Health Technology Assessment 2009; Vol. 13: No. 27

Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial

AD Hay, NM Redmond, C Costelloe,
AA Montgomery, M Fletcher,
S Hollinghurst and TJ Peters

May 2009
DOI: 10.3310/hta13270

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

How to obtain copies of this and other HTA programme reports
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to Direct Mail Works Ltd and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. HTA on CD is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial

AD Hay[1*], NM Redmond[1], C Costelloe, AA Montgomery[1], M Fletcher[2], S Hollinghurst[1] and TJ Peters[1]

[1]Academic Unit of Primary Health Care, NIHR National School for Primary Care Research, Department of Community Based Medicine, University of Bristol, Bristol, UK
[2]Faculty of Health and Social Care, University of the West of England, Bristol, UK

*Corresponding author

Declared competing interests of authors: none

Published May 2009
DOI:10.3310/hta13270

This report should be referenced as follows:

Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S et al. Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial. Health Technol Assess 2009; **13**(27).

Health Technology Assessment is indexed and abstracted in Index Medicus/MEDLINE, Excerpta Medica/EMBASE, Science Citation Expanded (SciSearch®) and Current Contents®/Clinical Medicine.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series Health Technology Assessment.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in Health Technology Assessment are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 03/09/01. The contractual start date was in December 2004. The draft report began editorial review in January 2008 and was accepted for publication in November 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.

Abstract

Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial

AD Hay[1*], NM Redmond[1], C Costelloe, AA Montgomery[1], M Fletcher[2], S Hollinghurst[1] and TJ Peters[1]

[1]Academic Unit of Primary Health Care, NIHR National School for Primary Care Research, Department of Community Based Medicine, University of Bristol, Bristol, UK
[2]Faculty of Health and Social Care, University of the West of England, Bristol, UK

*Corresponding author.

Objectives: To establish the relative clinical effectiveness and cost-effectiveness of paracetamol plus ibuprofen compared with paracetamol and ibuprofen separately for time without fever, and the relief of fever-associated discomfort in young children who can be managed at home.

Design: The trial design was a single-centre (multisite), individually randomised, blinded, three-arm trial comparing paracetamol and ibuprofen together with paracetamol or ibuprofen separately.

Setting: There were three recruitment settings, as follows: 'local' where research nurses were recruited from NHS primary care sites; 'remote' where NHS sites notified the study of potentially eligible children; and 'community' where parents contacted the study in response to local media advertisements.

Participants: Children aged between 6 months and 6 years with fever ≥37.8°C and ≤41°C due to an illness that could be managed at home.

Interventions: The intervention was the provision of, and advice to give, the medicines for up to 48 hours: paracetamol every 4–6 hours (maximum of four doses in 24 hours) and ibuprofen every 6–8 hours (maximum of three doses in 24 hours). Every parent received two bottles, with at least one containing an active medicine. Parents, research nurses and investigators were blinded to treatment allocation by the use of identically matched placebo medicines. The dose of medicine was determined by the child's weight: paracetamol 15 mg/kg and ibuprofen 10 mg/kg per dose.

Results: For additional time without fever in the first 4 hours, use of both medicines was superior to use of paracetamol alone [adjusted difference 55 minutes, 95% confidence interval (CI) 33 to 77 minutes; $p < 0.001$] and may have been as good as ibuprofen (adjusted difference 16 minutes, 95% CI –6 to 39 minutes; $p = 0.2$). Both medicines together cleared the fever 23 minutes (95% CI 2–45 minutes; $p = 0.015$) faster than paracetamol alone, but no faster than ibuprofen alone (adjusted difference –3 minutes, 95% CI 24–18 minutes; $p = 0.8$). For additional time without fever in the first 24 hours, both medicines were superior to paracetamol (adjusted difference 4.4 hours, 95% CI 2.4–6.3 hours; $p < 0.001$) or ibuprofen (adjusted difference 2.5 hours, 95% CI 0.6–4.5 hours; $p = 0.008$) alone. No reduction in discomfort or other fever-associated symptoms was found, although power was low for these outcomes. An exploratory analysis showed that children with higher discomfort levels had higher mean temperatures. No difference in adverse effects was observed between treatment groups. The recommended maximum number of doses of paracetamol and ibuprofen in 24 hours was exceeded in 8% and 11% of children respectively. Over the 5-day study period, paracetamol and ibuprofen together was the cheapest option for the NHS due to the lower use of health-care services: £14 [standard deviation (SD) £23] versus £20 (SD £38) for paracetamol and £18 (SD £40) for ibuprofen. Both medicines were also cheapest for parents because the lower use of health care services resulted in personal saving on travel costs and less time off work: £24 (SD £46) versus £26 (SD £63) for paracetamol and £30 (SD £91) for ibuprofen. This more than compensated for the extra cost of medication. However, statistical evidence for these differences was weak due to lack of power. Overall, a quarter of children were 'back to normal' by 48 hours and one-third by day 5. Five (3%) children were admitted to hospital, two with pneumonia, two with bronchiolitis and one with a severe, but unidentified 'viral illness'.

Conclusions: Young children who are unwell with fever should be treated with ibuprofen first, but the relative risks (inadvertently exceeding the maximum recommended dose) and benefits (extra 2.5 hours without fever) of using paracetamol plus ibuprofen over 24 hours should be considered. However, if two medicines are used, it is recommended that all dose times are carefully recorded to avoid accidentally exceeding the maximum recommended dose. Manufacturers should consider supplying blank charts for this purpose. Use of both medicines should not be discouraged on the basis of cost to either parents or the NHS. Parents and clinicians should be aware that fever is a relatively short-lived symptom, but may have more serious prognostic implications than the other common symptom presentations of childhood.
Trial registration: Current Controlled Trials ISRCTN 26362730.

Contents

List of abbreviations

BNFC	British National Formulary for Children
CI	confidence interval
COX	cyclo-oxygenase
CRF	case report form
DMSC	Data Monitoring and Safety Committee
EMIS	Egton Medical Information Systems
GP	general practitioner
ICER	incremental cost-effectiveness analysis
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
OTC	over-the-counter (medicine)
PG	prostaglandin
PDA	personal digital assistant
PIS	patient information sheet
SAE	serious adverse event
SAR	serious adverse reaction
SD	standard deviation
SOP	standard operating procedure
SUSAR	serious unexpected suspected adverse reaction
TSC	Trial Steering Committee
UBHT	United Bristol Hospitals Trust
WIC	walk-in centre

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Paracetamol and ibuprofen are increasingly used together for fever, despite a lack of evidence regarding their clinical effectiveness or cost-effectiveness.

Objectives

1. To establish the relative clinical effectiveness of both medicines compared with paracetamol and ibuprofen separately for time without fever in young children who can be managed at home.
2. To assess the relative clinical effectiveness of both medicines with paracetamol and ibuprofen separately for the relief of fever-associated discomfort.
3. To use qualitative methods to optimise the overall trial process and explore parents' and clinicians' beliefs about the use, effectiveness and side effects of paracetamol and ibuprofen.
4. To perform an economic evaluation from the perspectives of the NHS and parents comparing the cost and benefits of each treatment.
5. To describe the natural history of fever.

Design

The trial design was a single-centre (multisite), individually randomised, blinded, three-arm trial comparing paracetamol and ibuprofen together with paracetamol or ibuprofen separately.

Setting

There were three recruitment settings, as follows: 'local' where research nurses were recruited from NHS primary care sites; 'remote' where NHS sites notified the study of potentially eligible children; and 'community' where parents contacted the study in response to local media advertisements.

Participants

We recruited children aged between 6 months and 6 years with fever ≥37.8°C and ≤41°C due to an illness that could be managed at home. Children were excluded if they required hospital admission; were clinically dehydrated; had recently participated in another trial; had previously participated in PITCH; had a known trial medicine intolerance, allergy or contraindication; if they had a chronic neurological disease; and/or if their parents could not read or write English.

