The PITCH Trial

Paracetamol and Ibuprofen for the Treatment of fever in CHildhood

1. **Trial identifiers**

1a) *Title*

Ibuprofen and paracetamol in combination and separately for fever in pre-school children presenting to primary care: a randomised controlled trial.

1b) *Acronym*

PITCH

1c) *EUDRACT number*

2004-000160-28

1d *International Standard Randomised Controlled Trial Number*

ISRCTN26362730 - http://www.controlled-trials.com/isrctn/trial/l/0/26362730.html

1e) *Funder*

NHS R&D National Coordinating Centre for Heath Technology Assessment (NCCHTA)

1f) *HTA identification number*

HTA 03/09/01

1g) *Trial sponsor and contact details*

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This protocol has been written to meet MRC and HTA protocol requirements.

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3. **Planned investigation**

3a) *Research objectives*

i) To establish the relative clinical effectiveness of paracetamol alone, ibuprofen alone or paracetamol and ibuprofen for fever clearance in the first four hours post randomisation in children aged between 6 months and 6 years presenting to primary care with fever.

ii) To assess the relative clinical effectiveness of paracetamol alone, ibuprofen alone or paracetamol and ibuprofen for the relief of fever associated discomfort during the period 24 to 48 hours post randomisation.

iii) To use qualitative methods to optimise the overall trial process and explore parents' and clinicians' beliefs about the use, effectiveness and side effects of ibuprofen and paracetamol.

iv) To perform an economic evaluation from the perspective of the NHS and parents comparing the cost and benefits of each treatment.

v) To describe the natural history of fever.

3b) *The need for a trial*

Scale of the problem

Fever causes misery, parental anxiety and expense to the NHS. We have shown that it affects 70% of all pre-school children per annum[1] and disrupts the comfort, activity, appetite and sleep of young children. Parents are concerned about and want to control fever, and express concerns about its perceived associations with meningitis, convulsions and brain damage.[2 3] It is not surprising then that when children become febrile, one in five parents contact health services[4] and two in five pre-school children are seen for fever each year.[1] The vast majority of fever is managed by parents in the community with advice and support from primary care, that is NHS Direct, General Practitioners (GPs), nurse practitioners in Walk-in Centres (WICs) and Emergency Departments. For example, 22% of calls to NHS Direct are for pre-school children, most commonly for fever and upper respiratory tract symptoms,[5] and 5% of all consultations in Walk-in Centres are for pre-school children, again most commonly for respiratory tract

infections.[6] As fever is a symptom usually associated with self-limiting infection of the respiratory tract,[7] it is most prevalent during the winter months.[8 9] Despite antipyretics being available and commonly purchased over-the-counter, an estimated £0.2M was spent on prescribed paracetamol and ibuprofen suspensions for children in Wales alone in 2002,[10] equating to around £4.2M for the UK. The ratio of paracetamol to ibuprofen prescriptions was seven to one.[11] Add to this the cost of consultations and reconsultations, and it is clear that the burden of fever in pre-school children to the NHS is considerable. The cost to the NHS of intervention medicines is negligible as parents usually purchase them, so small differences in NHS costs between the treatment arms, particularly in terms of reconsultations, could make them cost-effective.

Defining fever

The literature does not agree on the definition of normal body temperature or fever in children, or on how best to measure temperature. For fever, definitions include a rise in body temperature of 1°C or more above the mean; that is, a rectal temperature of 1°C above 38°C or an axillary temperature of 1°C above 37.2°C.[12] Normal axillary temperature in infants is said to range between 35.6°C and 37.2°C,[13] and a review of websites' advice to parents gave a range for the upper limit of normal axillary temperature as 37.0 to 37.6 degrees C.[14] Another author states that normal childhood temperature fluctuates between 36.5°C and 37.5°C.[7] Unsurprisingly, parents prefer axillary to rectal thermometry[15] and our research has shown that the measurement of fever in pre-school children in primary care with tympanic thermometry is too insensitive for the detection of fever.[16] Most physicians (90%) and nurses (70%) would start treatment between 38°C and 40°C, and many (60% and 77% respectively) consider it necessary to confirm fever using a thermometer first.[17] Based on these data, we will recruit children with a measured axillary temperature of ≥ 37.8°C and our primary outcome will be based on an axillary temperature threshold of 37.2°C distinguishing raised from normal temperature.

Mechanisms and treatment of fever

The aim of the consultation for fever is to diagnose and manage its cause, and then symptomatic treatment may be offered. However, not all commentators agree that treatment of fever is necessary. While the exact biological mechanisms associated with fever are not known,[18] some argue that fever is an evolutionary by-product of the host response to the infection, conferring a protective advantage.[7] Others suggest fever may be a proxy marker for more severe illness. Although most children seen in primary care are not seriously ill, severe infection may stimulate the release of pyrogenic cytokines such as Interleukin-1, tumour necrosis factor, interferon and prostaglandins.[19] Others suggest that the aim of antipyresis should be to reduce the pain and discomfort associated with fever, but not the fever itself.[20] However, despite these controversies, the use of antipyretics is commonplace and there is evidence that antipyretic agents used at the correct doses are safe in children with fever.[21] In addition, it is important that parents' fears are addressed and that they are empowered in the care of the child.[22] Because of the strong desire to relieve the child's symptoms,[2 17] many parents have already used antipyretics before consulting health services,[4 23] and clinicians usually advise the use of antipyretics.[14] Our experience is that when children are seen in primary care, they have typically been given one antipyretic, usually paracetamol,[24 25] and less commonly, both paracetamol and ibuprofen together. While clinical practice varies between institutions, the use of combined therapy in secondary care is widespread. It is thought that paracetamol and ibuprofen exert their effects by blocking different points in the chemical pathway that leads to fever.[26 27] It is therefore biologically plausible that they could act synergistically. Therefore, the evidence most urgently needed by primary care clinicians relates to whether both agents together are superior to either agent alone in the relief of fever and fever associated symptoms.

Previous studies of paracetamol and ibuprofen

We searched the Medline (1966 to November 2003) and Cochrane databases and found just one study examining the effectiveness of the two agents combined.[28] This secondary care study in India randomised 89 children with temperatures greater than 38.5°C and respiratory tract infections to receive single doses of ibuprofen 10mg/kg and paracetamol 10mg/kg, each three times daily. Axillary temperature was measured at decreasing intervals for 48-hours. Graphically, the paper reports the paracetamol-ibuprofen combination more effective than paracetamol alone from 0.5 to 2 hours and less effective from 10 to 24 hours, but differences were not statistically significant. The study did not measure fever-associated discomfort. We found 15 studies comparing the effectiveness of paracetamol and ibuprofen separately in children. Nine studies suggest ibuprofen is more effective than paracetamol and six suggest equivalence of effectiveness. Since this search, a systematic review of studies in children aged less than 18 years has been published.[29] This suggests equivalence of action for pain and greater antipyretic effectiveness for ibuprofen, especially when used at the 10mg/kg dose.

None of the studies we identified were based in primary care, though some recruited children presenting to Emergency Departments. Comparisons between studies are difficult due to differing dosing regimens and outcome measures. Most studies use thermometry and some form of global measure of child well-being. Measures of temperature differed, with six studies using rectal, five axillary, two oral and one tympanic thermometry. Most studies used multiple measures, at intervals varying from 0.5 to 4 hours, with differing durations of follow up, from 3 to 48 hours. The timing of these measures is critical as either the interval or duration of follow up alone might

advantage one agent over the other. This is due to differences in the time to peak antipyretic: 133 minutes and 183 minutes for paracetamol and ibuprofen respectively.[30] Thus, if the primary outcome is measured at two hours, paracetamol could be advantaged and similarly, measurement at six hours could advantage ibuprofen. Most studies use one of three primary outcome measures: first, mean differences between pre and post dose temperatures, second, differences in the proportion of children without fever at one or multiple time points and third, the mean area under the temperature curve. None can be expressed as a clinically meaningful measure of effectiveness that is intuitive to parents or clinicians and the second is subject to the problems of multiple testing. To overcome these limitations, one systematic review author suggested that future trials should measure mean time to fever clearance, that is, the time taken for the temperature to first drop below a fever threshold.[31] We propose to measure both fever clearance in the first four hours after dosing using a 37.2°C fever threshold (primary outcome) and the mean time under the threshold in the first 24 hours (secondary outcome). With regard to fever-associated discomfort, there is little evidence of the measures being validated. Studies have used Likert scales of child symptoms (alertness, activity, mood, comfort, eating, drinking, crying, facial expression, general behaviour and irritability) and parent satisfaction. The only study examining the ibuprofen-paracetamol combination did not measure these, and two separate ibuprofen paracetamol studies[32 33] report equivalence of effectiveness for parent global assessment, though the latter reports improved sleep for the ibuprofen group. None report differences in measured adverse reactions. Despite primary care managing the majority of febrile children, we are aware of only one study exclusively in primary care (which examined the effectiveness of paracetamol and/or warm sponging).[34]

Parents and clinicians attitudes to the trial and antipyretic use

Qualitative work embedded in randomised controlled trials (RCTs) is widely accepted as useful to understand how and why they perform. Previous studies have used qualitative research in conjunction with RCTs to explore the acceptability of the intervention,[35] the way in which intervention messages are delivered[35 36] and as an aid to the development and presentation of trial information.[36 37] Of particular interest is a recent study exploring the attitudes of parents whose children had participated in an RCT.[38] In this research, parents described the meaning of their participation, their motivation for taking part and their understanding of the nature of the trial. Although previous research studies have focused on trial participants' perspectives, the views of clinicians are also likely to be important in influencing how trial information is explained and in how the meaning of trial participation is presented to potential participants. Clearly both views have a role in influencing trial uptake and attrition. We propose the use of qualitative research with both recruited participants and trial clinicians to investigate the acceptability of study information, to inform trial process and to determine respondents' perceptions and preferences regarding the different interventions concerned.

Previous authors have argued for the importance of exploring patients' preferences, orientation towards medicines and social context when assessing the appropriateness of their treatment.[39] This seminal research explored patients' beliefs about the properties of medicines, including ideas about dependency and side effects. More recent research has investigated how these beliefs can impact upon the use of medicines, where misunderstandings about medicines may lead people not to take them.[40] However, it is not only the patient's view that needs to be considered. There is also a need to explore health care professionals' views of the measurement of temperature and the medicines they prescribe and how these 'lay' views sit alongside their learned scientific views. As noted by the Royal Pharmaceutical Society of Great Britain, 'we need to understand better the influence of the health beliefs of doctors, nurses and pharmacists about drugs and the nature of the gap between these health beliefs and the patients'.[41] The question becomes, to what extent do patients and health care professionals share general and specific beliefs about medicines?

