysis of the full ISAAC Phase III data from 194,555 children aged 6 to 7 years, in 29 countries, estimated that use of paracetamol for fever in the first year of life was associated with an increased risk of wheeze in the last 12 months with an OR of 1.46 (95% CI 1.36 to 1.56) (32). Inverting this OR based risk, and based on a prevalence of between 22.2-23.6%, this is consistent with a RR of approximately 0.75 for wheeze in non-users of paracetamol.

We propose recruiting 3,922 participants into the PIPPA Tamariki study based on an event rate of wheezing or asthma, in the paracetamol group of 22%. This number (3,922) will give 90% power to detect a RR for wheeze of 0.8 in the ibuprofen group compared to the paracetamol group, with an alpha of 5%. This number also allows for an overall withdrawal/loss to follow-up rate of 10%, and for an efficacy dilution factor of 10% due to participants assigned to each intervention arm who are likely to be exposed to the alternative intervention within the first year of life. Previous studies of 6 year old children recruited in the
perinatal period by members of the study team have achieved > 90% follow-up with a similar frequency of scheduled participant contact to that proposed.

11.3. **The Level of Statistical Significance**
Comparisons will use two-sided tests at an overall significance level of 5%.

11.4. **Criteria for the Termination of the Trial**
There will be no statistical criteria for early termination of the trial.

11.5. **Procedure for Accounting for Missing, Unused, and Spurious Data.**
There will be no imputation for missing data.

11.6. **Inclusion in Analysis**
All randomised participants will be included in the analysis on an intention-to-treat basis.

11.7. **Procedures for Reporting any Deviation(s) from the Original Statistical Plan**
Any deviation(s) from the original statistical plan will be described and justified in the final report.

12. **DATA MANAGEMENT**

12.1. **Source Data**
Source documents are where data are first recorded, and from which participants’ CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, Study Diaries, microfiches, radiographs, correspondence, and the eCRF.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data).

eCRF entries will be considered source data if the eCRF is the site of the original recording (e.g. there is no other written or electronic record of data, or CRF).

12.2. **Access to Data**
Direct access will be granted to authorised representatives from the host institutions and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.3. **Data Recording and Record Keeping**
Study data will be collected and managed using REDCap (Research Electronic Data Capture) (65) electronic data capture tools. REDCap is a secure, HIPAA (United States Health Insurance Portability and
Accountability Act 1996) compliant web-based application designed to support data capture for research studies, providing:

1) an intuitive interface for validated data entry;
2) audit trails for tracking data manipulation and export procedures;
3) automated export procedures for seamless data downloads to common statistical packages, including de-identified data sets; and
4) procedures for importing data from external sources.

It is the intention of the Investigators to capture as much material as possible immediately into the eCRF, particularly with respect to parent/caregiver reported outcomes, National Dataset queries and researcher/parent/caregiver interactions. Data will be entered at point-of-interview via tablet devices (enrolment) or desk tops (telephone follow-up), or directly by parents/caregivers via online access, allowing immediate data validation of entered data. Participants will be encouraged to provide ad hoc information via text, smart-phone applications or online. Paper based case report forms (CRFs) will be available as back-ups.

As this study cohort is unique, there is the potential for additional research questions as yet unknown to the Investigators to be answered from it. Should an opportunity arise to analyse, collect or record further data, all necessary regulatory approvals will be sought prior to this occurring. During the study, eCRFs will be stored on the REDCap database at the Medical Research Institute of New Zealand (MRINZ). After study completion, all study data will be transferred to the guardianship of the Head of Department of Paediatrics: Child and Youth Health, The University of Auckland, and will be kept indefinitely.

All storage arrangements will comply with current GCP standards.

### 12.4. Quality Assurance Procedures

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures (SOPs).

Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The PIPPA Tamariki Steering Committee will meet regularly by teleconference and intermittently face-to-face. This committee will be responsible for the development of the study protocol, CRFs, SOPs, advertising, communications and social media materials, HDEC applications, Māori consultation and approval, as well as site staffing, recruitment and study-related processes.

The PIPPA Tamariki Advisory Group, comprising the Steering Committee and other named investigators, will provide specialised oversight for all aspects of the study. The SAG will meet regularly by teleconference, and intermittently face-to-face during the course of the study. This group will advise on scientific matters, relevant data to collect, Māori consultation, Pacific consultation, analysis and publication of data.
13. SERIOUS BREACHES
A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Host Organisation must be notified within 5 working days. The PI and the Steering Committee will review the breach and if appropriate will report it to the HDEC committee within one month.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Declaration of Helsinki
The PI and the Site Investigators (Site PIs) will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

14.2. Guidelines for Good Clinical Practice
The PI and the Site Investigators (Site PIs) will ensure that this trial is conducted in accordance with relevant regulations and in accordance with Good Clinical Practice.

14.3. Approvals
The protocol, ICF, PIS, questionnaires and any proposed advertising material will be submitted to a HDEC ethics committee, and study sites for written approval.

Regional approval from Maori Research Review Committees associated with each site will be obtained.

The trial will be prospectively registered on the Australia New Zealand Clinical Trials Registry ANZCTR: http://www.anzctr.org.au/default.aspx.

The PI will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.4. Reporting
The PI, on behalf of the study steering committee, shall submit once a year throughout the clinical trial, or on request, regular reports to the HDEC and the HRC in accordance with each organisation’s requirements.

14.5. Participant Confidentiality
All trial staff will ensure that the participants’ anonymity, and that of their family, is maintained.

This study will be conducted in accordance with NZ legislation, including the Health Information Privacy Code 1994, The Health and Disability Code 1996 and the NZ Bill of Rights Act 1990. All sites will be reminded
of their obligations with respect to Good Clinical Practice, confidentiality and privacy, and their obligations in relation to the HDC Code of Rights.

On the PIS/CF, within the demographic section of the eCRF, and in communications to healthcare providers, the participant will be referred to using any of their full name, date of birth and NHI number. In any other study related documentation not contained within the eCRF, the trial participant will be referred to by study number/code and initials, not by name.

All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Health Information Privacy Code.

14.6. Expenses and Benefits

It is intended that no participating families will be out of pocket as a result of participating in this study. Study participants may be given a small soft toy on enrolment, a phone voucher or equivalent up to the value of $20, as well as study related materials such as pens, stickers, Study Diaries, and medication bags.

14.7. Other Ethical Considerations

In this study the enrolled infant is a legally incompetent minor, and thus a legal parent or guardian will be required to complete the PIS/CF. In the event the legal parents / guardians are in disagreement about enrolling the infant into the study, the infant will not be enrolled.

15. FINANCE AND INSURANCE

15.1. Funding

This study is funded by the HRC.

15.2. Insurance

If participants were injured as a result of participating in this study, they would be eligible to apply for compensation from the Accident Compensation Corporation (ACC). This does not mean that any such claim will automatically be accepted.

16. PUBLICATION POLICY

It is the intention of the Investigators to disseminate of research findings, in order to ensure knowledge translation and implementation into practice. This will be in the form of peer reviewed journal publications, and abstracts at national and international scientific meetings.

Where possible, results will also be disseminated into national and international guidelines, including but not limited to: PREDICT (66), DHBs At Risk Individual (ARI) for child development group, Global Initiative for Asthma Assembly (GINA), the NZ Asthma and Respiratory Foundation asthma guidelines group, the American Academy of Pediatrics bronchiolitis guideline committee, ON TRACK Network (OTN) Strategic Research Initiative, and the Interdisciplinary Maternal Perinatal Australasian Collaborative Trials (IMPACT) Network.
Other activities will include providing feedback to participant families and organisations that have supported the research, writing commentaries and editorials in which research findings can be further disseminated, and presenting findings to lay audiences through established media links.

16.1. AUTHORSHIP

Authorship will be agreed in accordance with the International Committee of Medical Journal Editors (ICMJE) for abstracts, publications and other means of disseminating results (67). If authorship is to be designated by a Group Name, then all group members who can take credit and responsibility for the work as authors will be individually identified. Contributors who do not meet the ICJME criteria for authorship will be acknowledged in the disseminations.
17. REFERENCES


2. 2017 ICD-10-CM Diagnosis Codes J00-J99 : Diseases of the respiratory system.


19. Dimova S, Hoet PH, Dinsdale D, Nemery B. Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II


35. Beasley RW, Clayton TO, Crane J, Lai CK, Montefort SR, Mutius E, et al. Acetaminophen use and


66. PREDICT in Primary Care - The University of Auckland [Internet].
ICMJE | Recommendations | Defining the Role of Authors and Contributors.  
18. APPENDIX A: SCHEDULE OF PROCEDURES

Schedule of Trial Procedures

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Antenatal</th>
<th>Enrolment 0-8 weeks</th>
<th>Follow up #1 (1m)</th>
<th>Follow up #2 (3m)</th>
<th>Follow up #3 (6m)</th>
<th>Follow up #4 (9m)</th>
<th>Follow up #5 (1 year)</th>
<th>Follow up #6 (3 years)</th>
<th>Follow up #7 (6 years)</th>
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<td>Pre-enrolment</td>
<td>Notification of interest</td>
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<td>Enrolment</td>
<td>Eligibility Screen</td>
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<td></td>
<td>Written informed consent</td>
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<td></td>
<td>Randomisation</td>
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<td>Intervention</td>
<td>Paracetamol prescription/supply (as needed) OR Ibuprofen prescription/supply (as needed)</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Issue Study supplies as needed</td>
<td>Wallet cards, Diary, pen, stickers, study medication prescription/supply for siblings/cohabiting children &lt;10yrs of age</td>
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<td>X</td>
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Note: Q= Questionnaire
19. APPENDIX B: MATERNAL ENROLMENT QUESTIONNAIRE

I would like to start by asking for some details about yourself:

1. What do you like to be called? (your preferred name)

2. What is your date of birth? (confirm hospital record)

3. Which ethnic group do you belong to? Mark the space or spaces which apply to you.
   New Zealand European
   Māori
   Samoan
   Cook Island Māori
   Tongan
   Niuean
   Chinese
   Indian
   Other (Please state: eg, DUTCH, JAPANESE, TOKELAUA).