Interventions

The intervention was the provision of, and advice to give, the medicines for up to 48 hours: paracetamol every 4–6 hours (maximum of four doses in 24 hours) and ibuprofen every 6–8 hours (maximum of three doses in 24 hours). Every parent received two bottles, with at least one containing an active medicine. Parents, research nurses and investigators were blinded to treatment allocation by the use of identically matched placebo medicines. The dose of medicine was determined by the child's weight: paracetamol 15 mg/kg and ibuprofen 10 mg/kg per dose.

Main outcome measures

Primary outcome measures were time without fever in the first 4 hours and fever-associated discomfort at 48 hours, measured using continuous axillary thermometry and a symptom diary respectively. Secondary outcomes were fever clearance (time to first apyrexial); time without fever during the first 24 hours; other fever-associated symptoms (appetite, activity and sleep), digital axillary temperature and adverse effects at 24 hours, 48 hours and day 5. Directs costs to the NHS and parents were estimated at 48 hours and day 5; we assumed that parents had bought the study medicines over the counter.

Research findings

For additional time without fever in the first 4 hours, use of both medicines was superior to use of paracetamol alone [adjusted difference 55 minutes, 95% confidence interval (CI) 33 to 77 minutes; $p < 0.001$] and may have been as good as ibuprofen (adjusted difference 16 minutes, 95% CI –6 to 39 minutes; $p = 0.2$). Both medicines together cleared the fever 23 minutes (95% CI 2–45 minutes; $p = 0.015$) faster than paracetamol alone but no faster than ibuprofen alone (adjusted difference –3 minutes, 95% CI 24–18 minutes; $p = 0.8$). For additional time without fever in the first 24 hours, both medicines were superior to paracetamol (adjusted difference 4.4 hours, 95% CI 2.4–6.3 hours; $p < 0.001$) or ibuprofen (adjusted difference 2.5 hours, 95% CI 0.6–4.5 hours; $p = 0.008$) alone. No reduction in discomfort or other fever-associated symptoms was found, although power was low for these outcomes. An exploratory analysis showed that children with higher discomfort levels had higher mean temperatures. No difference in adverse effects was observed between treatment groups. The recommended maximum number of doses of paracetamol and ibuprofen in 24 hours was exceeded in 8% and 11% of children respectively.

Over the 5-day study period, paracetamol and ibuprofen together was the cheapest option for the NHS due to the lower use of health-care services: £14 [standard deviation (SD) £23] versus £20 (SD £38) for paracetamol and £18 (SD £40) for ibuprofen. Both medicines were also cheapest for parents because the lower use of health care services resulted in personal saving on travel costs and less time off work: £24 (SD £46) versus £26 (SD £63) for paracetamol and £30 (SD £91) for ibuprofen. This more than compensated for the extra cost of medication. However, statistical evidence for these differences was weak due to lack of power.

Overall, a quarter of children were 'back to normal' by 48 hours and one-third by day 5. After randomisation, five (3%) children were admitted to hospital, two with pneumonia, two with bronchiolitis and one with a severe, but unidentified 'viral illness'.

Conclusions

Implications for health care

Doctors, nurses and parents who want to use medicines to treat young children who are unwell with fever should be advised to use ibuprofen first and to consider the relative risks (inadvertently exceeding the maximum recommended dose) and benefits (extra 2.5 hours without fever) of using paracetamol plus ibuprofen over 24 hours. Pragmatically, we speculate that if a child remains unwell after a first dose of ibuprofen, subsequent use of both medicines will be more effective than either monotherapy. However, if two medicines are used, we recommend that all dose times are carefully recorded to avoid accidentally exceeding the maximum recommended dose. Manufacturers should consider supplying blank charts for this purpose. The economic analysis shows that the use of both medicines should not be discouraged on the basis of cost to either parents or the NHS. Parents and clinicians should be aware that fever is a relatively short-lived symptom, but may have more serious prognostic implications than the other common symptom presentations of childhood.

Recommendations for research (in order of priority)

1. Is a parent education programme that includes information regarding the accurate dosing (by weight) of antipyretics cost effective in improving parents' ability to care for children in the home?

2. Children's infections are the single largest contributor to NHS workload. Improving parents' confidence to care for children in the home, dose medicines accurately and to know when to seek medical help could have major benefits for the NHS.

3. The evidence base for the general components of an effective behavioural change intervention is well established. Previous parent interventions providing written information only regarding the management of common illnesses demonstrated little change in their use of health services. The PITCH study suggested that the 'dose by weight' use of combined antipyretic medicines might be cost effective, due to reductions in the use of primary care services when compared with the use of single medicines.

Trial registration

This trial is registered as ISRCTN 26362730.

Chapter 1
Introduction

Fever in children

Scale of the problem

Fever causes misery for children, parental anxiety and expense to the NHS. It affects 70% of all pre-school children each year[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 a child becomes febrile, one in five parents contact the health service[4] and that, overall, 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.[10] Add to this the cost of consultations and reconsultations, it is clear that the burden to the NHS of fever in pre-school children is considerable. The cost to the NHS of antipyretic 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.

Normal thermoregulation

Temperature is regulated by the anterior hypothalamus around 'set points'. These normally follow a circadian rhythm between 36.4°C in the morning and 36.9°C in the afternoon.[11] The hypothalamic neurones integrate afferent messages regarding core and skin temperatures and stimulate behavioural and physiological responses, such as seeking a warmer environment, shivering and cutaneous vasoconstriction, to control heat production and loss.

The fever response to infection

The vast majority of febrile episodes in children are in response to viral or bacterial infection. Microbial tissue invasion triggers an inflammatory response and the activation of endothelial cells and leucocytes.[11] The activated leucocytes release pyrogenic cytokines such as interleukin 1β, tumour necrosis factor, interferon and prostaglandins.[12] Carried via the bloodstream, these pyrogens stimulate the endothelial production of prostaglandin E_2 (PGE_2) in the hypothalamus. In response, the hypothalamus elevates the thermoregulatory set point, the new raised temperature being achieved through the combined physiological actions of enhanced heat production (such as shivering) and reduced heat loss (such as peripheral vasoconstriction). The hypothalamus continues to coordinate the physiological response to maintain the new, raised, temperature 'set point'.[11]

Defining fever

There is no universally agreed definition of normal body temperature or fever in children, or on how best to measure temperature, in the literature.[13] This is because normal body temperature varies with time, the anatomical site at which it is measured and the type of thermometer used. Definitions of fever include a rise in body temperature of 1°C or more above the mean, i.e. a rectal temperature of 1°C above 38°C or an axillary temperature of 1°C above 37.2°C.[14] Normal axillary temperature in infants is said to range between 35.6°C and 37.2°C,[15] and a review of websites' advice to parents gave a range for the upper limit of normal axillary temperature as 37–37.6°C.[16] Another author states that normal childhood temperature fluctuates between 36.5°C and 37.5°C.[7] Unsurprisingly, parents prefer axillary to rectal thermometry,[17] and our research has

shown that tympanic thermometry is too insensitive for the detection of fever in pre-school children in primary care.[18] 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.[19] Based on these data, the PITCH trial recruited children with a measured axillary temperature of at least 37.8°C and our 'time without fever' outcome was based on an axillary temperature threshold of less than 37.2°C.