Summary

In summary, there is no consensus on the optimal trial method and no evidence generalisable to the UK on which to base separate or combination antipyretic advice to parents of febrile children presenting to primary care, where most fever is managed. Therefore, our proposed trial will provide urgently needed evidence and is timely given the current focus on the health needs of children in the Children's National Service Framework.[42] This brief literature review supports our interpretation of the HTA commissioning brief in terms of investigating the effectiveness of ibuprofen and paracetamol together against either agent alone for fever clearance and fever associated discomfort, justifies why we believe the trial should be conducted in the community and primary care and the reasons for exploring parent knowledge and attitudes to the trial and intervention.

3c) *Research methods*

Study design

We are proposing a single centre (multi-site), individually randomised, blinded, three-arm trial consisting of paracetamol alone, ibuprofen alone and paracetamol and ibuprofen in combination with start-up phase qualitative interviews to optimise the trial process and explore parents' and trial clinicians' beliefs about the use, effectiveness and side effects of ibuprofen and paracetamol.

Recruitment

Recruitment will take place through two mechanisms: direct from the community and via the NHS.

Community recruitment:

Parents of pre-school children will be invited to contact a telephone "hotline" number in the event their child becomes pyrexial. The invitation will be via a study information sheet and fridge magnets given to parents by the study nurses in their day-to-day contacts. In addition, posters and information sheets will be distributed to nurseries, toddler groups, pre-school groups, schools, libraries and pharmacies advertising the study. Posters, information sheets and fridge magnets will stress that taking part in the study would not be instead of seeing their doctor.

The "hotline" telephone number will have an answer-phone message for evenings and weekends advising parents concerned about their children to seek medical advice from NHS Direct or their own GP. When calls are received from the community, the study secretary will establish whether the parent is calling with a general enquiry or because their child is currently febrile. For children in the second group, contact details will be passed to a (paediatric trained and registered) study nurse who will assess the child's clinical state for more serious underlying causes of fever in need of medical attention using methods as similar as possible to the appropriate NHS Direct telephone advice algorithms. These are some of the most commonly used triage algorithms within NHS Direct, yet critical events have been rare[43] (0.002% of all calls) and algorithms are updated in the light of such events. A record of all triage calls will be documented and stored for the study duration. Children not needing to see a doctor and potentially eligible will then be visited at home by the study nurses. From that point on, the child's pathway through the study will be the same as if recruited from an NHS site.

NHS recruitment

For NHS sites where patients see a clinician face-to-face, recruitment and progression of participants through the trial is summarised in the Figure 1 on page 17. To maximise generalisability and recruitment efficiency, we propose to recruit from primary care in its broadest sense. Recruitment sites will comprise general practices from the five Primary Care Trusts comprising the former Avon Health Authority, GP led out of hours centres (OHCs), a nurse led Walk-in Centre (WIC) and a Children's Emergency Department (CED). Using a similar method to that employed successfully in the past,[44] we propose that reception staff or triage nurses (depending on the recruitment site) identify children appearing under or of early school age. The parents of these children will be given a Patient Information Sheet (on site-specific headed paper) informing them of the study, confirming the child's age and asking if they have attended with 'fever indicators'. These indicators will be either a 'current fever' or 'the use of antipyretics for fever in the previous 24 hours'. Where possible, we will invite parents to check for themselves the presence of current fever using a single use, disposable study thermometer, Tempadot® manufactured by 3M. This thermometer strip has been chosen because it is sufficiently accurate to reduce false negatives without excessive false positives; with a sensitivity of 92% and a positive predictive value of 86%,[45] and is relatively inexpensive. Where parents have been overlooked by receptionists and not received the Patient Information Sheet (PIS) on arrival, they will have a second opportunity to collect one from the waiting room while waiting to be seen by the clinician. Only parents of those within the age range with fever indicators present will be invited to read the whole Patient Information Sheet and to participate. The Patient Information Sheet will be taken to the clinician (GP, CED doctor or nurse practitioner) 'prompting' an opportunity to answer questions about the trial and a first eligibility check by the clinician. At this stage, afebrile children who have received antipyretics will not be excluded. The practice will then give the parent's contact details direct to the recruitment nurse if present at the recruitment site, or by mobile telephone/fax following written consent. Finally, when the receptionist has overlooked a parent and the parent has not collected a PIS from the waiting room, clinicians will also be able to directly invite parents of potentially eligible children. In this instance, clinicians will be able to discuss the study and give the parent the PIS. Again, following written consent to release details, the parents contact details will be faxed to the PITCH study office.

As telephone triage and advice represents an important contemporary part of NHS primary care, we will also recruit children following telephone contact by nurses at the telephone advice centre (the Avon, Gloucester and Wiltshire NHS Direct Call Centre) or by GPs and GP nurse practitioners. Parents of children aged between 6 months and 5 years living within the Bristol area calling for advice regarding fever, and not subsequently being advised to attend their GP or Emergency Department (i.e. those 'disposed' to home/self care or pharmacy advice) will be asked for verbal permission to pass their contact details to the PITCH study office. Since all NHS Direct conversations are recorded and stored for 25 years and GPs routinely record telephone consultations in the medical record, a record of these conversations would be available for future reference if required.

The research nurse will then speak to the parent (face-to-face or by telephone) to briefly answer any questions, explain the trial and arrange a face-to-face meeting timed to coincide with the first time at which the child can receive both intervention medicines together without exceeding the recommended maximum dose in 24 hours. At

this meeting, a full trial explanation will be given and the child's participation consented. Just prior to treatment allocation, the nurse will perform a final temperature re-eligibility check to ensure that only children within the specified temperature range are randomised. Those not meeting the minimum temperature will be invited to contact the research nurse until the end of her shift should the child's temperature subsequently rise. While waiting for notification of eligible children, research nurses will be able to assist recruitment by visiting recruitment sites to ensure the waiting room posters are displayed and to remind receptionists to hand Parent Information Sheets to potential participants.

Inclusion criteria

We will invite previously well children aged between 6 months and six years with a nurse measured temperature of at least 37.8°C (100°F, the temperature close to that at which most clinicians would start antipyretic therapy)[17] and no more than 41°C (105.8°F) presenting for the first (for that episode of fever) time to multiple primary care sites in the Avon area.

Exclusion criteria

We will exclude children who have previously participated in the PITCH trial, those within 30 days of participation in another drug trial, those weighing less than or up to 7kg,[46] those with illnesses requiring hospital admission, epilepsy, dehydration,[47] any known study medicine intolerance, skin conditions precluding the use of adhesive tape and those with known study medicine contra-indications or cautions as identifed by the BNF. These are: previous or active peptic ulceration or bleeding, hypersensitivity to any NSAID - which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by any NSAID, coagulation defects, renal, cardiac, or hepatic impairment (including jaundice). We will exclude children with known current or previous conditions known to be side effects of the interventions: blood disorders, fluid retention, hypertension, papillary necrosis or interstitial fibrosis, hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, colitis, aseptic meningitis, connective tissue disorders (such as systemic lupus erythematosus). Where possible, these exclusion criteria will be identified by the clinician from the child's medical record. If the record is unavailable (e.g. in WICs), these criteria will be operationalised by asking parents for their knowledge of previous epilepsy or other chronic neurological disease (except where the impairment is sufficiently minor to allow the diary card to be completed in the normal manner), allergy or intolerance to the study medicine, peptic ulceration or bleeding, pulmonary (other than asthma; see section 3d), liver, renal or cardiac (under active follow up or treatment) disease. Children attending at inconvenient times (after 9pm) or whose parents cannot read/write English will also be excluded. Although the HTA brief stated the group of interest to be pre-school age children, we will use an age rather than school attendance exclusion criterion, as the age of children starting school can differ by up to one year. Children attending school will not be recruited unless they will be under parent/carer supervision for the data-logging period, that is the first 24-hour period immediately after treatment allocation.

Justification for proposed recruitment method

We have chosen to recruit children when they become symptomatic with fever and present to primary care because the NHS and clinicians need to know how best to manage fever at the point in its natural history when parents seek medical help. We believe this trial should be conducted in primary as opposed to secondary care because this is where most febrile children are managed.

We have chosen to complement the NHS recruitment strategy with a community method for two reasons. First, at least as many episodes of fever are managed by parents in the community without the assistance of the NHS as with it and so the external validity of the study will be enhanced. Second, initial study results showed that "supply" of febrile children through the NHS mechanisms to the study were likely to be insufficient for us to meet our recruitment target.

The role of the recruitment nurses

Recruitment will be rotated across time ('within' and 'out of' hours) and space (the Bristol area). On any given 'shift', nurses will be 'on-call' to receive notification (usually by mobile telephone) of febrile children from the community or recruitment sites. Once notified that a child may be eligible for trial participation, s/he will then contact the parent and can quickly travel to meet the child, usually at his/her home, at a time arranged to coincide with the child's next due antipyretic dose. While waiting for notification, s/he will be able to visit local recruitment sites to monitor and support recruitment activities, and do the first and second follow up visits for children recently recruited from the area. We anticipate that for busier recruitment sites such as OHCs, WICs and the CED, it will make most sense for the nurses to perform as many of the recruitment tasks as possible at the site.

Irrespective of the route of recruitment (community or NHS site), there is a small, but important, chance that a child recruited into the study may have a serious underlying cause for their fever, such as septicaemia or meningitis. All children are recruited by experienced paediatric trained and registered PITCH study research nurses. Although primarily fulfilling a research role, they also have a duty of (clinical) care to the participating children and use their

clinical experience and judgement to assess children at the 4 study contacts (at time zero, 24 hours, 48 hours and day 5) during the study period. By virtue of this follow up and consistent with many clinical studies, children in the PITCH study are arguably safer with respect to the assessment of children for serious underlying illness than those not participating. However, without the prior contact with the NHS that all study children currently have at time zero, our research nurses will not have the assessment or opinion of another health professional. Therefore, in addition to the NHS Direct telephone triage algorithms, the study nurses will have access to additional refresher training, such as the "Spotting the Sick Child" training DVD and/or sessions with NHS nurses at the WIC.