   If Maori, do you know the name(s) of your iwi (tribe or tribes)?
   No. Go to the next question.
   Yes. Print the name and home area, rohe or region of your iwi below. (Allow multiple listings)

       Iwi:

       Rohe (or region):

4. What is your height? (specify in cm or feet/inches)

5. What was your weight before 14 weeks of pregnancy (specify in kg, or stones/pounds, or pounds only)

6. What is your highest level of education? (Primary school, High school, University, Technical Institute, Other tertiary education)

Now I would like to get some contact details and / or confirm your contact details

7. Is your address correct? (yes, no) [pipe details from registration from]
   i. If no, please add record your correct address
8. Email
   a. Alternative email

9. Home phone

10. Mobile phone
    a. Alternative mobile phone

11. What are your preferred ways for us to contact you? (Tick your preferred methods)
    a. Text
    b. Email
    c. Phone
    d. Facebook ID:
    e. WhatsApp ID:
    f. Twitter ID:
    g. Other

I would like to ask about the household that Baby will be going home to / currently living in:

12. Including yourself, how many adults (aged 18 or over) in the household?
    a. 1 (yourself)
    b. More than 1_________
       i. How many of these other adults are ______ in relation to Baby?
          1. Other parent / mother’s partner
          2. Grandparent
          3. Siblings
          4. Uncles / aunts
          5. Cousins
          6. Flatmate / Boarder
          7. Other

13. How many children older than 10 and less than 18 are in the household?
    a. None
    b. More than 1_____
       i. How many of these are ______ in relation to Baby?
          1. Siblings
          2. Uncles / aunts
          3. Cousins
          4. Flatmate’s / Boarder’s child
          5. Other

14. Not counting Baby, how many children less than 10 years of age in the household?
    a. None – do nothing
b. More than 1______
   i. How many of these are ...... in relation to Baby?
      1. Siblings
      2. Uncles / aunts
      3. Cousins
      4. Flatmate’s / Boarder’s child
      5. Other
         a. Would you like us to provide them with the study medication also?
            1. No – do nothing
            2. Yes – Go to Appendix C and complete enrolment for each child <10 years receiving study medication

15. Is your family doctor going to be your Baby’s doctor?
   a. If yes: confirm / correct details [pipe details from registration form]
   b. If no, please add details for Baby’s doctor

I would like to get some details for other people to contact if we cannot get hold of you:

16. Please provide details of two other people whom we can contact in case you change address or phone number:
   a. Contact 1:
      i. Name
      ii. Relationship to you
      iii. Email
      iv. Phone
      v. Mobile
   b. Contact 2:
      i. Name
      ii. Relationship to you
      iii. Email
      iv. Phone
      v. Mobile

I would like to ask some questions about whether you have, or have had, asthma, eczema, and hayfever:

17. Have you ever been told by a doctor that you have asthma?
   a. Yes
   b. No
   c. Unsure
      i. If yes:
1. Do you still have asthma (by still have, I mean wheezing or taking asthma treatment in past 12 months)?
   a. Yes  
   b. No  
   c. Unsure  
      i. If yes  
         d. How was your asthma control during this pregnancy compared to before pregnancy?  
            i. A lot worse  
            ii. Slightly worse  
            iii. About the same  
            iv. Slightly better  
            v. A lot better  
   e. What treatment(s) did you take for asthma this pregnancy? (Tick all that apply. Please note: *does NOT include anti-histamines)  
      i. “Reliever” inhaler, also known as a Short-Acting Beta Agonist, e.g., Salbutamol, Ventolin, Asthalin, Respigen, SalAir  
      ii. “Preventer” inhaler, also known as a Steroid inhaler e.g., Flixotide, Floair, Pulmicort  
      iii. “Combined” inhaler, also known as a Combined Steroid & Long-Acting Beta Agonist inhaler, e.g., Seretide, RexAir, Symbicort, Vannair  
      iv. Prednisone tablets  
      v. Theophylline tablets  
      vi. Other asthma inhalers e.g., Sodium cromoglycate (SCG), Nedocromil

2. Pregnancy asthma control test:
   a. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work or at home?  
      i. All of the time  
      ii. Most of the time  
      iii. Some of the time  
      iv. A little of the time  
      v. None of the time  
   b. During the past 4 weeks, how often did you have shortness of breath due to your asthma?  
      i. More than once a day  
      ii. Once a day
iii. 3 to 6 times a week  
iv. 1 or 2 times a week  
v. Not at all

c. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?  
i. 4 or more nights a week  
ii. 2 or 3 nights a week  
iii. Once a week  
iv. Once or twice  
v. Not at all  

d. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication, such as salbutamol (Ventolin)?  
i. 3 or more times per day  
ii. 1 to 2 times per day  
iii. 2 to 3 times per week  
iv. Once or twice  
v. Not at all  

e. How would you rate your asthma control during the past 4 weeks?  
i. Not controlled at all  
ii. Poorly controlled  
iii. Somewhat controlled  
iv. Well-controlled  
v. Completely controlled

18. Have you ever been told by a doctor that you have hay fever?  
a. Yes  
b. No  
c. Not sure  
   i. If yes, did you have hay fever during this pregnancy?  
      1. Yes  
      2. No

19. Have you ever been told by a doctor that you have eczema?  
a. Yes  
b. No  
c. Not sure  
   i. If yes, did you have eczema during this pregnancy? (yes, no)

Now I would like to ask some questions about medications during your pregnancy

20. Did you take any of the following medications at any time during this pregnancy?
a. Paracetamol (Panadol)
   i. Yes
   ii. No
   iii. Don’t know
1. If yes:
   a. How many times did you take paracetamol in the first half of pregnancy (before 20 weeks or before the anatomy scan)
      i. Never
      ii. 1-3 times
      iii. 4-6 times
      iv. 7-9 times
      v. 10 or more times
   b. How many times did you take paracetamol in the second half of pregnancy (after 20 weeks or after the anatomy scan)
      i. Never
      ii. 1-3 times
      iii. 4-6 times
      iv. 7-9 times
      v. 10 or more times
b. Aspirin e.g., Disprin, Aspec, Aspro, Cartia, Cardiprin, Ethics Aspirin, Solprin
   i. Yes
   ii. No
   iii. Don’t know
1. If yes
   a. How many times did you take aspirin in the first half of pregnancy (before 20 weeks or before the anatomy scan)
      i. Never
      ii. 1-3 times
      iii. 4-6 times
      iv. 7-9 times
      v. 10 or more times
   b. How many times did you take aspirin in the second half of pregnancy (after 20 weeks or after the anatomy scan)
      i. Never
      ii. 1-3 times
      iii. 4-6 times
      iv. 7-9 times
      v. 10 or more times

c. Other anti-inflammatory medicines, e.g., ibuprofen (Nurofen, Brufen), diclofenac (Voltaren)
   i. Yes
   ii. No
   iii. Don’t know
1. If yes
a. How many times did you take anti-inflammatory medicines in the first half of pregnancy (before 20 weeks or before the anatomy scan)
   i. Never
   ii. 1-3 times
   iii. 4-6 times
   iv. 7-9 times
   v. 10 or more times
b. How many times did you take anti-inflammatory medicines in the second half of pregnancy (after 20 weeks or after the anatomy scan)
   i. Never
   ii. 1-3 times
   iii. 4-6 times
   iv. 7-9 times
   v. 10 or more times
d. Antibiotics
   i. Yes
   ii. No
   iii. Don’t know
      1. If yes, why did you take antibiotics (tick all that apply)?
         a. Respiratory / chest infection
         b. Urine infection
         c. Ruptured membranes (waters broken)
         d. Antibiotics in labour / at delivery
         e. Other
e. Did you take any other medications in pregnancy?
   i. Yes
   ii. No
   iii. Don’t know
      1. If yes, specify.
f. Did you have any immunisations during this pregnancy?
   i. Yes
   ii. No
   iii. Don’t know
   iv. Refused
      1. If yes, select all that apply
         a. Influenza
         b. Pertussis
         c. RSV
         d. Other (specify))

Now I would like to ask you about smoking
21. Did you smoke cigarettes regularly (every day) before you were aware you were pregnant?
   a. Yes
   b. No
   c. Refused
      i. If yes, how many cigarettes did you smoke per day, on average, before this pregnancy?
         [INSTRUCTIONS Enter as double digits range 1-80]

22. Are you currently smoking cigarettes?
   a. Yes
   b. No
   c. Refused
      i. If yes, how many cigarettes do you smoke per day, on average?
         [INSTRUCTIONS Enter as double digits range 1-80]

23. Did anyone smoke cigarettes in the same room as you during pregnancy?
   a. Yes
   b. No
   c. Refused
      i. If yes, How often?
         1. Rarely (less than once a week),
         2. Occasionally (a few times a week),
         3. Often (almost or every day of week))