Rationales for treating fever

The aim of any health service consultation for childhood fever is to diagnose and manage its cause. The extent to which symptomatic treatment should be offered is contested and not all rationales are evidence based. Indeed, not all commentators agree that the treatment of fever is even necessary. As long ago as 1666, Thomas Sydenham said: 'fever is nature's engine which she brings into the field to remove her enemy'[20] and many, like Sydenham, argue that fever is an evolutionary by-product of the host response to the infection, conferring protective advantages.[7] Kluger,[21] points to the number of different species (including mammals, birds, reptiles and insects) that demonstrate a fever response to infection. While it is unclear whether reducing core temperature is beneficial in humans, some animal models of infection suggest that fever plays an important role in host defence.[11] Others suggest that the aim of antipyresis should be to reduce the distress and discomfort associated with fever, but not the fever itself.[21]

Many clinicians are concerned that a raised temperature, especially when very high, is a proxy marker for severe illness. However, it is not known if a good response to antipyretics (in terms of the ease with which the temperature is reduced and the degree to which the child's overall condition improves) is a good prognostic indicator. Indeed, these are two of the research recommendations to be found in the 2007 National Institute for Health and Clinical Excellence (NICE) Feverish Illness in Children guidelines.[22]

Finally, because fever is the essential precursor to febrile convulsion, some clinicians and parents have concluded that antipyretics should prevent febrile convulsions. Indeed, the overuse of antipyretics could reinforce the fear that uncontrolled rises in temperature lead to convulsions, brain damage and death. This is known as the 'fever phobia', first described and studied by Schmidt in the 1980s,[23] and these views still appear to be held by some parents today.[24,25] In part, this may explain the strong desire to relieve children's symptoms,[2,19] and the fact that many parents have already used antipyretics before consulting health services[4,26] and that clinicians frequently advise the use of antipyretics.[16] Irrespective of whether children are treated with antipyretics, it is important that parents' fears are addressed and that they are empowered in the care of the child.[27]

Antipyretics

Temperature reduction can be achieved by physical or pharmacological methods. Physical methods include keeping the child lightly dressed and giving cool drinks. Tepid sponging is not recommended[22] because it may cause peripheral vasoconstriction and raise the core temperature higher than that intended by the hypothalamic set point. In this report, we will use the term 'antipyretic' to refer to the pharmacological methods.

A brief history of antipyretics

In the 1880s, attention was being focused on two compounds, acetanilide and phenacetin, that were already recognised for their antipyretic properties. Paracetamol was subsequently isolated from the urine of individuals who had taken phenacetin. Paracetamol was introduced to the US market for sale to adults in 1955 under the brand name Tylenol, and in the UK in 1956 as Panadol. In 1968, the children's formulation was released, known as Panadol Elixir.[28]

Dioscorides is thought to have been the first physician to have prescribed willow bark extract for patients suffering from rheumatism, while the antipyretic effect of willow bark was reported in detail for the first time in 1763.[29] Willow bark was found to contain salicin, a salicylate compound that was later converted to salicylic acid and aspirin. Aspirin was found to inhibit the cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) pathways and therefore to have potent analgesic and anti-inflammatory effects. However, aspirin causes gastric side effects and the pharmaceutical industry has been searching for a safer alternative ever since. In 1961, ibuprofen was first synthesised by a team of researchers at Boots, Nottingham. Following successful trials in patients with arthritis, it was introduced as a prescription-only medicine in the UK in 1969. Its reputation as the non-steroidal

anti-inflammatory drug (NSAID) with the fewest side effects grew, and in 1983 and 1984, Neurofen and Advil became available over the counter in the UK and US respectively.[30] Ibuprofen suspension was launched as a prescription medicine in the US in 1989 and became available as an over-the-counter (OTC) medicine in 1993 in the UK and in 1995 in the US. Since the withdrawal of aspirin for use in children due to its association with Reye syndrome, ibuprofen is the only NSAID licensed for use as an antipyretic.

Paracetamol and ibuprofen suspensions are now widely available in the UK, though only as two separate liquids. To our knowledge, only one pharmaceutical company has combined both agents in a single suspension in one bottle. The product is available in South Africa and is called Lotem.[31]

Pharmacokinetics

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 30–90 minutes post dose, peak antipyretic activity at 133 minutes[32] and the plasma half-life is in the range of 1–3 hours after therapeutic doses. The drug is widely distributed throughout most body fluids. Following therapeutic doses, 90–100% of the drug is recovered in the urine within 24 hours, almost entirely following hepatic conjugation with glucuronic acid (about 60%), sulphuric acid (about 35%) or cysteine (about 3%). Small amounts of hydroxylated and deacetylated metabolites have also been detected.[33]

Ibuprofen is absorbed from the gastrointestinal tract, and peak plasma concentrations occur about 1–2 hours after ingestion. Peak antipyretic activity is thought to occur later than paracetamol, at 183 minutes post ingestion,[32] and the elimination half-life is about 2 hours. It is metabolised to two inactive metabolites, and these are rapidly excreted in urine. About 1% is excreted in urine as unchanged ibuprofen and about 14% as conjugated ibuprofen. Ibuprofen is extensively bound to plasma proteins.[34]

Pharmacodynamics

The two pharmacological antipyretics licensed for fever in children are thought to exert their effects by blocking different points in the chemical pathway that leads to fever.[11,35] This means that it is biologically plausible that combined use could be more effective than when given separately. Paracetamol has analgesic and antipyretic effects similar to those of aspirin and is also useful in the treatment of mild to moderate pain. It is thought to reduce fever by inhibiting prostaglandin synthesis (PGE_2) centrally within the anterior hypothalamus through the direct inhibition of cyclo-oxygenase[11] as well as peripherally by suppressing inflammation and pyrogenic cytokine production.

Ibuprofen is a phenylpropionic acid derivative, which has analgesic, anti-inflammatory and antipyretic actions. These actions are thought to be due to non-selective peripheral inhibition of COX, resulting in reduced prostaglandin synthesis. Although selective COX-2 inhibitors have been shown to have antipyretic properties,[36] they are not licensed for antipyretic use.

Indications versus actual use

The British National Formulary for Children (BNFC) states that both antipyretics are indicated for the treatment of fever or mild to moderate pain.[37] Parents often initiate antipyretic treatment prior to seeking medical advice and at relatively low temperatures, e.g. 37.9°C.[24] Home dosing of antipyretics may be more frequent than recommended.[24] Paracetamol (and possibly ibuprofen) is given not just to treat the fever, but to calm children, and to help the child and whole family rest and sleep.[38] In a survey of American paediatricians, most stated they would start treatment at 38.3°C, with some using discomfort alone as a starting criterion.[39] It is likely that there is considerable between-family and between-clinician variation in the use of antipyretics.

Cost and frequency of over-the-counter antipyretic use

Table 1 shows that, although European expenditure on over-the-counter purchases of paediatric formulae antipyretics increased overall between 1997 and 2004, sales of paracetamol fell (Boots HealthCare International, Nottingham, UK, personal communication). Anecdotal evidence suggests large differences between nations' attitudes to the treatment of fever, with for, example, the British using considerably more antipyretics than their Dutch counterparts (Professor Chris Van Weel, University of Nijmegen, the Netherlands, personal communication). Our UK experience is that when children are seen in primary care, they have typically been given one antipyretic, usually paracetamol,[10,40] but that

TABLE 1 European expenditure (£ millions) on paediatric formulae antipyretics

Year	Paracetamol	Ibuprofen	Total
1997	188	65	253
2004	128	277	405

ibuprofen is being increasingly used, both with and without paracetamol. While clinical practice varies between institutions, the use of combined therapy in secondary care appears to be widespread.

Figure 1 shows the trends in UK pharmacy purchases of paediatric antipyretic formulae (paracetamol 120 mg/5 ml and ibuprofen 100 mg/5 ml) per 1000 children aged 0–6 years between 1995 and 2005, and suggests that paracetamol use is falling while ibuprofen use appears to be increasing (data source: IMS Health).[41] Average consumption per child aged 0–6 years in 2005 was equivalent to 200 ml of 120 mg/5 ml paracetamol and 100 ml of 100 mg/5 ml ibuprofen. However, these data cannot distinguish analgesic and febrile indications or the extent to which they are used together (alternately or in combination).