Allocation to trial groups

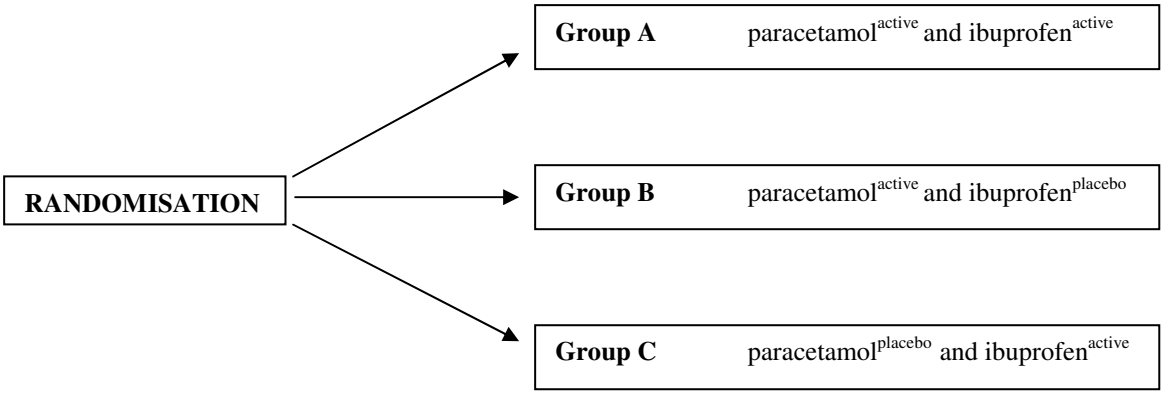
Written informed consent will be obtained before enrolment. As soon as a child is enrolled (s)he will be assigned a unique enrolment number. This enrolment number will be used as the identification number throughout the study. Allocation of study treatment will be via a centralised automated telephone system. This will be provided by the Health Services Research Unit at the University of Aberdeen, which has extensive experience of automated randomisation in blinded randomised controlled trials. Calls are made to the service via a free-phone number. Callers respond to a series of questions to confirm eligibility of the patient and to provide details of minimisation variables. We will minimise by age (6 to 17 months and 18 to 71 months), fever severity (37.8°C to 38.9°C and 39°C to 41°C),[48 49] symptom card discomfort score (2 or 3 and 4 or 5), prior fever duration (≤ 24 hours and > 24 hours) and current antibiotic use (yes/no). Responses are made by either speaking or by keying numbers on the telephone keypad. The attending research nurse will carry packs containing the three separate interventions, identified solely by a unique randomisation number. This randomisation number is unique to the medication pack assigned to the patient and is separate from the enrolment number. Following automated allocation, (s)he will then provide the parent with the appropriate blinded intervention as determined by the randomisation number allocated by the automated system.

3d) *Planned interventions*

The intervention will be the administration of the study medicines. The first dose will be timed to coincide with the child's next due dose of antipyretic, that is, respectively 4 to 6 and 6 to 8 hours post paracetamol and ibuprofen. As shown on the diagram below, consenting children will be randomised to receive either a) paracetamol^{active} and ibuprofen^{active} or b) paracetamol^{active} and ibuprofen^{placebo} or c) paracetamol^{placebo} and ibuprofen^{active}. Parents will each receive two medicine bottles and will be aware which is nominally paracetamol/placebo and which ibuprofen/placebo. All suspensions will be sugar free and supplied in licensed containers with approved child-resistant caps. The order in which medicines are administered will be determined randomly. The dose of medicine will be determined by the child's weight[17] and both timing and dose are as recommended by 'Medicines for Children'[50] and the Royal Pharmaceutical Society for Great Britain in the British National Formulary (BNF).[46] These are: paracetamol 15 mg/kg repeated every 4 to 6 hours (max. of 4 doses in 24 hours) and ibuprofen 10 mg/kg repeated every 6 to 8 hours (max. of 3 doses in 24 hours). The volume of suspension per dose will be calculated according to the child's weight, estimated by the recruiting research nurses using paediatric-approved scales. By using this dosing regimen, the intervention remains within BNF recommended (and licensed) use and as similar as possible to the way it is used by parents and clinicians in routine practice. Suspensions will be administered to the nearest 0.5 millilitre using 10ml syringes marked at 0.5 millilitre increments. In addition, we will give the parents detailed dosing advice to take account of intervention medicines received in the 24 hours prior to randomisation, in order to prevent the maximum 24-hour recommended dose being exceeded.

Immediately following randomisation and at the start of data logged thermometry, the research nurse will observe the administration of the first dose. This heralds the start of the four-hour '*efficacy period'* during which temperature will be measured every five minutes using sophisticated, electronic data logging and no further medicine will be given. Four to 24 hours will be the '*proactive period*' during which the parent will be asked to administer the medicines regularly, paracetamol four times and ibuprofen three times daily respectively, in line with BNF recommendations. Twenty-four to 48 hours will be the '*reactive period*'; during which parents will be asked to give the medicines as required, in response to the child's discomfort or temperature. In addition, guidance will be offered regarding what to do in the event of medicine spillage or subsequent vomiting. We believe we can reasonably expect parents to use the study medicines for between 24 and 48 hours, but that after this time, parents will be increasingly likely to abandon the study medicines in favour of known over-the-counter brands or stop using them altogether. We will therefore supply 48-hours worth of study medicine and we will collect and measure the remaining medicine in the study bottles at the second follow up visit at 48 hours. From 48 hours to day five, parents will be asked to use normal over-the-counter preparations as required. The exact duration and balance of proactive and reactive use of the intervention will be confirmed during the study start up phase. All parents will be given a standardised advice sheet regarding other cooling measures,[51] such as appropriate clothing, ambient temperature and tepid sponging.[52]

Diagram showing how the intervention will be randomised across the three groups



Blinding

All study participants, investigators and research nurses will be blinded to whether the child is receiving an active or placebo medicine using identical active and corresponding placebo suspensions (though all children will receive at least one active medicine). We have asked our supplier to produce placebos to match the look and taste of the active suspension counterparts, but we will not try to match the paracetamol and ibuprofen suspensions to each other as they have very different tastes related to their different physico-chemical properties. In any case, given that parents will need to administer the two medicines according to different regimens, they will need to be aware that the suspensions differ and again, this has the pragmatic advantage that it reflects more closely routine parent behaviour. We will blind the participants and research nurses to the manufacturer of the active medicines. This will minimise performance bias as from a young age, children form strong opinions regarding the palatability of over-the-counter paracetamol and ibuprofen suspensions and we wish to prevent unequal distribution of medicine rejection between the groups, and detection bias as we wish to measure the parents' perceptions of the severity of children's fever associated discomfort and other symptoms. We will ask parents at 48-hours which medicine/s they believe their child was receiving to check the validity of blinding.

Safety of the interventions

The planned interventions are safe. Randomised controlled trial evidence suggests that short-term renal impairment[53] and admission to hospital for anaphylaxis, gastro-intestinal bleeding and renal failure[54] is no more common with ibuprofen than paracetamol using 5 or 10mg/kg and 15 mg/kg respectively. The latter study randomised 84,192 children with fever recruited from out-patients and family practices in the USA to paracetamol or ibuprofen. Across both groups, absolute admission rates were low at 1%, did not differ between groups and were primarily for treatment of the underlying infectious disease. The rate of gastro-intestinal bleeding associated with ibuprofen was 7.2 per 100,000 children. There were no hospitalisations for acute renal failure or anaphylaxis. However, we are aware of two case reports[55 47] describing acute renal failure in young children hospitalised with fever and treated with ibuprofen and paracetamol. The first was a 14-month-old child given ibuprofen and paracetamol following admission for febrile status epilepticus. She made a full recovery. The second was a toddler admitted with fever and dehydration was thought to compound the known nephrotoxic effects of study medicines. Given the high frequency with which the study medicines are currently used in the community, these case reports suggest that such serious effects, if due to the study medicines, are rare. Regarding the effects of the medicines on asthma, in one study,[54] a subgroup analysis was performed to determine the safety of paracetamol and ibuprofen for the 1879 children with asthma (defined as those receiving ß agonists, theophyllines or inhaled steroids on the day before trial recruitment[56]). The authors found no evidence of increased hospital admissions or out patient attendances for asthma associated with ibuprofen compared with paracetamol. In fact, rates were higher in those receiving paracetamol. The cumulative incidence of out patient attendances in the month following treatment was 5% and 3% for paracetamol and ibuprofen respectively. We therefore feel it appropriate to include children with asthma provided they have not had a previous worsening of asthma symptoms associated with similar medicines. Although probably only offering limited gastric protection,[46] we will advise parents where possible to give the 'ibuprofen' medicine after the child has received something to eat or drink. A recent systematic review comparing the relative effectiveness of paracetamol and ibuprofen separately found no evidence of increased major or minor harm comparing active agents with each other or against placebo.[29]

Emergency unblinding

A set of emergency unblinding tools (scratch off cards which reveal the treatment allocated when scratched) will be kept by the Pharmacy Department at the Bristol Royal Infirmary and a second set will be kept by the trial team at the

University of Bristol. In the event that a child's treatment allocation is required to be unblinded, the clinician will be able to phone a number to discuss the matter with the trial team or will be able to call the Bristol Royal Infirmary Pharmacy department (24 hour service) for the treatment to be unblinded. The treatment code should only be broken in medical emergencies where the appropriate management of the child necessitates knowledge of the treatment allocated. The study team/pharmacy department will document any unblinding that occurs.

Adherence

Since parents will be observed administering the first dose at the start of the 'efficacy period', adherence is not a primary concern in this trial. However, one of the secondary outcomes assesses the antipyretic activity during the 'proactive period' and the other primary outcome assesses discomfort between 24 and 48 hours. Therefore, the amount of study medicines consumed is of interest, and we will measure this by weighing the bottles at the 24 and 48-hour nurse visits, the latter coinciding with the end of the two-day intervention period. As we are also interested in the differences between groups for symptom scores at 48 hours and five days (secondary outcomes), we will also collect information on the use of over-the-counter preparations.

3e) *Proposed outcome measures*

There are two primary outcomes for this study: (a) the period of time spent below a temperature of 37.2°C during the four hours following administration of the first treatment dose, and (b) symptom score for discomfort recorded on a diary card at 48 hours after the first dose, dichotomised between 1 and ≥2. Secondary outcomes are the period of time spent below a temperature of 37.2°C during the 24 hours following administration of the first treatment dose, symptom scores and digital axillary thermometry (at 0, 4, 8, 16, 24, and 48 hours, and five days), adverse events and the number of night time medicine doses.