I would like to ask you some questions about your diet during this pregnancy

24. During this pregnancy how often, on average, did you eat or drink the following? (Never, Only occasionally, Once or twice per week, Most or all days)
   a. Fish
      i. Never
      ii. Only occasionally
      iii. Once or twice per week
      iv. Most or all days
   b. Shellfish
      i. Never
      ii. Only occasionally
      iii. Once or twice per week
      iv. Most or all days
   c. Cow’s milk (including flavoured milk)
      i. Never
      ii. Only occasionally
      iii. Once or twice per week
      iv. Most or all days
   d. Other dairy (cheese, yoghurt, ice-cream)
      i. Never
ii. Only occasionally
iii. Once or twice per week
iv. Most or all days

e. Eggs
   i. Never
   ii. Only occasionally
   iii. Once or twice per week
   iv. Most or all days

f. Peanut
   i. Never
   ii. Only occasionally
   iii. Once or twice per week
   iv. Most or all days

g. Tree nuts (Hard-shelled nuts: almonds, brazil nuts, cashews, chestnuts, hazelnuts, macadamia nuts, pecans, pistachios, pinenuts, shea nuts, walnuts)
   i. Never
   ii. Only occasionally
   iii. Once or twice per week
   iv. Most or all days

h. Soy (e.g. soy milk, tofu)
   i. Never
   ii. Only occasionally
   iii. Once or twice per week
   iv. Most or all days

i. Wheat (e.g. bread, cereals)
   i. Never
   ii. Only occasionally
   iii. Once or twice per week
   iv. Most or all days

25. Are you happy to answer some questions about baby’s father?
   a. Yes
   b. No

   If yes:

   c. First name

   d. Family name

   e. Date of birth

   f. Are you living with baby’s father?
      i. Yes
      ii. Refused
iii. Other! (Specify)
iv. No
   1. If no, (and if known) Father’s address: [4 lines; postcode]

  g. Email

  h. Alternative email

  i. Mobile phone
     i. Alternative phone number

  j. Has the baby’s father ever had any of the following illnesses diagnosed by a doctor?
     i. Asthma
        1. Yes
        2. No
        3. Unsure
           a. If yes, has he been on treatment for asthma in the last 12 months?
              i. Yes
              ii. No
              iii. Unsure

     k. Hay fever
        i. Yes
        ii. No
        iii. Unsure
           1. If yes, has he been on treatment for Hayfever in the last 12 months?
              a. Yes
              b. No
              c. Unsure

     l. Eczema
        i. Yes
        ii. No
        iii. Unsure
           1. If yes, has he been on treatment for Hayfever in the last 12 months?
              a. Yes
              b. No
              c. Unsure

  m. Does this baby’s father currently smoke cigarettes?
     i. Yes
     ii. No
     iii. Unsure

  n. Did he smoke cigarettes at any time during this pregnancy?
     i. Yes
     ii. No
     iii. Unsure
### APPENDIX C: HOUSEHOLD MEMBERS <10 YEARS OF AGE TO BE PROVIDED WITH STUDY MEDICATION (COMPLETED ONLY WHEN REQUIRED)

1. Full Name.

2. Date of Birth.

3. Sex.

4. NHII. (To be entered by researchers from clinical records)

5. Relationship to PIPPA Tamariki participant?
   - Sibling
   - Cousin
   - Uncle or Aunt
   - Flatmate’s / boarder’s child
   - Other, please specify __________________________

6. Have you ever been told by a doctor that [name] has asthma?
   - Yes
   - No (go to 9)
   - Don’t know (go to 9)
   - Refused (go to 9)

7. In the last 12 months, has [name] had an attack of asthma?
   - Yes
   - No
   - Don’t know
   - Refused

8. Is [name] using regular medications (inhalers) for their asthma?
   - Yes
   - No
   - Don’t know
   - Refused

9. Have you ever been told by a doctor that [name] has eczema?
   - Yes
   - No (go to 11)
   - Don’t know (go to 11)
   - Refused (go to 11)

10. Is [name] using regular medications (creams or tablets or pills) for their eczema?
    - Yes
    - No
    - Don’t know
    - Refused

11. Have you ever been told by a doctor that [name] has hayfever?
    - Yes
    - No (go to 13)
c. Don’t know (go to 13)
   d. Refused (go to 13)

12. Is [name] using regular medications (intranasal spray or tablets or pills) for their hayfever?
   a. Yes
   b. No
   c. Don’t know
   d. Refused

13. Have you ever been told by a doctor that [name] has kidney (renal) disease?
   a. Yes (please specify)
   b. No
   c. Don’t know
   d. Refused

14. Have you ever been told by a doctor that [name] has liver disease?
   a. Yes (please specify)
   b. No
   c. Don’t know
   d. Refused

15. Have you ever been told by a doctor that [name] has a bleeding disorder or problem?
   a. Yes, please specify _________________________________
   b. No
   c. Don’t know
   d. Refused

16. Is [name] allergic to paracetamol or pamol?
   a. Yes
   b. No
   c. Don’t know
   d. Refused

17. Is [name] allergic to any ibuprofen or brufen or nurofen?
   a. Yes
   b. No
   c. Don’t know
   d. Refused

18. Is [name] allergic to any other medications?
   a. Yes, please list (up to 6)
   b. No
   c. Don’t know
   d. Refused

19. When was the last time you got [name] weighed?
   a. In the last 1 month
   b. In the last 2 to 3 months
   c. In the last 4 to 12 months
   d. Over a year ago (finish)
   e. Have never got weighed (finish)
   f. Don’t know (finish)
g. Refused (finish)

20. Can you remember what [name] weighed then?
   a. Yes, _______ . ______ Kg
   b. No
   c. Don’t know
   d. Refused

21. Does [name] have the same family doctor as Baby?
   a. Yes – no action
   b. No – obtain GP details for letter.
21. APPENDIX D: 1MONTH, 3 MONTH, 6 MONTH AND 9 MONTH QUESTIONNAIRE

1. Have you registered your baby’s formal name? (for 1/12 and 3/12 epoch)
   a. Yes, please specify __________________________
   b. No
   c. Don’t know
   d. Refused

2. Have you registered your baby with a general practitioner (GP)? (for 1/12 epoch)
   a. Yes, details already supplied
   b. Yes, please specify __________________________
   c. No
   d. Don’t know
   e. Refused
   f. Or, have you changed your baby’s general practitioner (GP)? (for epochs after 1/12)
      i. Yes, please specify __________________________
      ii. No
      iii. Don’t know
      iv. Refused

3. Which ethnic group does your baby belong to? Mark the spaces which apply. (for 1/12 epoch only)
   New Zealand European
   Maori
   Samoan
   Cook Island Maori
   Tongan
   Niuean
   Chinese
   Indian
   Other (Please state: eg DUTCH, JAPANESE, TOKELAUAN).

   If Maori, do you know the name(s) of your baby’s iwi (tribe or tribes)?
   No. Go to the next question
   Yes. Print the name and home area, rohe or region of your iwi below. (Allow multiple listings).
   Iwi:
   Rohe (or region):

Let’s talk about <<baby’s name’s>> study medication use since we last spoke to you... (If allocated to paracetamol, paracetamol is asked about first, if allocated to ibuprofen, ibuprofen is asked about first).

First I’d like to ask you about <<assigned study medication>>...

4. Think of the time between <<TIME>> and <<TIME>> of age. How many times <<baby’s name>> receive <<assigned study medication>>? (please look your PIPPA Tamariki Medication Diary)
   a. 0 GO TO QUESTION 14
   b. ______ times GO TO QUESTION 8
5. Think of the time between <<TIME>> and <<TIME>> of age. Are you able to estimate the likely number of times <<baby's name>> received <<assigned study medication>>? (please look your PIPPA Tamariki Medication Diary)
   a. Yes
      i. 0 GO TO QUESTION 14
      ii. 1 to 3 doses
      iii. 4 to 6 doses
      iv. Seven to nine doses
      v. 10 or more doses
   b. No GO TO QUESTION 14
   c. Don’t know GO TO QUESTION 14
   d. Refused GO TO QUESTION 14

6. Was the medicine given mainly for
   a. Fever
   b. Pain
   c. Both fever and pain
   d. Other
   e. Don’t know
   f. Refused

7. Was the medicine given mainly at the time of cough / runny nose / fast breathing / whistling in the chest or wheeze?
   a. Yes
   b. No
   c. Don’t know
   d. Refused

8. Was the medicine given mainly at the same time as (within 24 hours of) antibiotics
   a. Yes
   b. No
   c. Don’t know
   d. Refused

9. Think of the time between <<TIME>> and <<TIME>> of age. For each time a dose of <<assigned study medication>> was given please complete the following table (tick all options that apply, this table is exactly like your PIPPA Tamariki Medication Diary):

<table>
<thead>
<tr>
<th>Number of times</th>
<th>Date</th>
<th>Medicine</th>
<th>Reason</th>
<th>Symptoms in the past 24 hours</th>
<th>Antibiotic use in the past 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Paracetamol (Pamol, Panadol)</td>
<td>Ibuprofen (Brufen, Nurofen)</td>
<td>Fever</td>
<td>Pain</td>
</tr>
<tr>
<td>Example</td>
<td>6/8/17</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
10. Has <<Baby Name>> had any reactions to the <<assigned Study Medication>>? (ONLY FOR ALLOCATED STUDY MEDICATION??)
   a. Yes
   b. No  GO TO QUESTION 20

11. Describe the event (Free text field)

12. Did you see an emergency doctor or primary healthcare provider for this?
   a. Yes
   b. No  GO TO QUESTION 20

13. Was <<baby name>> admitted into hospital because of this event?
   a. Yes
   b. No

14. Did a doctor advise that the <<assigned Study Medication>> should not be administered to <<baby’s name>> ongoing?
   a. Yes  Stop providing prescription for <<assigned Study Medication>>
   b. No

Now I would like to ask you about <<non-allocated study medication>>... (If allocated to paracetamol, ibuprofen is asked about second, if allocated to ibuprofen, paracetamol is asked about second).