Frequency of combined medicine use

Despite the lack of evidence of effectiveness for combined use, which we will summarise below, there is both anecdotal (the authors' experience) and survey evidence that parents and clinicians are increasingly using both medicines, either simultaneously or alternately. These increases may vary between nations and, although we are not aware of UK-based survey data, data from 1999 show that paracetamol and ibuprofen were used in combination by up to 27% of parents[25] in the US and by 8% of parents of children attending an emergency department in the United Arab Emirates.[24] When US paediatricians were surveyed in 1999, 50% said that they routinely advised combined use and 29% thought that this was recommended practice.[39]

Evidence of effectiveness of antipyretics

In this section we will review the evidence for effectiveness of the different possible antipyretic strategies, both physical methods, and the different permutations of pharmacological agent use, with respect to their effects on temperature reduction and fever-associated discomfort and distress. We will also summarise the evidence of effectiveness for the prevention of febrile convulsions and evidence that temperature reduction is associated with reductions in temperature-associated

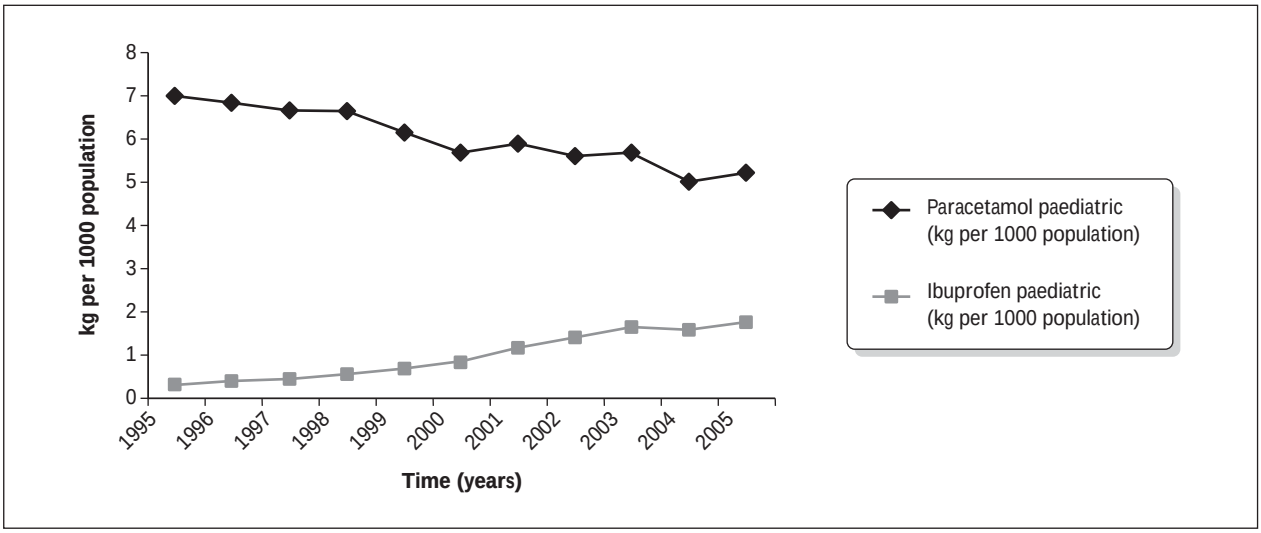


FIGURE 1 UK pharmacy purchases of antipyretics between 1995 and 2005.

symptoms. We will summarise the limitations of this evidence later.

Evidence for physical methods and antipyretic monotherapies

Physical methods of cooling include fanning, giving cool drinks and tepid sponging. One Cochrane review has collated the evidence from seven trials, involving 467 children.[42] The authors found one small trial (n = 30) comparing physical methods with drug placebo that did not demonstrate a difference in the proportion of children without fever by 1 hour after treatment. In two studies in which all children received paracetamol, physical methods resulted in a higher proportion of children without fever at 1 hour [n = 125; relative risk 11.7; 95% confidence interval (CI) 3.3–40.8]. In a third study (n = 130), which reported only mean change in temperature, no difference was detected. Mild adverse events (shivering and goose pimples) were more common in the physical methods group (three trials; relative risk 5.1; 95% CI 1.5–16.6). The authors concluded that a few small studies demonstrate that tepid sponging helps to reduce fever in children. However, because of concerns about inappropriately raising core temperatures too high, tepid sponging is no longer recommended.[22]

Meremikwu and Oyo-Ita[43] have also reviewed the literature regarding the effectiveness of paracetamol in reducing fever and preventing febrile convulsions. They found 12 trials (n = 1509 children) with heterogeneous outcomes and insufficient evidence to show whether paracetamol influenced the risk of febrile convulsions. In a meta-analysis of two trials (n = 120), the proportion of children without fever by the second hour after treatment did not differ significantly between those given paracetamol and those sponged. They concluded that there were insufficient placebo-controlled data to establish paracetamol effectiveness.

We are aware of just two placebo-controlled evaluations of ibuprofen monotherapy[44,45] both of which demonstrated evidence for the superiority of ibuprofen in reducing temperature in the 6–8 hours post dosing.

Evidence for paracetamol compared with ibuprofen

Two systematic reviews published in 2004 reached different conclusions regarding the relative effectiveness of paracetamol and ibuprofen monotherapy. The first,[46] concluded that their 'effectiveness and efficacy were similar, with slightly more benefits shown for ibuprofen'. Of the 14 studies reviewed, seven of which were subsequently reviewed by Perrott et al.,[47] 11 were randomised controlled trials. Twelve were conducted exclusively in secondary care (the remaining two in the offices of private paediatricians). Of the 10 single-dose studies, five concluded equivalence of action and five concluded that ibuprofen was superior to paracetamol. Of the four multiple-dose studies, three concluded that ibuprofen was superior. The review did not report outcomes other than fever. Thermometry (and timing of thermometry) differed between studies. Nor did the review include a funnel plot, leaving unassessed the possibility of publication bias. The second review[47] used data from ten studies (seven reviewed by Goldman et al.[46]) and concluded that 'ibuprofen is a more effective antipyretic than paracetamol at 2, 4 and 6 hours post dosing'.

Evidence for using paracetamol and ibuprofen together

Much of the following evidence summary was published in a BMJ editorial that was written in 2006.[41] We searched Medline (1966 to March 2006), Cochrane and our own databases and found five published studies comparing paracetamol and ibuprofen in combination with single-agent paracetamol or ibuprofen.[48–52] The first studied 89 children hospitalised in India with axillary temperatures > 38.5°C.[48] Children received ibuprofen 10 mg/kg singly or in combination with paracetamol 10 mg/kg, each three times daily. The paper reports the paracetamol–ibuprofen combination as being more effective than paracetamol alone from 0.5 to 2 hours and less effective from 10 to 24 hours, but differences appear to be less than 1°C and were not greater than would be expected by chance.

The second study randomised 123 children presenting to a UK emergency department with tympanic temperatures ≥ 38°C to receive paracetamol 15 mg/kg or ibuprofen 5 mg/kg or both, and measured tympanic temperature at 1 hour.[49] The investigators stated a priori that a clinically important treatment difference would be ≥ 1°C. Although they found a difference (p = 0.023) between all treatments, the temperature difference between the combined and paracetamol-only groups was 0.35°C, and between the combined and ibuprofen-only groups was 0.25°C. The CIs exclude the original target difference of 1°C so, if the 1°C threshold is accepted, the study was able to rule out a clinically important treatment difference

at 1 hour. Neither the Indian nor the UK study measured fever-associated symptoms.