Primary outcomes

The first, as suggested by the brief, will be temperature reduction and more specifically, as recommended by a Cochrane review,[31] fever clearance. This will be the time each child spends under a fever threshold of 37.2°C in the four hours (the efficacy period) following the first, observed study dose of medicine. We considered a longer primary observation period, but even though we will ask parents to give the medicines regularly during the proactive period, the BNF dosing recommendations allow some flexibility after four hours. Thermometry will be at five-minute intervals using a sophisticated electronic data logger attached to a skin thermistor under the child's arm using skin appropriate adhesive tape and connected to the data logger with a thin, childproof wire. The OMEGA precision temperature datalogger (OM-CP-RTDTEMP110) is a matchbox-sized instrument and will be put inside a soft, childproof, water resistant, case (to prevent the child tampering with the settings) and attached to a vest around the child's chest or in a small, child friendly backpack. This method is accurate to within 0.05 °C and has resolution (the smallest detectable change in temperature distinguishable) to within 0.01 °C. Output from the logger is exported in ASCII file format, compatible with most statistical software packages. It has been evaluated in another primary care study[34] and found to be feasible. In summary, as stated in section 3(b) above, the strengths of this primary outcome are that it does not disadvantage one treatment by virtue of arbitrarily selecting a single post dose time for thermometry, it avoids the statistical problems of multiple measures and results can be expressed using a clinically meaningful summary, that is, the difference in mean time spent without fever during the observation period. Data logged thermometry is superior to parent and health professional measured temperature in that timing is reliable, the time(s) at which the temperature crosses the fever threshold can be ascertained precisely and the measures are objective. We believe that relying on parents alone to record temperature would introduce observer bias, timing would be unacceptably unreliable and sufficient detail to identify the defined endpoint unobtainable.

Our second primary outcome will measure the child's discomfort at 48 hours post randomisation when parents are using the medicines as required, that is the reactive period. This is important, as it is possible that the study medicines may not reduce the child's temperature, but could improve their fever-associated discomfort, or vice versa. We will compare the proportions scoring ≥3 (not quite normal, quiet, not moving, not happy or worse) on the diary card at the 48-hour nurse visit. This score is based on behavioural pain scores[57] and has been specifically worded to promote consistency in response. We have chosen not to pain scores (such as face scales) as they are specific to the individual children, require a common state (or pain source) and do not allow for between child comparisons. Scales using a combination of more detailed recordings such as facial expression and response to stimuli are considered overly complicated for use in this context.[58]

Secondary outcomes

1. The time each child spends under a fever threshold of 37.2°C in the first 24 hours post randomisation when parents will be asked to use the study medicines proactively. We believe this longer period of data logged thermometry is important to allow for the different dosing regimens (up to three and four times in 24 hours for ibuprofen and paracetamol respectively) and times to peak antipyretic activity. Should the mean temperature fall

below the fever threshold within the first four hour period and then not subsequently rise above it during the following 20 hours, this measure becomes equivalent to the thermometry primary outcome.
2. Adverse events. As suggested by the HTA commissioning brief, we will record the proportion of children departing from the study protocol, where the randomisation code is broken, experiencing febrile convulsions, vomiting, diarrhoea, gastro-intestinal bleeding, bronchospasm and skin rashes as well as subsequent contacts with the GP, NHS Direct, out of hours service or hospital admission (with reason) for five days.
3. The pattern of discomfort scores between 4 and 48 hours from the symptom cards.
4. The number of night time (12 midnight to 6am) doses of medicine given in first 48 hours.
5. Fever, discomfort, activity, appetite and sleep for five days.
6. We will perform an economic evaluation from the perspective of the NHS to compare the cost of providing each treatment with the benefits, as measured by the percentage of children recovering (discomfort score of 2 which is normal) at 48 hours and five days.

<u>The symptom card</u>
One side will be used to record the child's name, diagnosis, unique study number (also then available for the purpose of emergency unblinding), and adverse events, other cooling interventions and health service contacts. It is important to be confident that parents are not delaying seeking further advice, to the possible detriment of their child's health, through inclusion in the study. Similarly, deviation from the protocol through external influences /advice needs documenting. The other side will be used to record the child's symptoms. To maximise the usability to parents and minimise the demands on time and effort, (and thus maximise the quality and quantity of complete data for each child) its development builds on the experience of the researchers and on the literature. Completion of the symptom card will be optimised by joint ownership between parents and research nurse and by ensuring the variables are relevant and easily understood. The research nurse, with the parents, will complete the first set of entries on the symptom card on recruitment to the study as the first dose of antipyretic is given. This will ensure that parents are shown how to complete the card and what information to include in each section. This will be completed at 4 and 8 hours after the first medicine dose, then 8 hourly until 48 hours have elapsed. The nurse will support completion at the time of collection, validating their perception of the child's state with the parent's. This will provide a (crude) readily applied mechanism for maximising the validity of between patient comparisons for data not recorded by the nurse.

Outcomes known to be important to parents are included as these are likely to have a significant impact on perception of symptom severity. Discomfort, and therefore pain (also an outcome measure and constructed as an ordered categorical variable) and sleep are listed specifically, partly to ensure documentation of these as it is recognised that parental monitoring of a child's recovery relies largely on the child's activity levels. A febrile child who is laughing and running around is less likely to receive close monitoring or antipyretic therapy than one who is inactive and disinterested in their surroundings. This may influence both antipyretic use and other symptom recording. Activity levels are therefore included, using an ordered categorical scale for cross group comparisons. In addition to giving a measure of well being, a child's appetite provides essential data on the tolerability of the drugs in question and potential adverse effects. By integrating this into the body of the symptom card, there is no suggestion that this is an anticipated side effect, thus avoiding reporting bias. As this is primarily for adverse effect reporting, the scale is categorical. 'Sleep' will assist the interpretation of the data regarding subsequent/missed doses and potential additional effects of combining drugs. Parents will be instructed to enter the value representing the child's state at the time of recording, or of the previous 10 minutes if this is more representative of their state at the time. This should minimise the likelihood of subjectivity influencing the parental responses.

The symptom card will also be used to record the administration of study medicines and over-the-counter antipyretics, as these are required to interpret symptom and temperature recordings after the first 4 hours. The data from the data loggers covers the first 24 hours and should address the primary temperature outcome. Over this period and subsequently, axillary digital thermometry will be used at 0, 4, 8, 12, 24, 48 hours and five days. This provides the parent with fever measures (as the data loggers do not display temperature) and may provide important supplementary data in the event of data logger failure or non-compliance.

<u>Economic data collection</u>
Patient level data on resource use will be collected during the 5 days following randomisation. The research nurse will collect data on resource use during scheduled contacts with participants: face-to-face at 48 hours and by telephone at 5 days. Use of NHS resources will include primary care consultations, secondary care contacts, prescribed drugs, and use of ambulance services. Resource use by patients and carers will include OTC drugs, travel costs, childcare, and loss of earnings.

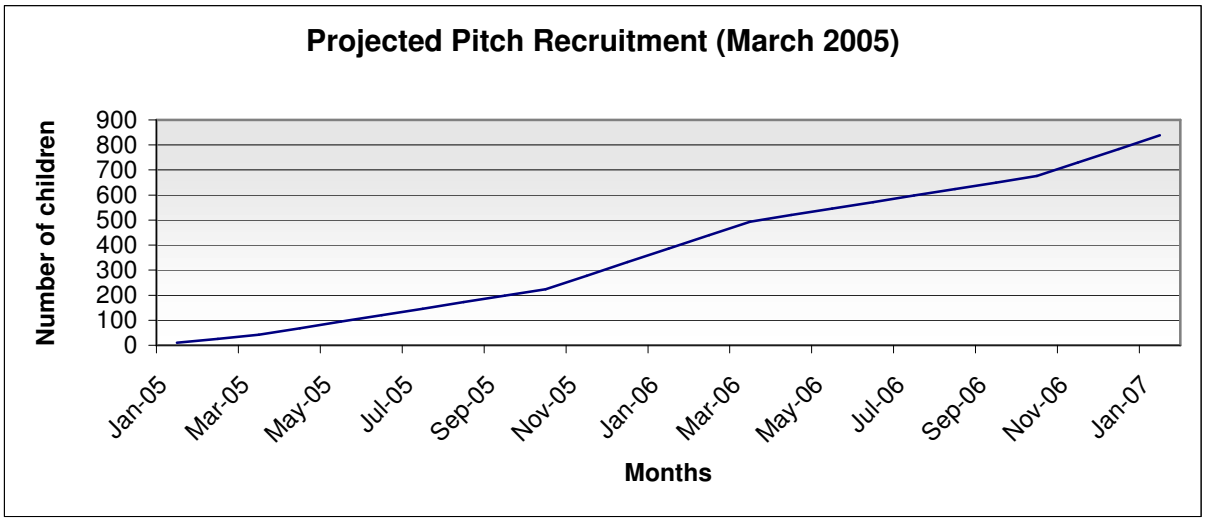
3f) *Proposed sample size justification*
It is a matter of opinion and judgement as to what constitutes the minimum difference worth detecting. We consider that 15 minutes is too small and not worth powering a study to detect, 20 minutes might be regarded by parents and

clinicians as useful, but 30 minutes would definitely be beneficial to child and parent. Should the temperature fall below the fever threshold and then not subsequently rise above it in the first four-hour period, this outcome effectively becomes the fever clearance time, that is, the time to first reducing fever below the threshold. A previous randomised controlled trial of paracetemol treatment in young children with fever using data logged thermometry[34] reported a standard deviation of about 80 minutes when temperature was recorded for four hours after administration of the first dose. For the other (binary) primary outcome of symptom score for discomfort between 24 and 48 hours post first dose, we estimate that 60% of children will score 2 (normal) and that a minimum clinically important difference is 15%. This is equivalent to an odds ratio of either 0.55 or 2.0.

Regarding the binary outcome, with a two-sided alpha of 0.027 allowing for multiple comparisons between combined therapy and each of the single therapy groups,[59] and 90% power to detect a difference of 60% vs. 75% in the proportion of children scoring 2 (normal) on the discomfort symptom score, 249 children are required per group. An achieved sample size of 747 will afford 97% power to detect a difference of 30 minutes (standardised difference 0.375). Furthermore, we will have 80% power to detect the smaller, and arguably still clinically important, difference of 22 minutes (standardised difference 0.274). Since we do not anticipate that large numbers will be lost through either withdrawal from the study or moving away, we have allowed conservatively for an attrition rate of 10% and will therefore recruit a total of 831 (249*3/0.9) children. For our primary outcomes, previous experience in children of similar age over the same follow up period gave 100% complete data for data loggers (and the investigators indicate that the devices are well-tolerated and not prone to failure[34]) and we achieved 89% complete data using similar symptom scores completed with telephone support over four weeks.[44] However, these follow-up rates will be verified during the trial start-up phase.