15. Think of the time between <<TIME>> and <<TIME>> of age. How many doses did <<baby’s name>> receive of <<non-allocated study medication>>? (please look at your PIPPA Tamariki Medication Diary)
   a. 0  GO TO QUESTION 20
   b. _____doses  GO TO QUESTION 19
   c. Don’t know/Uncertain
   d. Refused

16. Think of the time between <<TIME>> and <<TIME>> of age. Are you able to estimate the likely number of doses <<baby’s name>> received of <<non-allocated study medication>>? (please look your PIPPA Tamariki Medication Diary)
   a. Yes
      i. 0  GO TO QUESTION 20
      ii. 1 to 3 doses
      iii. 4 to 6 doses
      iv. Seven to nine doses
      v. 10 or more doses
   b. No  GO TO QUESTION 20
   c. Don’t know  GO TO QUESTION 20
   d. Refused  GO TO QUESTION 20

17. Was the <<non-allocated study medication>> given mainly for
   a. Fever
   b. Pain
   c. Both fever and pain
   d. Other
   e. Don’t know
18. Was the <<non-allocated study medication>> given mainly at the time of cough / runny nose / fast breathing / whistling in the chest or wheeze?
   a. Yes
   b. No
   c. Don’t know
   d. Refused

19. Was the <<non-allocated study medication>> given mainly at the same time as (within 24 hours of) antibiotics
   a. Yes
   b. No
   c. Don’t know
   d. Refused

20. Think of the time between <<TIME>> and <<TIME>> of age. For each time a dose of <<non-allocated study medication>> was given please complete the following table (tick all options that apply, this table is exactly like your PIPPA Tamariki Medication Diary):

<table>
<thead>
<tr>
<th>Number of times</th>
<th>Date</th>
<th>Medicine</th>
<th>Reason</th>
<th>Symptoms in the past 24 hours</th>
<th>Antibiotic use in the past 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>6/8/17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Now I’d like to ask about any other medications that <<name>> may have used

21. Think of the time between <<TIME>> and <<TIME>> of age. Did <<baby’s name>> receive any other medications prescribed by a doctor or nurse (oral medicine, drops, cream, inhaler, injection [do not include immunisations])?
   a. Yes, please specify (repeating instrument)
      vi. Medication
      vii. Length of use
      viii. Reason
      1. Chest illness
      2. Ear infection
      3. Skin problems
      4. Other, please specify, _______________________
   b. No
   c. Don’t know
   d. Refused

Let’s talk about <<baby’s name’s>> health since we last spoke with you….. Let’s start with respiratory problems like cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup.
22. Think of the time between <<TIME>> and <<TIME>> of age. How many times did <<baby's name>> have a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup? (Your baby should have had no symptoms for one day between episodes.)
   a. 0 times GO TO QUESTION 26
   b. ________ times GO TO QUESTION 23
   c. Don’t know/Uncertain
   d. Refused

23. Think of the time between <<TIME>> and <<TIME>> of age. Are you able to estimate the likely number of times <<baby's name>> had a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup? (<<baby's name>> should have had no symptoms for one day between episodes.)
   a. Yes
      ix. 0 times GO TO QUESTION 26
      x. 1 to 3 times
      xi. 4 to 6 times
      xii. 7 to 9 times
      xiii. 10 or more times
   b. No GO TO QUESTION 26
   c. Refused GO TO QUESTION 26

24. Think of the time between <<TIME>> and <<TIME>> of age. How many times did the above chest illnesses last more than a week?
   a. Never
   b. 1 time
   c. 2 times
   d. 3 times
   e. Don’t know
   f. Refused

25. Think of the time between <<TIME>> and <<TIME>> of age. How many times did <<baby's name>> see a doctor (GP, After Hours, or Emergency Department) for a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup?
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   e. 10 or more times
   f. Don’t know
   g. Refused

26. Think of the time between <<TIME>> and <<TIME>> of age. How many times did <<baby's name>> get admitted to hospital (stay at least one night in hospital) for a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup?
   a. Never
   b. ________ times
   c. Don’t know
   d. Refused

Now I would like to ask about skin problems like eczema and cellulitis and other skin infections:
27. Think of the time between <<TIME>> and <<TIME>> of age. How many times did <<baby's name>> see a doctor (GP, After Hours, or Emergency Department) for eczema, infected eczema, cellulitis, impetigo, or other skin infections?
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   e. 10 or more times
   f. Don’t know
   g. Refused
   GO TO QUESTION 28

28. Think of the time between <<TIME>> and <<TIME>> of age. How many times did <<baby's name>> get admitted to hospital (stay at least one night in hospital) for eczema, infected eczema, cellulitis, impetigo, or other skin infections?
   a. Never
   b. ______ times
   c. Never
   d. Don’t know
   e. Refused

And what about admission to hospital for any other reason?

29. Think of the time between <<TIME>> and <<TIME>> of age. How many times did <<baby's name>> get admitted to hospital (stay at least one night in hospital) for something other than a chest illness or skin problem?
   a. Never
   b. ______ times, specify reason for admissions
   c. Don’t know
   d. Refused

Let’s talk about whether you need any more study medication for <<baby name>>

30. Have you moved house since we last contacted you?
   a. Yes, please specify
   b. No
   c. Don’t know
   d. Refused

31. Think about the last time <<baby's name>> was weighed. How much did <<baby's name>> weigh?
   a. ______ kilos
   b. ______ grams
   c. ______ pounds
   d. ______ ounces
   e. Don’t know
   f. Refused

32. How old was << baby's name>> at the time he/she was last weighed?
   a. ______ months
   b. ______ weeks
   c. Don’t know
   d. Refused
32. Do you require any further study medication for << baby’s name >>?
   a. Yes  
       GO TO PRESCRIPTION, WEIGHT AND DETAILS SHOULD PIPE THROUGH
   b. No   
       GO TO QUESTION 34

33. What is the best way for you to get the medication?
   a. Fax prescription to pharmacy
   b. Post prescription to home address
   c. Study Medication delivered to house

34. Has the number of people that live in your house changed since we last contacted you?
   a. Yes
   b. No  
       GO TO QUESTION 38
   c. Don’t know
   d. Refused  
       GO TO QUESTION 38

35. Including yourself, how many adults (aged 18 or over) in the household?
   a. 1 (yourself)
   b. More than 1____________

   xiv. How many of these other adults are ...... in relation to <<name>>?
         1. Other parent / mothers’ partner
         2. Grandparent
         3. Siblings
         4. Uncles / aunts
         5. Cousins
         6. Flatmate / Boarder
         7. Other

36. How many children older than 10 and less than 18 are in the household?
   a. None
   b. >1_____

   xv. How many of these are ....... in relation to <<baby’s name>>?
       1. Siblings
       2. Uncles / aunts
       3. Cousins
       4. Flatmate’s / Boarder’s child
       5. Other

37. Not counting <<baby’s name>>, how many children less than 10 years of age in the household?
   a. None – do nothing
   b. >1_____

   xvi. How many of these are ...... in relation to <<name>>?
       1. Siblings
       2. Uncles / aunts
       3. Cousins
       4. Flatmate’s / Boarder’s child
       5. Other
38. Are there any new children under 10 years old in the household for whom you would like us to provide the study medication?
   a. No – do nothing
   b. Yes – complete enrolment form for each new child <10 years receiving study medication (Appendix C)

39. Regarding the currently listed children under 10 years, do any of them need more study medication?

40. For the child who needs more study medication, when was the last time <<name>> was weighed?
   a. In the last 1 month
   b. In the last 2 to 3 months
   c. In the last 4 to 12 months
   d. Over a year ago (finish)
   e. Has never been weighed (finish)
   f. Don’t know (finish)
   g. Refused (finish)

41. Can you remember what <<name>> weighed then?
   a. Yes, please state weight
   b. No
   c. Don’t know
   d. Refused

Repeat questions 46 and 47 for each child needing more study medication.

42. Has any other child in the household <10 years old had any reaction to <<assigned study medication>>?
   e. Yes (specify name of the child)
   f. No GO TO QUESTION 14

43. Describe the event (Free text field)

44. Did you see an emergency doctor or primary healthcare provider for this?
   g. Yes
   h. No GO TO QUESTION 14

45. Was <<name>> admitted into hospital because of this event?
   i. Yes
   j. No

46. Did a doctor advise that the <<assigned Study Medication>> should not be administered to <<name>> ongoing?
   k. Yes, Stop providing prescription for <<assigned Study Medication>> for <<name>>
   l. No

Repeat for each child <10 years who has had an AR to study medication.