The third study randomised 464 children with rectal temperatures of ≥38.4°C presenting to Israeli ambulatory care centres[50] to paracetamol 12.5 mg/kg every 6 hours, ibuprofen 5 mg/kg every 8 hours or both alternating 4-hourly. Irrespective of their intervention group, all children received a double loading dose of either paracetamol or ibuprofen. Rectal temperatures and distress scores were measured (at times determined by the parents) three times daily for 3 days, and the thermometry outcome used for the analyses was the maximum temperature recorded. The investigators found differences in temperatures (range 0.8–1.1°C) and distress scores lasting 3 days (all $p < 0.001$) between the alternating and monotherapy groups.

The fourth study, described as a pilot and without subsequent data published at the time of writing, randomised 70 children aged between 6 months and 12 years who were being treated in a secondary and tertiary care centre in Lebanon.[51] All had rectal temperatures ≥38.8°C and the study aimed to assess the benefits of adding paracetamol (15 mg/kg) or placebo 4 hours after a baseline dose of ibuprofen (10 mg/kg). The authors found that more children in the active group than in the placebo group (83% versus 58% respectively) were afebrile at 6 hours [number needed to treat (NNT) = 4], and that these effects persisted for up to 8 hours. They did not assess the subsequent effects of continued alternating dosing beyond the single dose of paracetamol given at 4 hours.

The fifth, a placebo-controlled study, randomised 38 children presenting to secondary care aged between 6 months and 6 years to either paracetamol (15 mg/kg) at time zero and 4 hours or paracetamol at time zero plus ibuprofen (10 mg/kg) at 3 hours. Clinically questionable differences in temperature were found at 4 and 5 hours post randomisation.

To our knowledge, one additional abstract has been presented at a conference.[53] This reports an interim analysis of an emergency department study of 28 febrile (> 38.3°C) children aged 3–10 years comparing combined paracetamol (15 mg/kg) and ibuprofen (10 mg/kg) with ibuprofen monotherapy. Oral temperatures were measured by the parents at home at 2, 4 and 6 hours and the results reported by telephone or post. Differences were observed in favour of combined treatment at 4 hours (0.7°C, $p = 0.05$) and 6 hours (3.5°C, $p = 0.02$), but the authors report results using a mixture of units (Fahrenheit and Celsius), giving rise to doubt regarding the true extent of the temperature differences, and at the time of writing (August 2008) final results had yet to be published.

We are aware of one other study in progress in the US led by Professor Ian Paul at Penn State College of Medicine, Hershey, PA, that has yet to report. Professor Paul told us that, at the time of writing (August 2008), recruitment was not complete (Ian Paul, Penn State College, Hershey, PA, personal communication).

Evidence that antipyretics prevent febrile convulsions

Given that fever is the essential precursor to febrile convulsion, it is logical that antipyretics could have a role in their prevention. However, the relationship between temperature and febrile convulsion is complex. It is said that febrile convulsions occur prior to the fever even being recognised by parents,[54] and that the risk is highest when the temperature rises fastest, so opportunities for prevention rely on early recognition of the fever. This, and the rarity of febrile convulsions, may be why studies to date have not demonstrated any beneficial effect of antipyretics on febrile convulsions.[43,55–58] Given their infrequency and the difficulties of ensuring compliance with study medications over a prolonged period of time in the community, it seems unlikely that a large enough study will ever be funded to investigate this relationship further, and alternative study designs may have to be used, such as ecological studies.[41]

Evidence for a relationship between temperature and discomfort

Among the studies comparing antipyretic monotherapies, we found two[59,60] in which both temperature and fever-associated symptoms were measured. In the first,[59] although no direct association between temperature and discomfort was described, at 6 hours temperature had fallen to a greater extent and discomfort levels had improved more in the ibuprofen group than in the paracetamol group. In the second study, reduction in temperature and improvement in discomfort levels were more or less equal in the two groups.[60] Among the combined treatment trials, we found no study investigating whether there is a relationship between a child's temperature and his or her level of discomfort.

Safety of antipyretics

We will discuss antipyretic safety in terms of adverse events, minor symptoms, and serious adverse events as defined by the European Clinical Trials Directive[61] (i.e. death, life-threatening illness, permanent disability or hospitalisation). Reports of adverse events are likely to be frequent in randomised controlled trials conducted under this directive as there is a mandatory requirement for investigators to ask all trial children about new symptoms or signs and try to establish causality, even before treatment group is known.

Adverse events

It has been found that number of children experiencing adverse events does not differ between those treated with paracetamol and those treated with placebo or between those treated with paracetamol and those treated with physical methods.[43] A trial of 234 children randomised to receive paracetamol 10 mg/kg or ibuprofen 7.5 mg/kg found a lower incidence of medication withdrawal due to adverse effects in the paracetamol group (0) than in the ibuprofen (7) group.[59] One child refused ibuprofen. One paracetamol-treated child experienced a rash, while, in the ibuprofen group, vomiting occurred in two children, diarrhoea in four, skin rashes in three and agitation in three. In another trial randomising 74 children to paracetamol 50 mg/kg/24 hours and 76 to ibuprofen 20 mg/kg/24 hours, no adverse events were thought to be even possibly related to paracetamol, whereas three adverse events (one each of urticarial rash, respiratory distress and diarrhoea) were thought to be 'possibly' related to ibuprofen.[60] In another trial of 64 children randomised to receive paracetamol 15 mg/kg or ibuprofen 10 mg/kg, three children in the paracetamol group withdrew after two doses due to hypothermia (exact definition not given) and one ibuprofen-treated child withdrew because of nausea, vomiting and abdominal pain. Additional mild adverse reactions to paracetamol included abdominal pain (3) and agitation (3), and to ibuprofen sweating (8) and 'gastrointestinal complaints' (7). Detailed laboratory tests did not establish any abnormality of renal or liver function associated with the medicines.[62] In another trial randomising 116 children to paracetamol 10 mg/kg or ibuprofen 10 mg/kg, two paracetamol-treated children vomited.[63] In another trial randomising 33 children to 10 mg/kg paracetamol, 32 to ibuprofen 5 mg/kg, 28 to ibuprofen 10 mg/kg and 34 to placebo, gastrointestinal symptoms were observed in the six paracetamol-treated children compared with 10 children treated with ibuprofen 5 mg/kg, six in the ibuprofen 10 mg/kg group and two in the placebo group. Renal and haematological tests did not differ between treatment groups.[45] Hypothermia (36.1°C) was reported 12 hours post dose in one child (out of 15) receiving ibuprofen 5 mg/kg,[45] and has previously been reported in a young child with pneumonia who received combined antipyretics.[64]

Given the small number and children randomised in the above studies, and the small number of adverse events, a systematic review is the best method for assessing safety. This was done in a comparison of paracetamol and ibuprofen monotherapies, and the authors commented that, although there were insufficient data to be conclusive, they did not find firm evidence that the medicines differed from each other (or placebo) in terms of the incidence of minor or major harm (17 safety trials; 1820 children).[47] These data suggest that there are no large differences in the prevalence of adverse effects, but that further research is needed to be more precise about less frequent, severe adverse events.

Serious adverse events

In the small number of placebo-controlled trials of paracetamol monotherapy that have been conducted, no severe adverse events have been reported.[43] There have been long-standing concerns regarding the toxic effects of NSAIDs on children (and adult) kidneys. Four recent case reports of children given NSAIDs, many of whom were fluid depleted and went on to develop renal failure, highlights these concerns among dehydrated children.[65–68] Fortunately, 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. Nonetheless, there are particular concerns about possible interactions between paracetamol and ibuprofen, highlighted in the recent NICE fever in children guidelines.[67] These arise because ibuprofen inhibits the production of glutathione in the kidney, which detoxifies renal paracetamol metabolites.[69]

We are aware of two monotherapy,[45,70] and two combined treatment trials[48,50] that investigated renal, hepatic and/or haematological abnormalities associated with antipyretics. None found any medicine-attributable, laboratory-confirmed adverse events. In one study,[50] children underwent laboratory testing for renal and liver function and faecal occult blood on days 0, 3, 5 and then every 2 weeks for 12 weeks. There were no differences in renal or liver function at baseline or follow-up and there were no drug-related serious adverse events.