Recruitment rate

We base our estimate of the time taken to recruit these 831 children on our experience from an observational, primary care study of acute cough in pre-school children, which used similar recruitment methods.[44] In this study, run during the winter months with one researcher, we recruited an average of 1.3 children per consulting session (morning or evening surgery) from general practices with list sizes of at least 8000. Although our research has shown the prevalence of fever in the community, and the proportion of pre-school children consulting with fever are similar to cough,[1] fewer children will be febrile at the final pre-randomisation eligibility check and some parents may be more reluctant to participate in a trial than an observational study. We will therefore assume a conservative recruitment rate of 10% of our previous study, that is between one and two children per ten sessions (per general practice). In any given week, we propose concentrating recruitment from groups of around five practices. During a typical nurse shift, we estimate that this time allows for a maximum of two new children to be recruited and four existing trial children visited at 24 and 48 hours. Thus, using the groups of practices and the WIC, OHC and CED, we believe there will be sufficient children available for the nurses to reach the saturation point of two daily. However, to be conservative, we will base the estimate of our recruitment period on a daily rate of 1.5 children per nurse. Based on this, and allowing for annual and sickness leave, it will take two full time nurses 54 winter weeks (13 winter months or two full winters) plus one full time nurse working eight months in the second winter to recruit 831 children. Our proposed recruitment targets across the duration of the trial are shown in the graph below.



Given that we do not expect to receive final notification from the HTA until the end of June 2004, we aim to commence our start up phase in September, in time to inform recruitment proper by November. Thus, we expect to

be able to recruit during most of winter 1 (2004-2005) and all of winter 2 (2005-2006). We will compensate for any shortfall in winter 1 during the intervening summer, when, if fewer children are available, nurse time can be spent entering and cleaning data.

3g) *Statistical analysis*

This analysis plan may require adjustment according to the results of piloting during the start up phase. The data will be analysed and the study reported in accordance with the CONSORT guidelines for randomised controlled trials.[60] The first stage of the analysis will be to use summary statistics to describe the group of individuals recruited to the trial in relation to those eligible, and to investigate comparability of the trial arms at baseline using descriptive statistics of, for example, clinician diagnosis and the use of any recent antipyretic medication given. The primary intention-to-treat analyses will be for each of the two primary outcomes, comparing the combined ibuprofen plus paracetemol group with each of the single therapy groups. We will use multivariable linear or logistic regression models as appropriate in order to adjust for baseline temperature or discomfort score and the other minimisation variables. Full attention will be paid to the estimates and the confidence intervals for these comparisons as well as the p-values, with the latter adjusted for multiple comparisons using Dunnett's test.[59] The (secondary) comparison between the ibuprofen and paracetamol alone arms will also be performed. Secondary analyses will then be conducted using regression models with further adjustment for any prognostic factors that exhibit marked imbalance at baseline. Secondary outcomes will then be analysed in the same way, using appropriate (linear or logistic) regression models depending on the nature of the outcome measure. Bonferroni corrections for multiple testing will be considered for the secondary outcomes. Data from symptom cards, recorded on repeated occasions between 4 and 48 hours, will be analysed using appropriate random effects regression models. This will include investigation of divergence or convergence between groups over time by fitting appropriate interaction terms in the models. Regarding missing data from the data loggers, as described above we anticipate minimal effects of attrition but we shall nonetheless investigate the effects of various pragmatic assumptions about missing values using sensitivity analyses around the primary analysis including children with observed outcome data. For these measures and the symptom card outcomes, the primary analysis will be conducted on a last observation carried forward basis, with again different assumptions and imputation methods for missing data being investigated in sensitivity analyses.

Other secondary analyses will involve investigation of the effects of adherence in explanatory regression analyses, and pre-planned subgroup analyses employing appropriate interaction terms in the above regression models to ascertain any differential effects of the combined compared with single therapies across the following categories of children: age (6 to 17 months and 18 to 71 months), fever severity (37.8°C to 38.9°C and 39°C to 41°C), symptom card discomfort score (2 or 3 and 4 or 5), current antibiotic use (yes/no) and diagnosis of otitis media (yes/no). Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, the results of these essentially exploratory analyses will be presented using confidence intervals as well as p-values, and interpreted with due caution.

Resources will be valued using national data sets such as Unit Costs of Health and Social Care (http://www.kent.ac.uk/PSSRU/) and National Reference Costs http://www.doh.gov.uk/nhsexec/refcosts.htm); published evaluations of primary care services such as Walk-in Centre (http://www.epi.bris.ac.uk/wic/pdf/WIC%20Evaluation%20Report%20-%20Final.pdf) and NHS Direct (http://www.shef.ac.uk/scharr/mcru/reports/nhsd3.pdf); and other published sources will be used to value prescribed medication. These data will be used to estimate the average cost per patient for each treatment, and to form incremental cost effectiveness ratios, which will estimate the extra cost per extra child recovering at (i) 48- hours and at (ii) 5 days. Discounting will not be necessary as the study period is less than a year but we will conduct sensitivity analyses where there is uncertainty about resource use and/or the value of resources.

3h) *Start-up phase/qualitative study*

This first qualitative focus will last two months and will use interviews to assess the acceptability to trial clinicians and parents of the recruitment method, intervention and outcomes. Specifically, it will investigate respondents' views on: the process by which parents are approached to participate in the trial; how study information is presented, both verbally and in written form (such as how equipoise in the treatment options is presented); the acceptability and face validity of the symptom card, the likely duration of study medicine use; the different outcomes used in the trial (such as which are the more important) and for parents only, what they like and do not like about participating in the trial. We are proposing that these interviews be conducted by the trial coordinator (under the close supervision of MW) allowing him/her to become completely familiar with the running of the trial. Findings from this first part of the qualitative study will be available quickly and used to improve the content and presentation of information, as well as the conduct of the trial.

The second focus for the qualitative study will involve an in-depth exploration of parents' and trial clinicians' beliefs about the use, effectiveness and side effects of ibuprofen and paracetamol. Specifically, this aspect of the study will explore: the use of ibuprofen and paracetamol, for example, a discussion of the triggers (e.g. influential

clinical symptoms) that would predispose them towards starting an anti-pyretic and perceptions and ideas about the medicines' dependency, side effects and efficacy. This will include a discussion of their general attitude or willingness to take/give medicines, positive or negative experiences of using the medicines and the other qualities they attribute to ibuprofen or paracetamol. We will explore the circumstances in which they might increase or leave off a dose, a discussion of the process by which they come to this decision and other non-drug or non-allopathic medicine measures they might take to reduce fever in a child. This will include views of the relative safety and effectiveness of other methods of fever reduction compared with antipyretics, and the point at which they might switch from non-drug measures or non-allopathic medicines to allopathic medicines. A final theme to be investigated in the qualitative interviews will be an exploration of how the trial has influenced parent behaviour with respect to medicine administration and contacts with health care professionals. For the trial clinicians, these issues will be investigated from the perspective of their use of these medicines as a prescriber and as a parent (or, where appropriate, as a hypothetical parent).

For both qualitative foci, the diversity and size of the respondent samples will be iterative. Data analysis will inform the data collection instruments making it possible for recruitment to continue until saturation of the relevant themes has occurred. Although exact numbers cannot be pre-determined, previous experience suggests that approximately 15 trial clinicians and 15 parents will be required for the start-up phase and 20 trial clinicians and 30 parents for the later phase. Participants will include trial clinicians from the four primary care sites (general practices, OHCs, WIC and the CED) and we will target clinicians from sites with low recruitment rates. Parents agreeing to participate in the main trial will be asked if they would like to take part in the qualitative study. From those indicating they are amenable, parents will be selected for their diversity on the following parameters: age of child recruited into the study (6 to 17 months and 18 to 59 months), whether the child has a sibling and the site of recruitment.

Analysis of the data will use a systematic and rigorous approach based upon the constant comparative method described by Green.[61] The data will be sorted, organised and indexed using both descriptive categories (e.g. derived from the data) and conceptual categories (derived from relevant sociological literature). These categories will be further interrogated and grouped together in order to clarify the relationships between categories and to refine emerging ideas. Emerging explanations will be investigated using deviant case analysis such that data, ideas or relationships that do not fit the emerging conceptual framework will be sought. Explanations will be refined in the light of this process and the confines of the explanation elaborated. The process of data analysis will facilitate data collection such that questions or ideas emerging from the data will be used to develop new areas of enquiry to be pursued during data collection. The qualitative data analysis package, Atlas.ti, will be used to facilitate data handling and analysis.

3i) *Natural history arm*

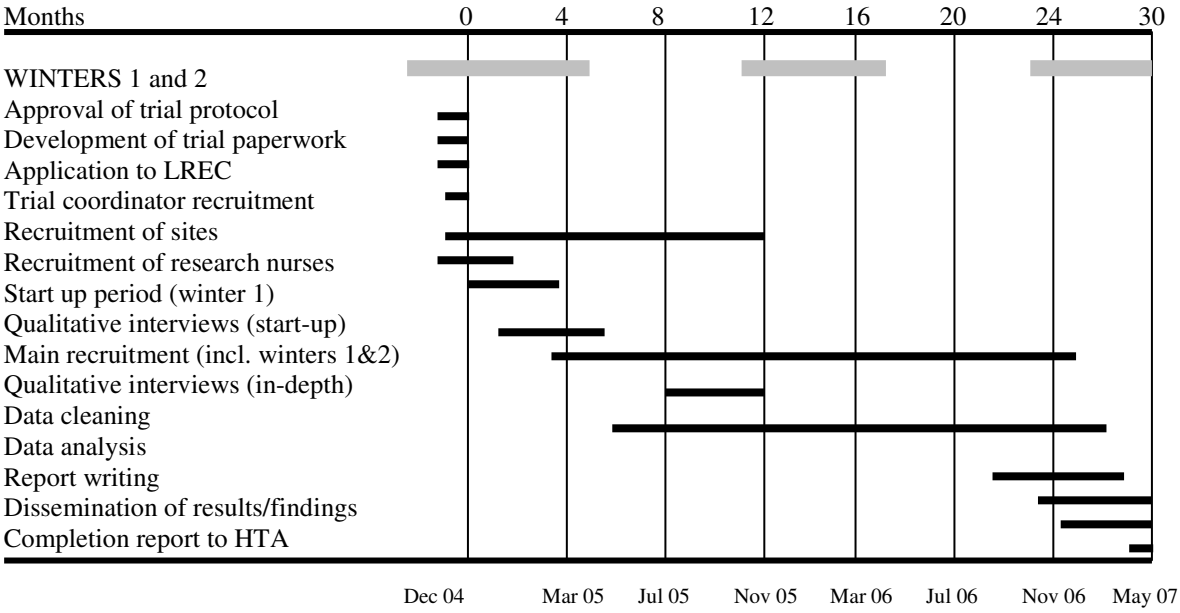
We will describe the natural history of fever in pre-school children presenting to primary care in terms of fever and associated symptom duration and severity. Referring to Figure 2 (page 17) we will invite children meeting the trial criteria at the final (research nurse) re-eligibility check, but not consenting to use the study medicines, to participate in an observational study. Parents will be advised to use antipyretics as per usual their normal practice and asked to complete the symptom card as per the trial protocol. Instead of recording which intervention medicines are used, we will ask parents to record the antipyretics (and doses) they administer. Thermometry data will be collected as in the trial using axillary digital thermometers and, depending on nurse time for logger collection and logger availability, using the data loggers.