Thank you.
22. APPENDIX E: 1 YEAR QUESTIONNAIRE

1. Please tell us your relationship to <<baby’s name>>
   a. Mum
   b. Dad
   c. Caregiver
   d. Other

2. What is <<baby name’s>> ethnicity?

Now I’d like to ask you about <<assigned study medication>>?

3. Think of the time between 9 months of age and now. Are you able to estimate the likely number of doses <<baby’s name>> received of <<assigned study medication>>? (please look your PIPPA Tamariki Medication Diary)
   a. Yes
      i. 0 GO TO QUESTION 12
      ii. 1 to 3 doses
      iii. 4 to 6 doses
      iv. 7 to 9 doses
      v. 10 or more doses
   b. No GO TO QUESTION 12
   c. Don’t know GO TO QUESTION 12
   d. Refused GO TO QUESTION 12

4. Was the <<assigned study medication>> given mainly for
   a. Fever
   b. Pain
   c. Both fever and pain
   d. Other
   e. Don’t know
   f. Refused

5. Was the <<assigned study medication>> given mainly at the time of cough / runny nose / fast breathing / whistling in the chest or wheeze?
   a. Yes
   b. No
   c. Don’t know
   d. Refused

6. Was the <<assigned study medication>> given mainly at the same time as (within 24 hours of) antibiotics
   a. Yes
   b. No
   c. Don’t know
   d. Refused
7. Think of the time between 9 months of age and now. For each dose of <<assigned study medication>> given please complete the following table (tick all options that apply, this table is exactly like your PIPPA Tamariki Medication Diary):

<table>
<thead>
<tr>
<th>Number of times</th>
<th>Date</th>
<th>Medicine</th>
<th>Reason</th>
<th>Symptoms in the past 24 hours</th>
<th>Antibiotic use in the past 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>6/8/17</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8. Think of the time between 9 months of age and now. Has <<baby's name>> had any reactions to the <<assigned Study Medication>>?
   a. Yes  
   b. No   GO TO QUESTION 12
   c. Don’t know  
   d. Refused

9. Describe the event (Free text field)

10. Did you see an emergency doctor or primary healthcare provider for this?
   a. Yes  
   b. No  GO TO QUESTION 12
   c. Don’t know  
   d. Refused

11. Was <<baby's name>> admitted into hospital because of this event?
   a. Yes  
   b. No  
   c. Don’t know  
   d. Refused

12. Did a doctor advise that the Study Medication should not be administered to <<baby's name>> ongoing?
   a. Yes Stop providing prescription for <<assigned study medication>>
   b. No  
   c. Don’t’ know  
   d. Refused

   “Now I’d like to ask you about <<non-allocated study medication>>.......’ (if allocated to paracetamol, ibuprofen is asked about second, if allocated to ibuprofen, paracetamol is asked about second).

13. Think of the time between 9 months of age and now. How many doses did <<baby's name>> receive of <<non-allocated study medication>>? (please look at your PIPPA Tamariki Medication Diary)
   e. 0  GO TO QUESTION 18
   f. _____ doses  GO TO QUESTION 17
   g. Don’t know  
   h. Refused
14. Think of the time between 9 months of age and now. Are you able to estimate the likely number of doses <<baby’s name>> received of <<non-allocated study medication>>? (please look your PIPPA Tamariki Medication Diary)
   a. Yes
      i. 0 GO TO QUESTION 18
      ii. 1 to 3 doses
      iii. 4 to 6 doses
      iv. 7 to 8 doses
      v. 10 or more doses
   b. No GO TO QUESTION 18
   c. Don’t know GO TO QUESTION 18
   d. Refused GO TO QUESTION 18

15. Was the <<non-allocated study medication>> given mainly for
   a. Fever
   b. Pain
   c. Both fever and pain
   d. Other
   e. Don’t know
   f. Refused

16. Was the <<non-allocated study medication>> given mainly at the time of cough / runny nose / fast breathing / whistling in the chest or wheeze?
   a. Yes
   b. No
   c. Don’t know
   d. Refused

17. Was the <<non-allocated study medication>> given mainly at the same time as (within 24 hours of) antibiotics
   a. Yes
   b. No
   c. Don’t know
   d. Refused

18. Think of the time between 9 months of age and now. For each dose of <<non-allocated study medication>> given please complete the following table (tick all options that apply, this table is exactly like your PIPPA Tamariki Medication Diary):

<table>
<thead>
<tr>
<th>Number of times</th>
<th>Date</th>
<th>Paracetamol</th>
<th>Ibuprofen</th>
<th>Reason</th>
<th>Symptoms in the past 24 hours</th>
<th>Antibiotic use in the past 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(Pamol, Panadol)</td>
<td>(Brufen, Nurofen)</td>
<td>Fever</td>
<td>Pain</td>
<td>Other (please specify)</td>
</tr>
<tr>
<td>Example</td>
<td>6/8/17</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>2</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

   Now I’d like to ask about other medications that <<baby’s name>> may have used...

PIPPA Tamariki Protocol Version 1.0, 7 November 2017
Page 67 of 92
19. Think of the time between 9 months of age and now. Did <<name>> receive any other medications prescribed by a doctor or nurse (oral medicine, drops, cream, inhaler, injection (do not include immunisations))?
   a. Yes, please specify (repeating instrument)
      i. Medication
      ii. Length of use
      iii. Reason
         1. Chest illness
         2. Ear infection
         3. Skin problems
         4. Other, please specify
   b. No
   c. Don’t know
   d. Refused

Let’s talk about <<baby’s name’s>> respiratory (breathing-related) health since we last spoke with you…..

20. Think of the time between 9 months of age and now. How many times did <<baby’s name>> have a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup? (Your baby should have had no symptoms for one day between episodes.)
   a. _______ times  GO TO QUESTION 21
   b. Never  GO TO QUESTION 24
   c. Don’t know/Uncertain
   d. Refused

21. Think of the time between 9 months of age and now. Are you able to estimate the likely number of times <<baby’s name>> had a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup? (<<baby’s name>> should have had no symptoms for one day between episodes.)
   a. Yes
      i. Never  GO TO QUESTION 24
      ii. 1 to 3 times
      iii. 4 to 6 times
      iv. 7 to 9 times
      v. 10 or more times
   b. No  GO TO QUESTION 24
   c. Refused  GO TO QUESTION 24

22. Think of the time between 9 months of age and now. How many times did the above chest illnesses last more than a week?
   a. Never
   b. 1 time
   c. 2 times
   d. 3 times
   e. Don’t know
   f. Refused
23. Think of the time between 9 months of age and now. How many times did <<baby name’s>> see a doctor (GP, After Hours, or Emergency Department) for a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup?
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   e. 10 or more times
   f. Don’t know
   g. Refused

24. Think of the time between 9 months of age and now. How many times did <<baby name’s>> get admitted to hospital (stay at least one night in hospital) for a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup?
   a. _____ times
   b. Never
   c. Don’t know
   d. Refused

Now I would like to ask about skin problems like eczema, cellulitis and other skin infections: (Eczema: Diagnostic Criteria) (From the UK Diagnostic Criteria for Atopic Dermatitis (UKDCAD)): http://www.nottingham.ac.uk/~mzzfaq/dermatology/eczema/Section6-3Appendix1.html

25. In the last year, has <<baby name’s>> had an itchy skin condition – by itchy, we mean scratching or rubbing the skin?
   a. Yes
   b. No
   GO TO QUESTION 27

26. Has <<baby name’s>> had this itchy skin condition in the last week?
   a. Yes
   b. No

27. Has this skin condition ever affected the skin creases in the past - by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?
   a. Yes
   b. No

28. In the last year, has <<baby name’s>> suffered from a dry skin in general?
   a. Yes
   b. No

29. In the last year, has <<baby name’s>> suffered from any of the following skin complaints: (select as many as apply)
   a. Warts
      i. Yes
      ii. No
   b. Psoriasis
      i. Yes
      ii. No
   c. Facial spots
d. Eczema
   i. Yes
   ii. No
   GO TO QUESTION 36

**Eczema**

30. Over the last week, on how many days has <<baby name’s>> skin been itchy because of his/her eczema?
   a. Never
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

31. Over the last week, on how many nights has <<baby name’s>> sleep been disturbed because of his/her eczema?
   a. Never
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

32. Over the last week, on how many days has <<baby name’s>> skin been bleeding because of his/her eczema?
   a. Never
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

33. Over the last week, on how many days has <<baby name’s>> skin been weeping or oozing clear fluid because of his/her eczema?
   a. Never
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

34. Over the last week, on how many days has <<baby name’s>> skin been cracked because of his/her eczema?
   a. Never
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
35. Over the last week, on how many days has <<baby name’s>> skin been flaking off because of his/her eczema?
   a. Never
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

36. Over the last week, on how many days has <<baby name’s>> skin felt dry or rough because of his/her eczema?
   a. Never
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

Now thinking more generally about skin problems only between our last contact and now:

37. Think of the time between 9 months of age and now. How many times did <<baby name>> see a doctor (GP, After Hours, or Emergency Department) for eczema, infected eczema, cellulitis, impetigo, or other skin infections?
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   e. 10 or more times
   f. Don’t know
   g. Refused
   GO TO QUESTION 38

38. Think of the time between 9 months of age and now. How many times did <<baby name>> get admitted to hospital (stay at least one night in hospital) for eczema, infected eczema, cellulitis, impetigo, or other skin infections?
   a. ______ times
   b. No times
   c. Don’t know
   d. Refused
   GO TO QUESTION 38

Now I would like to ask about some other specific health problems that <<baby’s name>> may have had in the last 12 months

39. In the past 12 months, how many times has <<baby’s name>> had an ear infection? (GUINZ, Child Proxy 9 month: C10)
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   GO TO QUESTION 42
40. How many of these times did <<baby's name>> see a doctor because of these ear infections? (GUINZ, Child Proxy 9 month: C11)
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   e. 10 or more times
   f. Don’t know
   g. Refused

41. How many times has <<baby's name>> been admitted to hospital because of an ear infection? By admitted, I mean <<baby's name>> stayed in hospital at least one night. (GUINZ, Child Proxy 9 month: C12)
   a. Number of admissions
   b. Don’t know
   c. Refused

42. At what age did <<baby’s name>> have his/her first ear infection? (GUINZ, Child Proxy 9 month: C13)
   a. Age in months
   b. Age in weeks
   c. Don’t know
   d. Refused

Since our last contact and now, what about hospital admissions for any other reason?