Although measured, the authors do not present any data on the incidence of positive faecal occult blood.

Randomised controlled trial evidence suggests that short-term renal impairment[71] and admission to hospital for anaphylaxis, gastrointestinal bleeding or renal failure[72] is no more common with ibuprofen 5 or 10 mg/kg than paracetamol 15 mg/kg. This study randomised 84,192 children with fever recruited from outpatient departments and family practices in the US 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 gastrointestinal bleeding associated with ibuprofen was 7.2 per 100,000 children. There were no hospitalisations for acute renal failure or anaphylaxis.

To determine the effects of the medicines on asthma in one study,[72] a subgroup analysis was performed to determine the safety of paracetamol and ibuprofen in the 1879 children with asthma[73] (defined as those receiving β-agonists, theophyllines or inhaled steroids on the day before trial recruitment). The authors found no evidence of increased hospital admissions or outpatient attendances for asthma associated with ibuprofen compared with paracetamol. In fact, rates were higher among those receiving paracetamol. The cumulative incidence of outpatient attendances in the month following treatment was 5% and 3% for asthmatic children treated with paracetamol and ibuprofen respectively.

Observational studies have found an association between the use of ibuprofen and development of necrotising fasciitis in children with chicken pox infection,[74,75] possibly mediated by NSAID-induced impairment of neutrophil blood cell function.[76] However, as the ibuprofen use could be due to the increased pain associated with the soft-tissue infection, experimental studies are necessary before causation can be established.

Antipyretic guidelines for feverish children

Once 'red flag' symptoms (e.g. of meningitis) have been excluded, the NHS Direct website advises the use of paracetamol only for a young child with a fever and upper respiratory tract infection symptoms.[77] NICE has issued guidance saying, in summary, that antipyretics should be used only for children with fever and distress, and that either paracetamol or ibuprofen (no dose recommendation or preference stated) should be used but not both simultaneously. NICE also states that the drugs should not routinely be given alternately unless there is no response to first agent.[22] In addition, guidance on the NHS Clinical Knowledge Summaries (formerly PRODIGY) website states that dosing should be by weight (paracetamol 15 mg/kg and ibuprofen 10 mg/kg), and that simultaneous dosing is preferred to alternating dosing as it is less likely to lead to dosing errors. Simultaneous treatment should be instituted 6-hourly and only for fever/pain not controlled on monotherapy.[78] No US guidance was found when searches of the National Guideline Clearing House and Agency for Health care Research and Quality (AHRQ) were undertaken (10 July 2007).

Antipyretic doses

Two dosing methods are available. 'Dosing by age' is probably typically used by parents because the quantities are available on the medicine packaging and this method is easy to use. The more complex but appropriate alternative, typically used in secondary care and to some extent in primary care too, is 'dosing by weight'. The National Service Framework for children, young people and maternity services[79] states that children should receive age-, weight- and development-appropriate medicines and that, in order to reduce medication error and improve dosing, prescribing should be by weight. It also states that, in order to reduce medication error, the intended dose should be prescribed in mg/kg. In common with all paediatric formularies, the BNFC presents all dosing information per kilogram. There is some evidence from a survey of parents attending an American children's emergency department that dose by weight is more accurate and less likely to lead to dose error.[80] In Israel, 70% of doctors, 70% of nurses and 30% of parents are already dosing by weight.[19] In this section we will describe the differences in total medicine dose a child receives if calculated by weight or age. Figure 2 and Figure 3 show the total medicine doses for paracetamol and ibuprofen, respectively, if calculated by weight (given two extreme and one central weight percentiles) and age. They both show that age calculations produce stepped doses and the differences in total daily doses that are produced between weight and age calculations. They also illustrate that calculations by weight are superior as

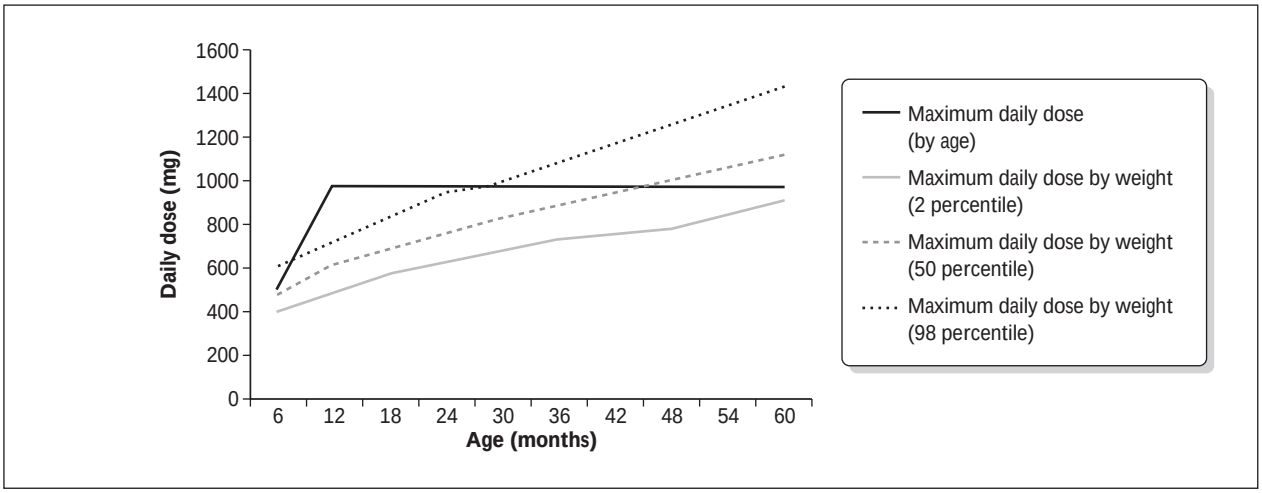


FIGURE 2 Comparison of total daily doses of paracetamol calculated by weight and age.

they are more likely to be consistent with a child's pharmacokinetics.

Summary of the justification for the PITCH study

Summary of limitations of previous research

It is striking that, among the dozens of published studies investigating antipyretic effectiveness, only a few have used a non-pharmacological (6) or a placebo (8) comparator, and those that used placebos were all published on or before 1992.[43–45] In the UK at least, this is not surprising because of the predominant fever treatment culture, which would make recruitment to such studies challenging, and the difficulties of convincing an ethics committee of the clinical equipoise.