3j) *Benefits of this research*

Results from this research will be valuable to parents, primary care clinicians and policy makers. Specifically, results will (a) be generalisable to children at the point of most clinical uncertainty in the management of fever, that is, at presentation to health services, (b) be generalisable to the part of the NHS shouldering the greatest burden, that is, in primary care, with recruitment from the full range of primary care providers, (c) be objective, through the use of sophisticated (data logged) thermometry and nurse/parent completed symptom scores, (d) give equal weight to temperature reduction and the child's overall well-being, thereby capturing the full breadth of important outcome data and (e) find out how and why these medicines are used by parents in the way that they are.

We are confident we will reach our recruitment target because we have taken the burden of recruitment away from busy frontline clinicians. Using tried and tested methods, a dedicated nursing team will steer parents through the recruitment and allocation process and visit and support the parents and children during the 48-hour intervention and five day follow up periods. We will actively seek parental and clinician participation during the start up phase, through a series of qualitative interviews, in order to enhance the recruitment process and the intervention.

3k) Project timetable and milestones



3k) Collaborators

The five (former) Avon PCTs, the Children's Emergency Department (United Bristol Health Trust), North Bristol Doctors (General Practitioner Co-operative) Ltd, BrisDoc (OHC), the South Bristol NHS Walk-in Centre and the Avon, Gloucester and Wiltshire NHS Direct Call Centre have agreed to collaborate with us in this study.

4. Research Governance

4a) *Ethical issues*

Ethical approval for the study will be sought using the DoH guidelines according to the Central Office for Research Ethics Committees (COREC) from the Southmead LREC, Bristol. As pre-school children are vulnerable and too young to give informed consent, all parents/carers will be asked to provide written informed consent, though with care not to inadvertently induce participation, for example through the supply of free medicines and thermometer.

While we believe that the research question that has been posed by the HTA presents a situation of true clinical equipoise and the risk of harm to participants is no higher than non-participants, the safety of participating children remains paramount. Emergency care for any child experiencing a febrile convulsion will be managed in the usual manner, and we will ask the independent Data Monitoring and Ethics Committee (DMEC) to examine closely such events to see if the trial was in any way responsible. In the management of children with fever, the clinician should be satisfied that a cause for the fever has been established and that serious causes have been ruled out. We do not propose to interfere with the diagnostic or management process and propose only to recruit children deemed safe to be managed at home. If the child's general condition causes concern, or the fever continues to rise despite the use of study medicines and other cooling methods, parents will be advised to contact their GP in the usual manner. Under these circumstances, responsible clinicians will have 24-hour access (via first the randomisation centre and as a second back-up, an on-call pharmacist) to break the study code and full clinical freedom to manage the child. As we are recruiting children with fever, we do not wish to substantially delay treatment (time between recruitment and treatment will be monitored). Therefore, since the time between learning about the trial and giving consent is relatively short, parents will be explicitly told that they will be free to withdraw their consent and stop taking part in the trial at any time without having to give a reason. We will display posters in all participating centres providing detailed information about the trial, possible benefits and known risks of the intervention(s), giving parents an opportunity to learn about the study before they are approached. Parents of eligible children will be given an information sheet with details about the trial while waiting to see the doctor or nurse to provide a background for further questions.

Both paracetamol and ibuprofen are available without prescription at any pharmacy and can be used safely unless contraindications exist, for which study children will be screened. All children taking part in the trial will receive at least one active preparation, paracetamol, ibuprofen or both. Manufacture, safety monitoring of patients, reporting and recording adverse reactions and events will comply with the European Union Directive 2001/20/EC. We do not believe the trial will contravene guidance on the clinical investigation of medicinal products in the paediatric

population (CPMP/ICH/2711/99). Patient data will be anonymised and stored for 10 years in a secure place according to the Data Protection Act 1998.

We will aim to recruit nurses with paediatric experience to assist trial recruitment. Thus, there will be the additional security for children in the trial that those with serious illness are more likely to be recognised earlier. All trial staff with direct contact with children will have the appropriate honorary NHS contracts, will be CRB checked and trained in the implications of the Children's Act (1989). In the unlikely event that child welfare concerns are identified, these will be discussed with the responsible clinician.

4b) *Management and supervision of trial*

The day-to-day running of the trial will be the responsibility of the trial coordinator, with the guidance and support from the applicants. It is envisaged that the trial coordinator will meet formally with the main applicants (AH, AM, TP and MF) in a Trial Management Group (TMG) at least weekly in the early stages of the trial, and regularly as required thereafter, with additional informal individual contact as necessary. In addition, the trial coordinator will maintain regular contact with the applicants and, once they are in post, with the research nurses. As well as these arrangements, there will be regular, formal meetings throughout the period of the study. This Trial Advisory Group (TAG) will comprise all applicants, the trial coordinator and, when appropriate, the research nurses. For the first six months the TAG will meet monthly, with variable frequency subsequent to this as deemed helpful for the coordination of the trial. Throughout the conduct of the trial, the trial coordinator will hold regular meetings with the research nurses in order to review progress and maintain trial procedures.

In terms of independent supervision of the trial, a Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC) have been constituted. Professor Ann Louise Kinmonth will chair the TSC, with independent members Professors Chris Butler (Cardiff) and Janet Peacock (Brunel) and a consumer representative (tba) in addition to the main applicants and the trial coordinator. Other applicants will attend TSC meetings as and when required. Although the interventions are licensed medicines, the trial will recruit children, a vulnerable group, and with underlying conditions that could lead to serious adverse events, for example, febrile convulsions. We therefore propose a DMEC to monitor trial safety (serious adverse events), the sample size assumptions and new and emerging evidence. We do not think a formal interim analysis will be required. Dr Bragonier, an NHS Consultant General Paediatrician in North Bristol with no formal links to the University of Bristol, will chair the DMEC. Dr Montgomery will be the trial statistician on the DMEC and the independent statistician will be Dr Sally Kerry (St George's Hospital Medical School). A third independent member, ideally an experienced paediatric nurse is being identified. The role and function of these Committees will be in accordance with MRC guidelines and will meet between three and six times. We will invite representation from the NCCHTA and, if desired, from the Commissioning Board.

4c) *Quality control and quality assurance*

There will be documented managerial lines of responsibility; specifically the recruitment nurses will be responsible for accurate data collection and data entry. They will be accountable to the trial coordinator, who in turn will be accountable to the lead applicant and the TMG.

4d) *Data handling and record keeping*

Most data will be first written and then entered onto a secure MS Access database using validation data entry rules. The qualitative interviews will be tape recorded and then anonymously transcribed. Data from the thermometry loggers will be uploaded directly onto ASCII files. All data in-house will have a unique study number. Only the study number goes onto the database, which will be password protected. Information relating number and personal data are stored separately in a locked cabinet. All data will be analysed and reported in summary format. No individual will be identifiable. Data analysis will take place at the Division of Primary Health Care, University of Bristol by members of the trial team under the guidance of Dr Alan Montgomery and Professor Tim Peters. The lead applicant will control and act as custodian for the data with advice from Ms Carolyn Picton, Departmental Administrator and Data Protection Officer. Regular back up copies will be made. Only immediate members of the study team will have access to the data generated by the study. As per the EU directive, data will be stored for 10 years.

4e) *Financial and insurance matters*

The University of Bristol will be responsible for and administer the financial aspects of the grant. Clinical trials insurance is being purchased to cover the University for the aspects of this trial not covered by its standard indemnity arrangements. In addition, the trial applicants and research staff employed on the study will hold honorary contracts with the appropriate Primary Care Trusts and the United Bristol Healthcare Trust, conferring the protection of the NHS clinical negligence arrangements for staff.

4f) *Publication and dissemination policy*

In addition to the required final report and monograph for the HTA Programme, we will publish the main trial results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of our collaborators we will disseminate the study findings to a wide NHS and general audience. This will include presentations at meetings and written executive summaries for key stakeholder groups such as Primary Care Trusts, Walk-in Centres, Out of Hours Centres, NHS Direct, health visitor groups, general practices and service users.

4g) *Adverse events (AEs) and Serious adverse events (SAEs)*

At each patient visit adverse event data will be collected from (a) spontaneous reporting by the parent (b) spontaneous reporting by a clinician or (c) in response to open questioning such as the following: 'how has your child been? Has your child had any health/medical problems since the last visit?'

Serious adverse events as defined below:

- Results in death
- Is immediately life-threatening
- Requires in patient hospitalisation
- Results in persistent or significant disability or incapacity

These will be reported to the study team whether deemed causally related to study medication or not.
A causality assessment will be made and all SAEs discussed with the DMSC. The trial team will ensure that any SAEs that are deemed to be SUSARs (Suspected Unexpected Serious Adverse Reactions) are reported to the regulatory authority and ethics committee promptly but no later than the timelines set by the EU Clinical Trials Directive and The Medicines for Human Use (Clinical Trials) Regulations 2004, as follows:

- For fatal or life threatening SUSARS:
  not later than **7 days** after the trial team received information that the case fulfilled the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.
- For all other SUSARs:
  not later than **15 days** after the trial team received information that the case fulfilled the criteria for a SUSAR.

All serious adverse reactions (expected and unexpected) will be reported to the MHRA and the ethics committee annually.

Expected adverse events

These will be collated and presented to the DMSC on an annual basis. There are three categories of AEs. Those associated with the child's underlying condition, those related to the conduct of the trial and those related to the trial medicines.

- Associated with the child's underlying condition causing the fever:

While fever is a normal part of pre-school life,[62] there are a number of rare, but potentially life threatening causes of fever which, given our sample size, some children in the trial may experience. Previous data suggest we should expect around 2% of our sample to be hospitalised.[63] Recent data from a study of 3066 infants aged 3 months or younger with temperatures of at least 38 ºC initially treated by office-based paediatricians (i.e. children in whom we should expect higher rates of serious disease)[64] suggest disease rates of bacteraemia and bacterial meningitis were 1.8% (2.4% of those tested) and 0.5% respectively. Well-appearing infants aged 25 days or older with fever of less than 38.6 ºC had a rate of 0.4% for bacteraemia/bacterial meningitis. Other reasons for hospital admission are likely to include urinary tract infection, otitis media, upper and lower respiratory tract infections, pneumonia, bronchiolitis, asthma and gastroenteritis.