43. Think of the time between 9 months of age and now. How many times did <<baby’s name>> get admitted to hospital (stay at least one night in hospital) for something other than a chest illness or skin problem?
   a. _______ times, specify reason for admissions
   b. Never
   c. Don’t know
   d. Refused

Now I would like to ask some questions about breastfeeding for <<baby’s name>>

44. Are you the biological mother of <<baby’s name>>?
   a. Yes
   b. No

45. Did you ever breastfeed <<baby’s name>>? (Breastfeeding includes feeding expressed milk, and/or supplementing with formula and solids). (GUINZ, Child Proxy 9 month: C51)
   a. Still breastfeeding
   b. Breastfed but stopped
   c. Never breastfed
   d. Don’t know
46. How many times per day do you currently breastfeed <<baby's name>>? (GUINZ, Child Proxy 9 month: C52)
   a. Times per day __________
   b. Less than once per day
   c. Don't know
   d. Refused

47. For how long did you exclusively breastfeed <<baby's name>>? (By exclusive, we mean feeding <<name>> only breastmilk (including expressed breast milk), and not any water, milk Formula, other liquids or solids. (GUINZ, Child Proxy 9 month: C54.
   a. ___ (Number of) months, or
   b. ___ (Number of) weeks or
   c. ___ (Number of) days
   d. Don't know
   e. Refused

48. If you have stopped breastfeeding, how old was <<baby's name>> when you stopped breastfeeding? (any breastfeeding, whether exclusive or not) (GUINZ, Child Proxy 9 month: C56)
   a. Age in months, or
   b. Age in weeks, or
   c. Age in days
   d. Don't know
   e. Refused

49. Why did you stop breastfeeding? (GUINZ, Child Proxy 9 month: C57 ONCE ANSWERED, GO TO QUESTION 51. (Multiple options allowed)
   a. I had breastfed long enough
   b. Baby had trouble latching on
   c. Didn't have enough milk
   d. Breast milk alone did not seem to satisfy baby
   e. Painful breasts
   f. Baby not gaining enough weight
   g. I wanted / needed someone else to feed baby
   h. Went back to work and expressing milk not convenient / possible
   i. New pregnancy
   j. Baby was old enough that the difference between breastmilk and formula was minimal
   k. Other (please specify

50. Was <<baby's name>> breastfed? (GUINZ, Child Proxy 9 month: C58)
   a. Yes
   b. No
   c. Don't know
   d. Refused

51. How old was <<baby's name>> when breastfeeding ended? (GUINZ, Child Proxy 9 month: C59)
   a. Age in months, or
   b. Age in weeks, or
   c. Age in days
   d. Still being breastfed
   e. Don't know
52. Has <<baby's name>> ever had infant milk formula or milk other than breast milk? (GUINZ, Child Proxy 9 month: C60)
   a. Yes
   b. No
   c. Don’t know
   d. Refused

53. How old was <<baby's name>> when he/she was first fed this infant milk formula, or other milk? (GUINZ, Child Proxy 9 month: C61)
   a. Age in months, or
   b. Age in weeks, or
   c. Age in days
   d. Don’t know
   e. Refused

54. In the last 12 months which of these different milk formulas or milks have been given to <<baby name's>>? (GUINZ, Child Proxy 9 month: C62) (Multiple options allowed)
   a. Pasteurized / bottled cows’ milk
   b. Cow’s milk infant formula
   c. Follow-on formula
   d. Soy formula
   e. Goats’ milk formula
   f. Hypoallergenic formula
   g. Other milk (specify)
   
   Now I would like to ask some questions about any allergies or reactions to foods <<baby name>> may have had

55. Does <<baby's name>> have any allergies to any of the following? (GUIAus Wave Three plus seafood question)
   a. Peanuts
   b. Hens’ eggs
   c. Cows’ milk
   d. Soy
   e. Sesame
   f. Wheat
   g. Seafood
   h. Other (specify)
   i. For each of the allergies specified: (repeating question), what age was <<baby name>> when you first knew he/she had the allergy (GUIAus Wave Three)
      1. Age in months, or
      2. Age in weeks, or
      3. Age in days
      4. Refused
      5. Don’t know
i. Describe the symptom(s) <<baby name>> has when he/she eats this food (University of Michigan, division of Food Allergy and Clinical Immunology, Food allergy questionnaire)

1. Hives
2. Nausea
3. Passed out
4. Behaviour change
5. Wheezing
6. Vomiting
7. Shock
8. Itching
9. Eczema / atopic dermatitis
10. Diarrhoea
11. Anaphylaxis
12. Not exposed, but told by doctor after tests were done
13. Other (specify)
14. Was there any need to seek medical care in a hospital because of these reactions?

Now I would like to ask more general questions about your household

56. Has the number of people that live in your house changed since we last contacted you?
   a. Yes
   b. No
   c. Don’t know
   d. Refused

57. Including yourself, how many adults (aged 18 or over) in the household?
   a. 1 (yourself)
   b. More than 1___________
      i. How many of these other adults are ....... in relation to <<name>>?
         1. Other parent / mothers’ partner
         2. Grandparent
         3. Siblings
         4. Uncles / aunts
         5. Cousins
         6. Flatmate / Boarder
         7. Other

58. How many children older than 10 and less than 18 are in the household?
   a. None
   b. More than 1______
      i. How many of these are ......... in relation to <<name>>?
         1. Siblings
         2. Uncles / aunts
         3. Cousins
         4. Flatmate’s / Boarder’s child
         5. Other
59. Not counting <<baby’s name>>, how many children less than 10 years of age in the household?
   a. None – do nothing
   b. More than 1______
      i. How many of these are ...... in relation to <<name>>?
         1. Siblings
         2. Uncles / aunts
         3. Cousins
         4. Flatmate’s / Boarder’s child
         5. Other

60. How many houses have you and <<baby’s name>> lived in since your baby was born?
   a. Number of houses
   b. Not moved
   c. Don’t know
   d. Refused

61. Do you, or anyone else who lives there, own or partly own the dwelling you are living in (with or without a mortgage)? (GUINZ Mother Questionnaire 9 months M213). (If house is owned by a family trust, CODE NO)
   a. Yes                        GO TO QUESTION 62
   b. No
   c. Don’t know
   d. Refused

61. Who owns the dwelling you are living in? (GUINZ Mother Questionnaire 9 months M214).
   a. Private person, trust or business
   b. Family trust
   c. Local Authority or City Council
   d. Housing New Zealand
   e. Other state owned corporation or state owned enterprise, or Government Department or Ministry
   f. Don’t know
   g. Refused

62. Do you, or anyone else who lives there, pay rent to an owner or to an agent for that house/flat? (GUINZ Mother Questionnaire 9 months M215).
   a. Yes
   b. No
   c. Don’t know
   d. Refused

63. Do you, or anyone who lives in your dwelling, make mortgage payments on that dwelling? (GUINZ Mother Questionnaire 9 months M216).
   a. Yes
   b. Know
   c. Don’t know
   d. Refused

64. How many Bedrooms are there in the house? Please count any room furnished as a bedroom even if no one sleeps in it, and sleep-outs and caravans if they are furnished as a bedroom. Do not
count any other room, e.g., living room unless the only bedroom facilities are in that room) (GUINZ Mother Questionnaire 9 months M56)
   a. Number of Bedrooms
   b. Don’t know
   c. Refused

65. How often would you say the house where <<<baby’s name>>> lives was damp? (GUINZ Mother Questionnaire 9 months M60)
   a. Never/hardly ever
   b. Not very often
   c. Quite often
   d. Always/almost always
   e. Don’t know
   f. Refused

66. How often was there heavy condensation in the room where <<<baby’s name>>> sleeps at night, that is, water trickling down the inside of the window or walls, or a puddle of water at the bottom of the window or wall? (GUINZ Mother Questionnaire 9 months M61)
   a. Never/hardly ever
   b. Not very often
   c. Quite often
   d. Always/almost always
   e. Don’t know
   f. Refused

67. Thinking about the past two weeks, has there been mould or mildew on the walls or the ceilings where <<<baby’s name>>> sleeps at night? This does not include the insides of cupboards or wardrobes. Mildew is a fungus that causes black marks that appear and re-appear around windows, skirting boards and walls. (GUINZ Mother Questionnaire 9 months M62)
   a. Yes
   b. No

68. Did you heat your house in the last 12 months? (Modified GUINZ Mother Questionnaire 9 months M57)
   a. Yes
   b. No GO TO QUESTION 68
   c. Don’t know
   d. Refused GO TO QUESTION 68