The two systematic reviews comparing monotherapies[46,47] drew compatible conclusions, namely that ibuprofen is probably more beneficial for fever reduction than paracetamol but that both

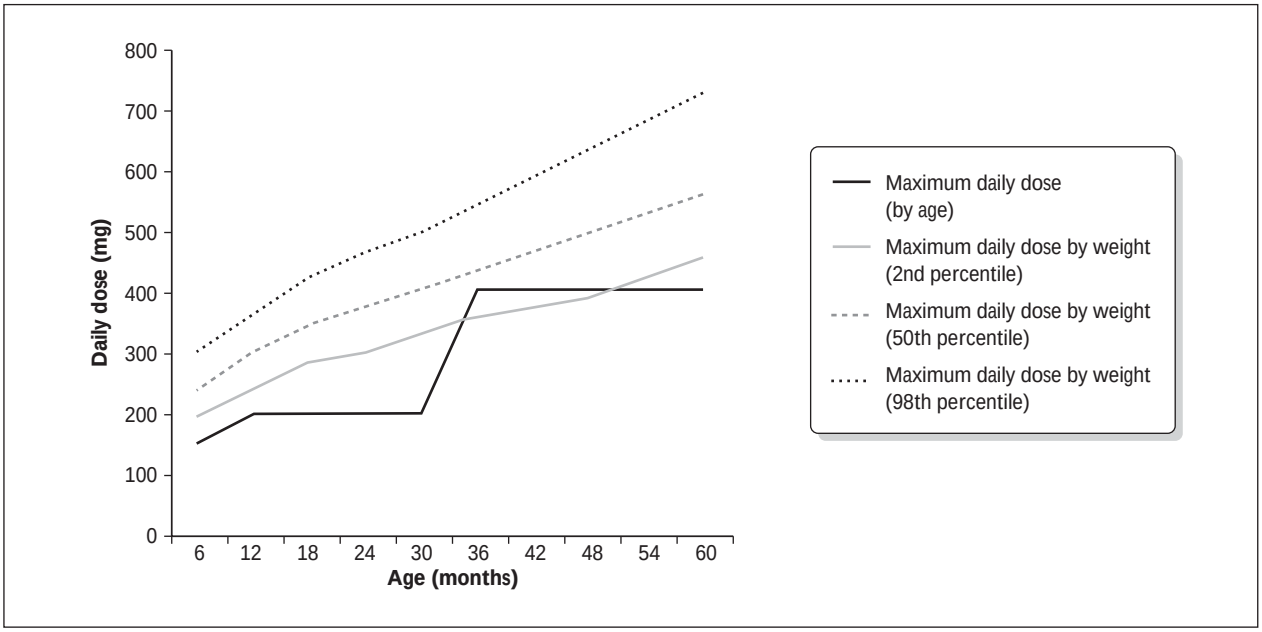


FIGURE 3 Comparison of total daily doses of ibuprofen calculated by weight and age.

medicines should be given at full doses.[46] Neither examined effects on fever-associated discomfort.

The children in the studies comparing combined versus monotherapies were probably more unwell than the majority of febrile children, who are managed in the home. Comparison of the evidence is limited by inconsistent medicine doses and thermometry methods, and only one study measured the child's discomfort.[50] The results of the Indian study[48] suggest that there is no advantage in using combined over monotherapy, but it may have been underpowered. The UK study[49] points to an absence of clinically important early treatment effects, but further data are needed beyond 1 hour. The Israeli study[50] design appears to be difficult to interpret as half the children received both medicines in the first 24 hours and parents determined the timing of thermometry and distress scores. The Lebanese study[51] was probably accepted for publication as a pilot because of the large, statistically and clinically significant treatment effects in favour of combined treatment up to 4 hours post paracetamol dosing, but may be an example of publication bias. The American study found statistically but probably clinically unimportant temperature differences at 4 and 5 but not 6 hours when ibuprofen was added to paracetamol after 3 hours.[52] Four of the studies investigated the effect of single medicine doses,[49,51–53] which does not reflect usual clinical or parental practice and could miss important late or cumulative effects of multiple dosing.

Given the differences in time to peak plasma concentration (90 and 120 minutes) and time to maximum antipyretic activity (120 and 180 minutes) for paracetamol[33] and ibuprofen,[34] the timing of thermometry is crucial to the fairness with which antipyretics are compared in all antipyretic studies. For example, a measure at 1 hour may be too early for either medicine to work; 2 hours after dosing may advantage paracetamol, while a 3-hour measure could advantage ibuprofen. This is a problem particularly with community-based studies,[50] which may rely on parents to measure temperatures and so cannot be overly restrictive in stipulating their timing.

It is not only the timing of thermometry that is important: how it is reported determines its interpretability and relevance to clinicians and parents. For example, most papers report temperature reductions at given time points, and some have stated that only differences of at least 1°C would be meaningful.[49] However, as with many 'minimum clinically important differences', it is not clear how this target difference has been established and, even if generally accepted, a reduction of 1°C from, say, 40°C without improvement in the child's discomfort may not be clinically useful. With the above timing limitations in mind, we believe that it is preferable for studies to report 'normalisation' of temperature or the proportion of children without fever at given times.[51,81]

We believe that the fairest and most clinically relevant method to measure temperature effects is continuous thermometry, used in one published study we know of to date.[82] This methods allows the derivation of a mean 'time without fever' outcome which, in a trial, can be translated into the additional time spent without fever. We believe that this is both a fair and intuitive outcome that can be understood by parents and clinicians.

Only a few studies have measured temperature-associated symptoms, and only one combined therapy trial measured distress.[50] Although this study reported statistically and clinically significant improvements in distress in the combined versus monotherapy groups, the results could have been susceptible to observer bias as parents chose when to record the outcome. Thus, more data are needed on the effectiveness of combined treatments for fever-associated symptoms.

To our knowledge, there are no published studies of the cost-effectiveness of treating fever with paracetamol and/or ibuprofen. Although one study[50] concluded that children given both medicines had fewer missed daycare episodes, no formal economic evaluation was performed. This information is essential in making a fully informed recommendation about a preferred treatment regime. Evidence on potential differences in resource use and their cost implications must be considered alongside the information on clinical effectiveness. Additionally, it is known that fever is a common reason for children to consult in primary care, and information about the cost of an episode of illness, along with more knowledge about the natural history of fever, would enhance service planning and indicate the need for tools to manage the condition.

The National Coordinating Centre for Health Technology Assessment research brief

In March 2003, the National Coordinating Centre for Health Technology Assessment (NCCHTA) published its research brief HTA number 03/09 asking: what is the clinical effectiveness of paracetamol alone, ibuprofen alone and paracetamol and ibuprofen in combination in the management of fever in pre-school children? The technology was to be combined treatment, with the comparators paracetamol and ibuprofen alone. The NCCHTA wanted a three-arm randomised controlled trial and specified temperature reduction, disease/symptoms scores and adverse events as outcomes, with pre-school children recruited from the community, primary or secondary care. The brief came from a pharmaceutical panel and the motives were twofold: first, to determine if combined antipyretics would reduce temperature and in doing so (although not to be measured as an outcome) to reduce the risk of febrile convulsion; and, second, to determine if more parents could be empowered to manage children at home.

How the PITCH team responded to the NCCHTA brief

We decided to recruit children while febrile (literally 'hot recruitment') rather than when well with instructions to parents to enrol the child when fever developed ('cold recruitment') for three reasons. First and foremost, we believed that many parents would not participate if the study explanation and contact had occurred several weeks or even months prior to their child's illness. Second, we were concerned that cold recruitment would mean that study medicines were in the community for long periods of time with the associated risk of inadvertent use prior to the study and the potential for wastage. Finally, we were concerned that there would not be standardisation of study entry criteria if parents were deciding when to start study medicines. We decided to recruit from a combination of primary care and community settings, where the majority of childhood fever is managed.

Since there was little point in assessing paracetamol or ibuprofen effectiveness at doses less than the licensed maximum dose, we selected the maximum fever dose by weight regimens, that is paracetamol 15 mg/kg 4- to 6-hourly, to a maximum of four doses in 24 hours, and ibuprofen 10 mg/kg 6- to 8-hourly, to a maximum of three doses in 24 hours. We agreed with the brief that both temperature reduction and fever-associated symptoms should be the primary outcomes and chose to use continuous automated thermometry to overcome the issues of parent-initiated thermometry at single or restricted multiple time points.

In addition, we decided to carry out an economic evaluation from the perspectives of the parents and the NHS alongside the randomised controlled trial and to describe the natural history of fever.

Aims of the PITCH study

1. To establish the relative clinical effectiveness of both medicines compared with paracetamol and ibuprofen separately for time without fever in the first four hours in children aged between six months and six years presenting to primary care and/or being managed at home.
2. To assess the relative clinical effectiveness of both medicines compared with paracetamol and ibuprofen separately for the relief of fever-associated discomfort at 48 hours post randomisation.
3. To use qualitative methods to optimise the overall trial process and explore parents' and clinicians' beliefs about the use, effectiveness and side effects of paracetamol and ibuprofen.
4. To perform an economic evaluation from the perspectives of the NHS and parents comparing the cost and benefits of each treatment.
5. To describe the natural history of fever.