- Trial conduct:

The trial will be conducted in a manner to avoid the occurrence of a febrile convulsion due to delay in trial medicine administration. Fortunately, for any given febrile episode, they are rare occurrences and do not usually result in permanent neurological sequelae.[65] The cumulative incidence has been estimated at 2% in the first five years of life[65] and 4% in childhood.[7] Predicting occurrence is difficult, but they are more likely to occur in children with previous febrile seizures[7] (up to one third may experience a second seizure within two years)[66] and those with underlying neurological disease (the latter is an exclusion criterion). Given these facts, we would regard the occurrence of a febrile seizure within the trial as a 'predicted SAE', though we will examine the circumstances of all such seizures to ensure trial procedure (e.g. significant delay in administering trial medicines) were not implicated. We will ensure all trial staff in contact with children have appropriate training in the immediate management of febrile convulsions.

- Associated with the intervention medicines:

Remembering that the study medicines are widely available for over-the-counter purchase and that, in general, side effects are rare, the BNF comprehensively lists the side effects that can be anticipated for paracetamol and ibuprofen.[46] For paracetamol: rashes, blood disorders; following overdosage, liver damage (and less frequently renal

damage), for ibuprofen: gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration occur. Other side-effects include hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm), headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, hearing disturbances such as tinnitus, photosensitivity, and haematuria. Blood disorders have also occurred. Fluid retention may occur and blood pressure may be raised. Rarely, papillary necrosis or interstitial fibrosis associated with NSAIDs may lead to renal failure. Hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, eye changes, Stevens-Johnson syndrome and toxic epidermal necrolysis are other rare side-effects. Induction of or exacerbation of colitis has been reported. Aseptic meningitis has been reported rarely with NSAIDs; patients with connective tissue disorders such as systemic lupus erythematosus may be especially susceptible. Since we are excluding children with these conditions from trial participation, should they occur, we would regard these as expected adverse events.

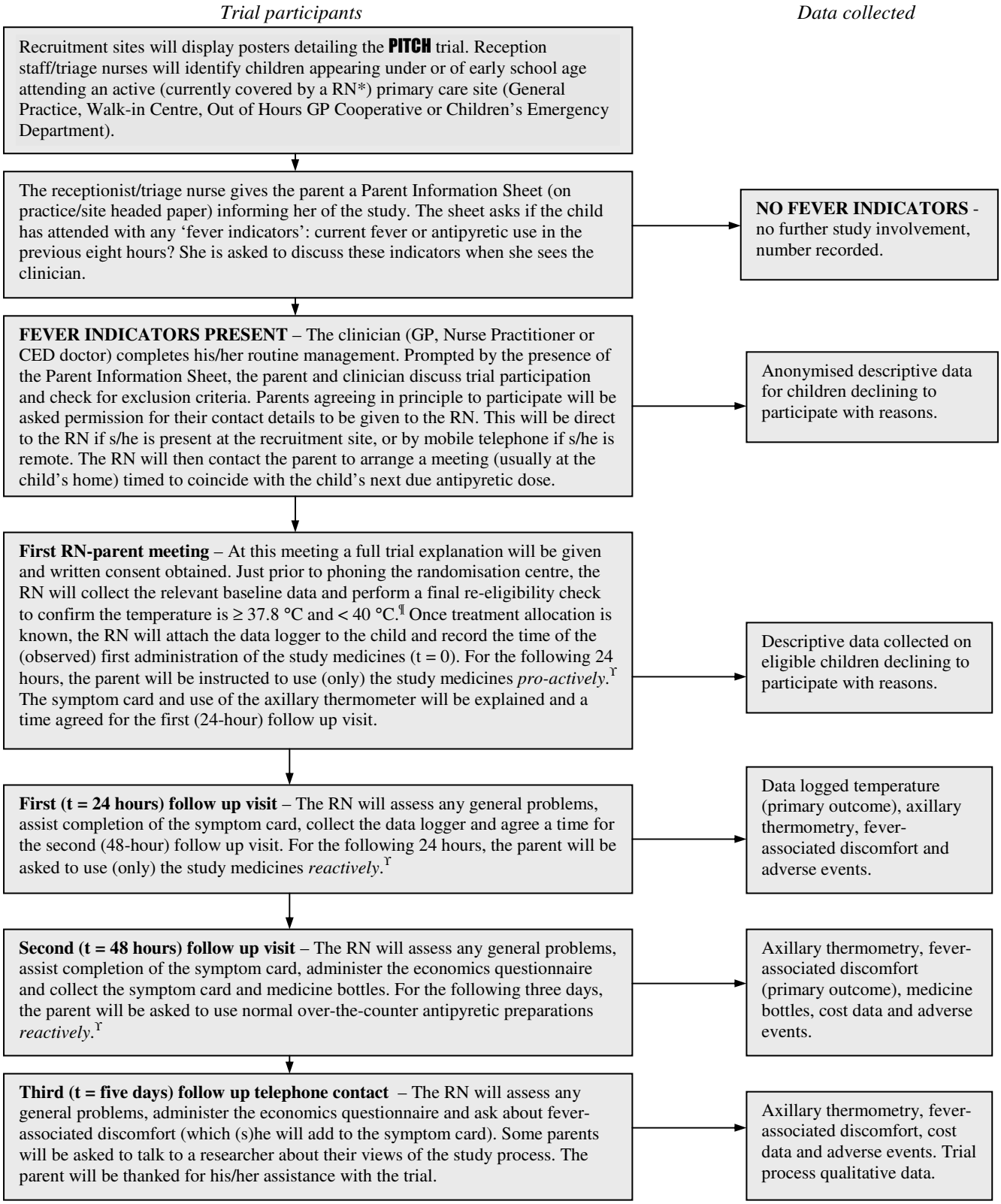
4h) *Definition of end of trial*

Trial recruitment will end when the stated sample size has been achieved or at the request of the TSC following advice from the DMEC.

4i) *Protocol amendments*

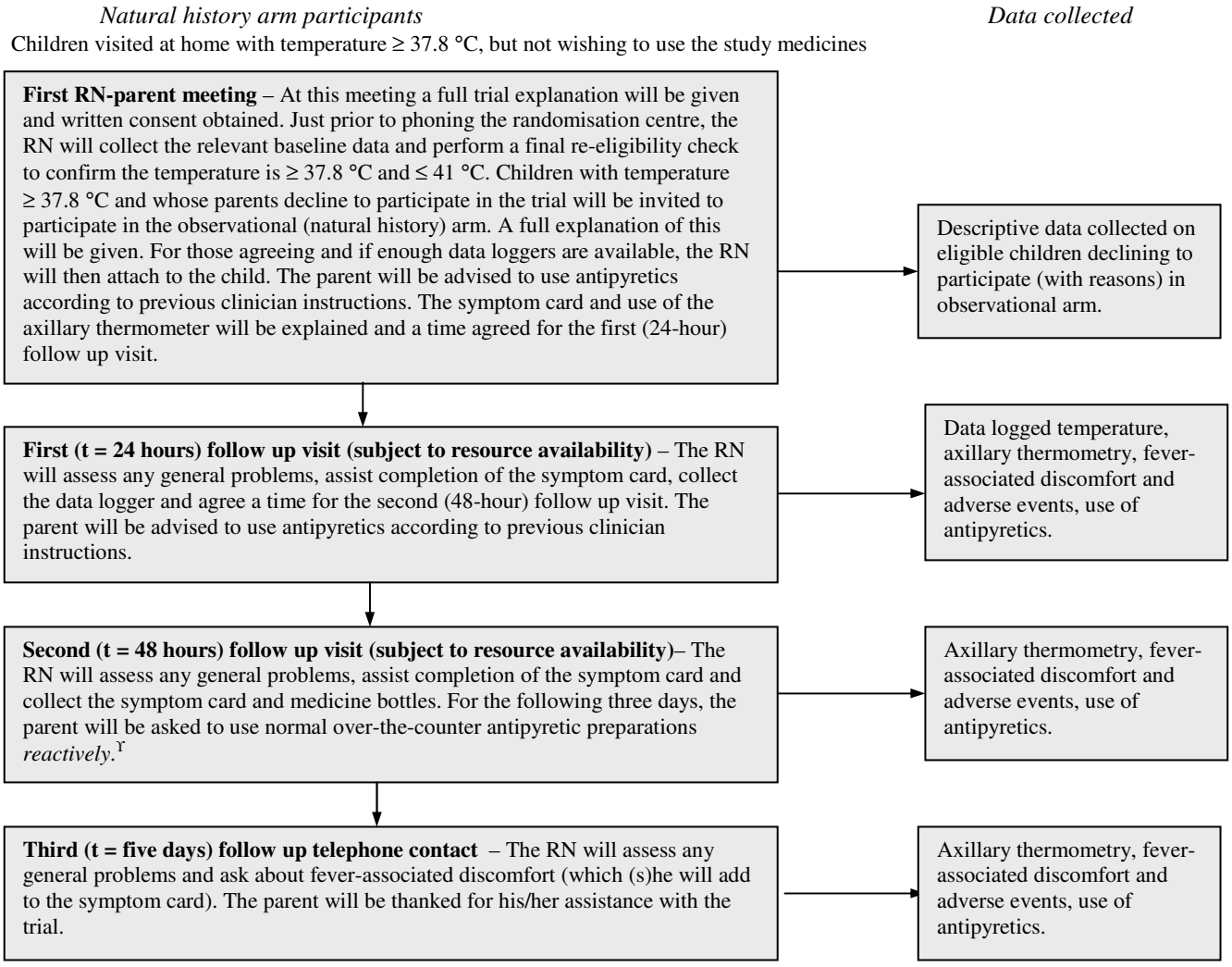
We will notify the MRHA, ethics committee and research sponsor of any substantial protocol amendments, for example, changes to the eligibility criteria, the investigational medicinal product (IMP), the trial coordinator or lead applicant.

Figure 1 showing the proposed recruitment, data collection and progression of participants through the trial



* RN = Research Nurse covering a group of recruitment sites in close proximity and so able to travel to meet a child.
ϒ See section 3d for full explanation.
¶ See Figure 2 (page 17) for flow diagram describing natural history arm. At the first RN-parents meeting, those not wishing to use the study medicines will be invited to participate in the non-interventional natural history arm.

Figure 2 showing the proposed recruitment, data collection and progression of participants in the natural history arm.



8. Reference List

(1) Hay AD, Heron J, Ness A, the ALSPAC study team. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. Fam Pract 2005; 22(4):367-374.