69. What forms of heating did you use? (We want to know about all forms of heating that you use. (GUINZ Mother Questionnaire 9 months M58)
   a. Electricity
   b. Flued gas heater
   c. Unflued gas heater
   d. Wood
   e. Coal
   f. Solar
   g. Kerosene
   h. Other (specify)
   i. Don’t know
   j. Refused
70. What forms of heating did you use in the room where <<baby's name>> sleeps at night? I want to know about all the heating that you used for that room. (GUINZ Mother Questionnaire 9 months M59)
   a. Electricity
   b. Flued gas heater
   c. Unflued portable gas heater
   d. Wood
   e. Coal
   f. Solar heating equipment
   g. Kerosene
   h. Other (specify)
   i. No heating
   j. Don’t know
   k. Refused

Now I would like to ask about pets and smoking

71. Do you currently smoke regularly, at least one cigarette a day? (GUINZ Mother Questionnaire 9 months M69)
   a. Yes
   b. No
   c. Don’t know
   d. Refused

72. How many cigarettes do you smoke per day, on average? (GUINZ Mother Questionnaire 9 months M70)
   a. Number of cigarettes
   b. Don’t know
   c. Refused
   d. Refused

73. Where do you smoke cigarettes? (all locations)
   a. In the house
   b. On a porch or doorway of the house
   c. In the car
   d. Away from the house but within the boundary of the property
   e. Only outside the boundary of the property

74. How many people who live in your household smoke cigarettes? (Please count yourself as well) (GUINZ Mother Questionnaire 9 months M71)
   a. Number
   b. None
   c. Don’t know
   d. Refused

75. Do any other smokers in the household smoke cigarettes in the house?
   a. Yes
   b. No

76. In the past 12 months have you had a cat in your home? (ISAAC Phase Three EQ. 20)
   a. Yes
   b. No
   c. Don’t know
77. Do you currently have a cat in your home?
   a. Yes
   b. No
   c. Refused

78. In the past 12 months have you had a dog in your home? (ISAAC Phase Three EQ. 21)
   a. Yes
   b. No
   c. Don’t know
   d. Refused

79. Do you currently have a dog in your home?
   a. Yes
   b. No
   c. Refused

80. Has any other child in the household <10 years old had any reaction to <<assigned study medication>>? (ONLY FOR ALLOCATED STUDY MEDICATION??)
   a. Yes (specify name of the child)
   b. No

81. Describe the event (Free text field)

82. Did you see an emergency doctor or primary healthcare provider for this?
   c. Yes
   d. No

83. Was <<name>> admitted into hospital because of this event?
   e. Yes
   f. No

84. Did a doctor advise that the <<assigned Study Medication>> should not be administered to <<name>> ongoing?
   g. Yes Stop providing prescription for <<assigned Study Medication>> for <<name>>
   h. No

Repeat for each child <10 years who has had an AR to study medication.

That is all for today. Thank you very much for your time.
23. APPENDIX F: 3 AND 6 YEAR QUESTIONNAIRE

Let’s talk about <<child’s name>> paracetamol / ibuprofen use since we last spoke to you… First I’d like to ask you about paracetamol…’

1. Thinking of the last 12 months, how often on average have you given <<child’s name>> paracetamol, Pamol, Panadol junior, Parapaed, Paracare, or Pamol infant drops? (Extension of ISAAC Phase Three EQ, 6/7 year olds)
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   e. 10 or more times
   f. Don’t know
   g. Refused

2. Now I’d like to ask you about ibuprofen…’ Thinking of the last 12 months, how often on average have you given <<child’s name>> ibuprofen, Brufen, Nurofen, or Fenpaed?? (Extension of ISAAC Phase Three EQ, 6/7 year olds)
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   e. 10 or more times
   f. Don’t know
   g. Refused

Let’s talk about <<child’s name>> respiratory (breathing-related) health since we last spoke with you…..

Wheeze: (ISAAC Phase III questionnaire for asthma 6/7 year olds: (http://isaac.auckland.ac.nz/phases/phasethree/corequestionnaire_6-7.pdf)

3. Has <<child’s name>> ever had wheezing?
   a. Yes
   b. No – go to question 8

4. Has <<child’s name>> had whistling or wheezing in the chest in the past 12 months?
   a. Yes
   b. No – got to question 8

5. How many attacks of wheezing has <<child’s name>> had in the past 12 months?
   a. 0
   b. 1 to 3
   c. 4 to 12
   d. more than 12

6. In the past 12 months, how often on average has <<child’s name’s>> sleep been disturbed due to wheezing?
   a. Never woken with wheezing
   b. Less than one night per week
   c. One or more nights per week
7. In the past 12 months, has wheezing ever been severe enough to limit <<child's name's>> speech to only one or two words at a time between breaths?
   a. Yes
   b. No

8. Has <<child's name>> ever had asthma?
   a. Yes
   b. No

9. In the last 12 months has <<child's name's>> chest sounded wheezy during or after exercise?
   a. Yes
   b. No

10. In the past 12 months, has <<child's name>> had a dry cough at night, apart from a cough associated with a cold or chest infection?
    a. Yes
    b. No

11. Is <<child's name>> currently taking any medication for their wheezing, whistling in the chest, or asthma?
    a. Yes
       i. List ______________________________
    b. No

12. Thinking of the last 12 months, how many times did <<name>> have a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup? (<<child's name>> should have had no symptoms for one day between episodes.)
    a. Never
    b. ______ Times Go to Question 14
    c. Don’t know/Uncertain
    d. Refused

13. Thinking of the last 12 months, which of these medications did <<child's name>> take for their cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup? List
    a. Reliever inhaler (list names)
       i. Yes
       ii. No
       iii. Don’t know
       iv. Refused
    b. Preventer inhaler
       i. Yes
       ii. No
       iii. Don’t know
       iv. Refused
    c. LABA (name some)
       i. Yes
       ii. No
       iii. Don’t know
iv. Refused
d. Combined inhalers
   i. Yes
   ii. No
   iii. Don’t know
   iv. Refused
e. Oral steroids (redipreds etc)
   i. Yes
   ii. No
   iii. Don’t know
   iv. Refused
f. Montelukast
   i. Yes
   ii. No
   iii. Don’t know
   iv. Refused
g. Antibiotics
   i. Yes
   ii. No
   iii. Don’t know
   iv. Refused
h. Other?
   i. Yes
   ii. No
   iii. Don’t know
   iv. Refused

14. Think of the last 12 months, how many times did the above chest illness/es last more than a week?
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   e. 10 or more times
   f. Don’t know
   g. Refused

15. Thinking of the last 12 months, how many times did <<child's name>> see a doctor for a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup?
   a. Never
   b. 1 to 3 times
   c. 4 to 6 times
   d. 7 to 9 times
   e. 10 or more times
   f. Don’t know
   g. Refused
Now we are going to ask about the last 2 (3) years....

16. Think of the time between <<epoch>> and now, how many times did <<child's name>> get admitted to hospital (stay at least one night in hospital) for a cough, chest infection, whistling in the chest or wheeze, bronchiolitis, bronchitis, asthma, pneumonia or croup?
   a. Never
   b. ______ Times
   c. Don’t know
   d. Refused

17. Think of the time between <<epoch>> and now, how many times did <<child's name>> get admitted to hospital (stay at least one night in hospital) for a something other than a chest illness?
   a. Never
   b. ______ Times, specify reason for admissions
   c. Don’t know
   d. Refused

Now I would like to ask about any skin problems <<name>> may have: Eczema: Diagnostic Criteria
(From the UK Diagnostic Criteria for Atopic Dermatitis: http://www.nottingham.ac.uk/~mzzfaq/dermatology/eczema/Section6-3Appendix1.html )

18. In the last year, has <<child's name>> had an itchy skin condition – by itchy, we mean scratching or rubbing the skin?
   a. Yes
   b. No – go to question 23

19. Has <<child's name>> has this itchy skin condition in the last week?
   a. Yes
   b. No

20. How old was <<child's name>> when this skin condition began?
   a. Under 2 years of age
   b. Between 2 years and 5 years of age
   c. 6 or older

21. Has this skin condition ever affected the skin creases in the past - by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck, or around the eyes?
   a. Yes
   b. No

22. In the last year, has <<child's name>> suffered from a dry skin in general?
   a. Yes
   b. No

23. In the last year, has <<child's name>> suffered from any of the following skin complaints: (PLEASE CIRCLE ONE OR MORE).
   a. Warts
   b. Psoriasis
   c. Facial spots
   d. None of these
Eczema
  i. Yes – continue
  ii. No – Go to Question 33

Eczema (POEM score:
http://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-
resources/poem-for-proxy-completion.pdf)

24. Over the last week, on how many days has <<child’s name’s>> skin been itchy because of their eczema?
   a. 0 days
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

25. Over the last week, on how many nights has <<child’s name’s>> sleep been disturbed because of their eczema?
   a. 0 days
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

26. Over the last week, on how many days has <<child’s name’s>> skin been bleeding because of their eczema?
   a. 0 days
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

27. Over the last week, on how many days has <<child’s name’s>> skin been weeping or oozing clear fluid because of their eczema?
   a. 0 days
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

28. Over the last week, on how many days has <<child’s name’s>> skin been cracked because of their eczema?
   a. 0 days
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

29. Over the last week, on how many days has <<child’s name’s>> skin been flaking off because of their eczema?
   a. 0 days
   b. 1 to 2 days
30. Over the last week, on how many days has <<child's name's>> skin felt dry or rough because of their eczema?
   a. 0 days
   b. 1 to 2 days
   c. 3 to 4 days
   d. 5 to 6 days
   e. Every day

31. Is <<child's name's>> currently using any medications for their eczema?
   a. Yes
      i. List
   b. No

Now I would like to ask about symptoms of Hayfever for <<child’s name>>. Rhinitis: ([ISAAC Phase III questionnaire for asthma 6/7 year olds:](http://isaac.auckland.ac.nz/phases/phasethree/corequestionnaire_6-7.pdf)

32. Has <<child’s name>> ever had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?
   a. No – Go to question 38

33. In the past 12 months, has <<child’s name>> had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?
   a. Yes – Got to question 35
   b. No – Go to question 38

34. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?
   a. Yes
   b. No

35. In which of the past 12 months did this nose problem occur? (Please tick all which apply).
   a. January
   b. February
   c. March
   d. April
   e. May
   f. June
   g. July
   h. August
   i. September
   j. October
   k. November
   l. December

36. In the past 12 months, how much did this nose problem interfere with <<child’s name’s>> daily activities?
   a. Not at all
b. A little
c. A moderate amount
d. A lot

37. Has <<child's name>> ever had hayfever?
   a. Yes
   b. No

38. Is <<child's name>> currently using any medication for their sneezing, runny or blocked nose
   (when they did not have a cold or flu), or their hayfever?
   a. Yes
      i. (List)
   b. No

39. Does <<child's name>> use any other medications (other than those already discussed) for any
   other reason?
   a. Yes
      i. List
   b. No

Now I would like to ask some questions about any allergies or reactions to foods <<name>> may
   have had

40. Does <<child's name>> have any allergies to any of the following? (GUIAus Wave Three plus
    seafood question)
    a. Peanuts
    b. Hen’s eggs
    c. Cow’s Milk
    d. Soy
    e. Sesame
    f. Wheat
    g. Seafood
    h. Other (specify)
    i. For each of the allergies specified
       i. What age was <<child's name>> when you first knew he / she had the allergy
          (GUIAus Wave Three)
       ii. Describe the symptom(s) <<name>> has when they eat this food (University of
           Michigan, division of Food Allergy an Clinical Immunology, Food allergy
           questionnaire)
           1. Hives
           2. Nausea
           3. Passed out
           4. Behaviour change
           5. Wheezing
           6. Vomiting
           7. Shock
           8. Itching
           9. Eczema / atopic dermatitis
           10. Diarrhoea
           11. Anaphylaxis
12. Not exposed, but told by doctor after tests were done  
13. Other (specify)  

iii. Was there any need to seek medical care in a hospital because of these reactions?

**Now I would like to ask more general questions about your household**

41. Has the number of people that live in your house changed since we last contacted you?  
   a. Yes  
   b. No  
   c. Don’t know  
   d. Refused  

42. Including yourself, how many adults (aged 18 or over) in the household?  
   a. 1 (yourself)  
   b. More than 1__________  
      i. How many of these other adults are ....... in relation to <<name>>?  
         1. Other parent / mothers’ partner  
         2. Grandparent  
         3. Siblings  
         4. Uncles / aunts  
         5. Cousins  
         6. Flatmate / Boarder  
         7. Other

43. How many children older than 10 and less than 18 are in the household?  
   a. None  
   b. More than 1______  
      i. How many of these are ....... in relation to <<name>>?  
         1. Siblings  
         2. Uncles / aunts  
         3. Cousins  
         4. Flatmate’s / Boarder’s child  
         5. Other

44. Not counting <<child's name>>, how many children less than 10 years of age in the household?  
   a. None – do nothing  
   b. More than 1______  
      i. How many of these are ...... in relation to <<name>>?  
         1. Siblings  
         2. Uncles / aunts  
         3. Cousins  
         4. Flatmate’s / Boarder’s child  
         5. Other

45. How many houses have you and <<child's name>> lived in since <<child's name>> was born?  
   a. Number of houses
b. Not moved
c. Don’t know
d. Refused

46. Do you, or anyone else who lives there, own or partly own that dwelling (with or without a mortgage)? (GUINZ Mother Questionnaire 9 months M213). If House is owned by a family trust, CODE NO
   a. Yes Go to Question 49
   b. No
c. Don’t know
d. Refused

47. If nobody who lives there owns that dwelling, who owns it? (GUINZ Mother Questionnaire 9 months M214).
   a. Private person, trust or business
   b. Family trust
   c. Local Authority or City Council
   d. Housing New Zealand
   e. Other state owned corporation or state owned enterprise, or government department or ministry
   f. Don’t know
g. Refused

48. Do you, or anyone else who lives there, pay rent to an owner or to an agent for that house/flat? (GUINZ Mother Questionnaire 9 months M215).
   a. Yes
   b. No
   c. Don’t know
d. Refused

49. Do you, or anyone who lives in your dwelling, make mortgage payments on that dwelling? (GUINZ Mother Questionnaire 9 months M216).
   a. Yes
   b. Know
c. Don’t know
d. Refused

50. How many bedrooms are there in the house? Please count any room furnished as a bedroom even if no one sleeps in it, and sleep-outs and caravans if they are furnished as a bedroom. Do not count any other room, e.g., living room unless the only bedroom facilities are in that room) (GUINZ Mother Questionnaire 9 months M56)
   a. Number of Bedrooms
   b. Don’t know
c. Refused

51. How often would you say the house where <<child's name>> lives was damp? (GUINZ Mother Questionnaire 9 months M60)
   a. Never / Hardly ever
   b. Not very often
c. Quite often
d. Always / almost always

PIPAA TAMARIKI PROTOCOL VERSION 1.0, 7 NOVEMBER 2017
Page 88 of 92
52. How often was there heavy condensation in the room where <<child's name>> sleeps at night, that is, water trickling down the inside of the window or walls, or a puddle of water at the bottom of the window or wall? (GUINZ Mother Questionnaire 9 months M61)
   a. Never / Hardly ever
   b. Not very often
   c. Quite often
   d. Always / almost always
   e. Don’t know
   f. Refused

53. Thinking about the past two weeks, has there been mould or mildew on the walls or the ceilings where <<child's name>> sleeps at night? This does not include the insides of cupboards or wardrobes. Mildew is a fungus that causes black marks that appear and re-appear around windows, skirting boards and walls. (GUINZ Mother Questionnaire 9 months M62)
   a. Yes
   b. No

54. Did you heat your house in the last 12 months? (Modified GUINZ Mother Questionnaire 9 months M57)
   a. Yes
   b. No  GO TO QUESTION 57
   c. Don’t Know  GO TO QUESTION 57
   d. Refused

55. What forms of heating did you use? (We want to know about all forms of heating that you use. (GUINZ Mother Questionnaire 9 months M58)
   a. Electricity
   b. Flued gas heater
   c. Unflued gas heater
   d. Wood
   e. Coal
   f. Solar
   g. Kerosene
   h. Other (specify)
   i. Don’t know
   j. Refused

56. What forms of heating did you use in the room where <<baby's name>> sleeps at night? I want to know about all the heating that you used for that room. (GUINZ Mother Questionnaire 9 months M59)
   a. Electricity
   b. Flued gas heater
   c. Unflued portable gas heater
   d. Wood
   e. Coal
   f. Solar heating equipment
   g. Kerosene
   h. Other (specify)
   i. No heating
   j. Don’t know
k. Refused

Now I would like to ask about pets and smoking

57. Do you currently smoke regularly, at least one cigarette a day? (GUINZ Mother Questionnaire 9 months M69)
   a. Yes
   b. No Go to Question 61
   c. Refused Go to Question 61
   d. Don’t know Go to Question 61

58. How many cigarettes do you smoke per day, on average? (GUINZ Mother Questionnaire 9 months M70)
   a. Number of cigarettes: ____________
   b. Don’t know
   c. Refused

59. Where do you smoke cigarettes? (all locations)
   a. In the house
   b. On a porch or doorway of the house
   c. In the car
   d. Away from the house but within the boundary of the property
   e. Only outside the boundary of the property

60. How many people who live in your household smoke cigarettes? (Please count yourself as well) (GUINZ Mother Questionnaire 9 months M71)
   a. Number of people
   b. Don’t know
   c. Refused

61. Do any other smokers in the household, smoke cigarettes in the house?
   a. Yes
   b. No

62. In the past 12 months have you had a cat in your home? (ISAAC Phase Three EQ. 20)
   a. Yes
   b. No Go to Question 66
   c. Don’t know
   d. Refused

63. Do you currently have a cat in your home?
   a. Yes
   b. No Go to Question 66
   c. Don’t know Go to Question 66
   d. Refused Go to Question 66

64. In the past 12 months have you had a dog in your home? (ISAAC Phase Three EQ. 21)
   a. Yes
   b. No THE END!
c. Don’t know
d. Refused

65. Do you currently have a dog in your home?
   a. Yes
   b. No            THE END!
   c. Don’t know
   d. Refused
## 24. APPENDIX X: AMENDMENT HISTORY

<table>
<thead>
<tr>
<th>Amendment No.</th>
<th>Protocol Version No.</th>
<th>Date issued</th>
<th>Author(s) of changes</th>
<th>Details of Changes made</th>
</tr>
</thead>
</table>

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to HDEC for approval.