(2) Kai J. What worries parents when their preschool children are acutely ill, and why: a qualitative study. BMJ 1996; 313(7063):983-986.

(3) Blumenthal I. What parents think of fever. Fam Pract 1998; 15(6):513-518.

(4) Impicciatore P, Nannini S, Pandolfini C, Bonati M. Mother's knowledge of, attitudes toward, and management of fever in preschool children in Italy. Prev Med 1998; 27(2):268-273.

(5) Munro J, Nicholl J, O'Cathain A, Knowles E. Impact of NHS direct on demand for immediate care: observational study. BMJ 2000; 321(7254):150-153.

(6) Salisbury C, Chalder M, Scott TM, Pope C, Moore L. What is the role of walk-in centres in the NHS? BMJ 2002; 324(7334):399-402.

(7) Management of childhood fever. Lancet 1991; 338(8774):1049-1050.

(8) Monto AS, Cavallaro JJ. The Tecumseh study of respiratory illness. II. Patterns of occurrence of infection with respiratory pathogens, 1965-1969. Am J Epidemiol 1971; 94(3):280-289.

(9) Ayres JG. Seasonal pattern of acute bronchitis in general practice in the United Kingdom 1976-83. Thorax 1986; 41(2):106-110.

(10) National Assembly for Wales.
Headline Statistics Wales. National Assembly for Wales [2003 [cited 2003 Nov. 13]; Available from: URL:http://www.wales.gov.uk/keypubstatisticsforwales/content/publication/health/2003/sdr33-2003/sdr33-2003-chems-g-o.xls

(11) National Assembly for Wales.
Headline Statistics Wales. National Assembly for Wales [2003 [cited 2003 Nov. 13]; Available from: URL:http://www.wales.gov.uk/keypubstatisticsforwales/content/publication/health/2003/sdr33-2003/sdr33-2003-chems-g-o.xls

(12) El-Radhi S, Carroll J. Fever in Paediatric Practice. Oxford: Blackwell Science; 1994.

(13) Morley CJ, Hewson PH, Thornton AJ, Cole TJ. Axillary and rectal temperature measurements in infants. Arch Dis Child 1992; 67(1):122-125.

(14) Impicciatore P, Pandolfini C, Casella N, Bonati M. Reliability of health information for the public on the world wide web: systematic survey of advice on managing fever in children at home. BMJ 1997; 314(7098):1875.

(15) Kai J. Parents' perceptions of taking babies' rectal temperature. BMJ 1993; 307(6905):660-662.

(16) Hay AD, Peters TJ, Wilson AD, Fahey T. The use of infrared thermometry for the detection of fever. Br J Gen Pract 2004; 54:448-450.

(17) Sarrell M, Cohen HA, Kahan E. Physicians', nurses', and parents' attitudes to and knowledge about fever in early childhood. Patient Education & Counseling 2002; 46(1):61-65.

(18) Kluger MJ. Fever revisited. [Review] [63 refs]. Pediatrics 1992; 90(6):846-850.

(19) Dinarello CA, Wolff SM. The Role of Interleukin-1 in Disease. N Engl J Med 1993; 328(2):106-113.

(20) Kluger MJ. Fever revisited. [Review] [63 refs]. Pediatrics 1992; 90(6):846-850.

(21) Kramer MS, Naimark LE, Roberts-Brauer R, McDougall A, Leduc DG. Risks and benefits of paracetamol antipyresis in young children with fever of presumed viral origin. Lancet 1991; 337(8741):591-594.

(22) Kai J. Parents' difficulties and information needs in coping with acute illness in preschool children: a qualitative study. BMJ 1996; 313(7063):987-990.

(23) Rylance GW, Woods CG, Cullen RE, Rylance ME. Use of drugs by children. BMJ 1988; 297(6646):445-447.

(24) Havinga W. Time to counter 'fever phobia'. Br J Gen Pract 2003; 53:253.

(25) National Assembly for Wales.
Headline Statistics Wales. National Assembly for Wales [2003 [cited 2003 Nov. 13]; Available from: URL:http://www.wales.gov.uk/keypubstatisticsforwales/content/publication/health/2003/sdr33-2003/sdr33-2003-chems-g-o.xls

(26) Mackowiak PA, Plaisance KI. Benefits and risks of antipyretic therapy. [Review] [52 refs]. Annals of the New York Academy of Sciences 1998; 856:214-223.

(27) Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. [Review] [96 refs]. American Journal of Medicine 2001; 111(4):304-315.

(28) Lal A, Gomber S, Talukdar B. Antipyretic effects of nimesulide, paracetamol and ibuprofen- paracetamol. Indian J Pediatr 2000; 67(12):865-870.

(29) Perrott DA, Piira T, Goodenough B, Champion GD. Efficacy and Safety of Acetaminophen vs Ibuprofen for Treating Children's Pain or Fever: A Meta-analysis. Arch Pediatr Adolesc Med 2004; 158(6):521-526.

(30) Kelley MT, Walson PD, Edge JH, Cox S, Mortensen ME. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. Clin Pharmacol Ther 1992; 52(2):181-189.

(31) Meremkwu M, Oyo-Ita A. Paracetamol for treating fever in children (Cochrane Review). Cochrane Library, Issue 1, 2003: Update Software 2003.

(32) Autret E, Reboul-Marty J, Henry-Launois B, Laborde C, Courcier S, Goehrs JM et al. Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever. Eur J Clin Pharmacol 1997; 51(5):367-371.

(33) McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. Arch Dis Child 1996; 74(2):164.

(34) Kinmonth AL, Fulton Y, Campbell MJ. Management of feverish children at home. BMJ 1992; 305(6862):1134-1136.

(35) Moore L, Campbell R, Whelan A, Mills N, Lupton P, Misselbrook E et al. Self help smoking cessation in pregnancy: cluster randomised controlled trial. BMJ 2002; 325(7377):1383.

(36) Koops L, Lindley RI. Thrombolysis for acute ischaemic stroke: consumer involvement in design of new randomised controlled trial. BMJ 2002; 325(7361):415.

(37) Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters T et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study * Commentary: presenting unbiased information to patients can be difficult. BMJ 2002; 325(7367):766-770.

(38) Glogowska M, Roulstone S, Enderby P, Peters TJ, Campbell R. Who's afraid of the randomised controlled trial? Parents' views of an SLT research study. Int J Lang Commun Disorder 2001; 36(suppl):499-504.

(39) Britten N. Patients' ideas about medicines: a qualitative study in a general practice population. Br J Gen Pract 1994; 44(387):465-468.

(40) Britten N, Stevenson FA, Barry CA, Barber N, Bradley CP. Misunderstandings in prescribing decisions in general practice: qualitative study. BMJ 2000; 320(7233):484-488.

(41) Royal Pharmaceutical Society. From compliance to concordance. Achieving shared goals in medicine taking. 1997. **London**, Royal Pharmaceutical Society of Great Britain.
Ref Type: Report

(42) Department of Health. The Children's National Service Framework. London [2003 [cited 3 A.D. Jan. 7]; Available from: URL:http://www.doh.gov.uk/nsf/children.htm

(43) Munro J, Nicholl J, O'Cathain A, Knowles E. Evaluation of NHS Direct first wave sites (second interim report to the Department of Health). 2000.
Ref Type: Report

(44) Hay AD, Wilson AD, Fahey T, Peters TJ. The natural history of cough in pre-school children: a prospective cohort study. Fam Pract 2003; 20:696-705.

(45) Morley C, Murray M, Whybrew K. The relative accuracy of mercury, Tempa-DOT and FeverScan thermometers. Early Hum Dev 1998; 53(2):171-178.

(46) British National Formulary. 44 ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2004.

(47) Moghal NE, Hegde S, Eastham KM. Ibuprofen and acute renal failure in a toddler. Arch Dis Child 2004; 89(3):276-277.

(48) Walson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. Clin Pharmacol Ther 1989; 46(1):9-17.

(49) Wilson JT, Brown RD, Kearns GL, Eichler VF, Johnson VA, Bertrand KM et al. Single-dose, placebo-controlled comparative study of ibuprofen and acetaminophen antipyresis in children. J Pediatr 1991; 119(5):803-811.

(50) Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group. Medicines for Children. 2 ed. London: British Paediatric Association; 2003.

(51) Purssell E. Physical treatment of fever. Arch Dis Child 2000; 82(3):238.

(52) Meremikwu M, Oyo-Ita A. Physical methods for treating fever in children. [Review] [38 refs]. Cochrane Database of Systematic Reviews 2003;(2):CD004264.

(53) Lesko SM, Mitchell AA. Renal function after short-term ibuprofen use in infants and children. Pediatrics 1997; 100(6):954-957.

(54) Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner- based randomized clinical trial. JAMA 1995; 273(12):929-933.

(55) Del Vecchio MT, Eric R, Jonathan B, Mayoral CE, Rosenfeld W, Marino RV et al. Alternating Antipyretics: Is This an Alternative? Pediatrics 2001; 108(5):1236-1237.

(56) Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children.[see comment]. Pediatrics 2002; 109(2):E20.

(57) Robieux I, Kumar R, Radhakrishnan S, Koren G. Assessing pain and analgesia with a lidocaine-prilocaine emulsion in infants and toddlers during venipuncture. J Pediatr 1991; 118(6):971-973.

(58) Royal College of Nursing. The recognition and assessment of acute pain in children. National Electronic Library for Health [2003 Available from:
URL:http://www.nelh.nhs.uk/guidelinesdb/html/front/AcutePainInChildren.html

(59) Zar J. Biostatistical analysis. 2 ed. Englewood Cliffs, New Jersey: Prentice-Hall; 1994.

(60) Moher D, Schulz KF, Altman DG, Lepage L. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 2001; 357(9263):1191-1194.

(61) Green J. Commentary: Grounded theory and the constant comparative method. BMJ 1998; 316:1060.

(62) Hay AD, Heron J, Ness A. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. Fam Pract 2004; (in press).

(63) Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. Br J Gen Pract 2002; 52:401-409.

(64) Pantell RH, Newman TB, Bernzweig J, Bergman DA, Takayama JI, Segal M et al. Management and Outcomes of Care of Fever in Early Infancy. JAMA: The Journal of the American Medical Association 2004; 291(10):1203-1212.

(65) Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. II-- Medical history and intellectual ability at 5 years of age. BMJ 1985; 290(6478):1311-1315.

(66) van Stuijvenberg M, Derksen-Lubsen G, Steyerberg EW, Habbema JD, Moll HA. Randomized, controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile seizure recurrences. Pediatrics 1998; 102(5):E51.