Chapter 2
Methods

Trial design, funding and approval

The trial was a single-centre (multisite), individually randomised, blinded, three-arm trial comprising paracetamol alone, ibuprofen alone or paracetamol and ibuprofen together. The trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme and started in December 2004 (reference number 03/09/01). The trial was approved by the Bath Research Ethics Committee, UK (reference number 04/Q2001/197), and is registered with the International Standard Randomised Controlled Trial Register (reference number 26362730) and Eudract (number 2004-000160-28).

Participants

According to the original protocol, children were eligible to participate in the study if they were between the ages of 6 months and 5 years and were previously well, but had a fever of between 38°C and 40°C due to any underlying illness that could be managed in the community. Owing to recruitment difficulties, the eligibility criteria were revised and approved seven times during the trial. They expanded to allow the recruitment of previously well children aged between 6 months and 6 years with a nurse-measured temperature of at least 37.8°C and up to 41°C presenting for the first time (for that episode of fever).

Final eligibility criteria

Inclusion

The inclusion criteria were any previously well children who:

- were aged between 6 months and 6 years at the time of randomisation;
- had an axillary nurse-measured temperature between 37.8°C and 41°C at the time of randomisation due to an illness that could be managed in the community; and
- were living in the recruitment area with a parent or legal guardian.

Exclusion

The exclusion criteria were any children who:

- had previously participated in the PITCH trial;
- were within 30 days of participation in another drug trial;
- weighed 7 kg or less;
- had an illnesses requiring hospital admission;
- had epilepsy or other chronic neurological disease;
- had an allergy or intolerance to the study medication;
- had a known study medicine contraindication or caution as identified by the BNFC;
- had skin conditions precluding the use of adhesive tape (for the attachment of the axillary temperature probe);
- had peptic ulceration or bleeding;
- had known diagnosis or any ongoing investigation into suspected
  - cardiac disease
  - pulmonary disease
  - liver disease
  - renal disease; and
- had parents/legal guardians who could not read or write English.

These exclusion criteria were mostly identified by the child's clinician where they had access to their medical record. If the record was unavailable (for example, in walk-in centres or when the parent contacted the trial directly to participate), criteria were operationalised by asking parents for their knowledge of any previous known conditions in the exclusion criteria.

Recruitment location and settings

The trial was based in the Bristol area and adjacent suburbs. Recruitment took place within an approximate 12-mile radius of Bristol city centre. This recruitment area covered a wide variety of socioeconomic dwellings. Bristol NHS primary care organisations were targeted and 68 organisations were invited to assist with recruitment. These included general practices, out-of-hours general practice cooperatives, the local NHS Direct centre and the South Bristol NHS Walk-in Centre. The Royal Bristol Children's Hospital Emergency

Department was also invited to participate due to the primary care function it performs.

Recruitment methods

Recruitment commenced in January 2005 and was completed at the end of May 2007. Over the course of the recruitment period, recruitment methods were expanded to maximise the number of children coming into contact with the study. For the last 13 months of the trial, three recruitment methods were in place, termed 'local', 'remote' and 'community'.

Local recruitment strategy

The local recruitment method was used throughout the whole recruitment period. During local recruitment, a research nurse was stationed in the waiting area of the collaborating NHS sites. Posters (Appendix 3) containing the site letterhead were on display giving details of the trial, and parents were requested to ask the research nurse for more information if they were interested in taking part. Receptionists were also asked to give trial invitation letters and summary parent information sheets, printed on site headed paper (Appendix 4), to the accompanying parents of any children appearing to be in the appropriate age range. The parent was asked to indicate on this letter first if their child was in the eligible age group and, second, whether the child had any 'fever indicators'. These were a current fever or history of fever in the last 24 hours. Parents answering 'yes' to both questions were invited to read the accompanying summary parent information sheet and if interested were given the opportunity to discuss the trial further with the research nurse. If they did not wish to discuss the trial further, they were asked if they would give the reason. Carers who were not the parent or legal guardian of potentially eligible children were asked to take a patient information sheet (PIS) (Appendix 5) along with the research nurse's contact details so that the parent had the opportunity to telephone and discuss the trial. All completed invitation sheets were collected by the receptionist or research nurse during the session. The research nurses made every effort to approach all potentially eligible children and their parents entering the waiting room. The research nurses recorded the outcome of all children who appeared to be in the eligible age range attending the consultation sessions in order to monitor the potential number of eligible and ineligible children.

If parents of a potentially eligible child were interested in taking part, the research nurse gave a brief overview of how the trial would proceed following the consultation with the clinician. The research nurse ensured that parents were aware that showing interest at this stage did not commit them to taking part and that they had opportunities to discuss the trial with the clinician or research nurse prior to signing the consent form. Parents who were happy to proceed were asked to give the clinician paperwork (Appendix 6) to the doctor or nurse examining their child. The clinician paperwork comprised three sections: first, the study medicine prescription details and confirmation that the child met the eligibility criteria; second, information regarding the child's current illness, including the temperature (if taken), type of thermometer used, cause of fever; severity of illness; current medication (if any), new medicines prescribed and which antipyretic medication they would normally have recommended to the parent; and, third, a 'permission for release' to the trial team of details of the child's current illness, any treatment, and the parent and child's contact details. This was signed by the parent either prior to seeing the clinician or at the end of the consultation. After the consultation, the parent returned the completed clinician paperwork to the research nurse in the waiting area. If the child was eligible, a mutually convenient time for a home visit was arranged between the parent and the research nurse to proceed with the trial.

Remote recruitment strategy

As local recruitment was labour intensive, and in order to capitalise on the number of sites that were collaborating with the trial, we developed the remote recruitment strategy, which was implemented in May 2005 (4 months into the recruitment period). The remote recruitment method allowed clinicians at all sites to fax details (directly to the trial office) of potentially eligible children they had seen or with whose parents they had had telephone consultations. This allowed a far greater potential for recruitment, as, effectively, all sites were actively recruiting to the trial, regardless of whether a research nurse was present.

All sites taking part in remote recruitment were provided with a folder containing the trial paperwork to aid their discussion and recruitment of children to the trial. Clinicians were asked to give parents of eligible children presenting with a current or recent history of fever information about the trial at the end of the consultation. Interested parents together with the clinician completed the

clinician paperwork in the same way as with local recruitment. Clinicians were asked to give the family a PIS and to inform them that they could withdraw at any time and that a trial research nurse would contact them by telephone within 24 hours. Until then, antipyretic treatment should continue in accordance with usual clinical advice. In the case of telephone consultations, verbal consent was obtained. The clinician paperwork was then faxed to a secure machine in the trial office. Once a fax had been received, a research nurse made contact with the child's parent within 24 hours of receipt but, on most occasions, within 1 hour. The research nurse explained the trial, answered any questions and arranged a face-to-face meeting with the family.

Facilitators of remote recruitment

A number of methods were developed to remind clinicians to refer to the trial. All sites were provided with a referral prompt sticker (Appendix 7) to place on their computer monitor to remind them of the eligibility criteria and to refer to the trial. General practices using the Egton Medical Information Systems (EMIS LV5.2) computer software were given additional support to facilitate referrals of potentially eligible children. First, a 'macro' to automatically print referral paperwork and, second, a 'prompt' to alert clinicians to potentially eligible children.

The macro was designed to automatically collate and print the clinician paperwork onto a two-page letter at the click of a button. The macro was designed to extract the appropriate clinical information from the current consultation only, along with other details, for example date of birth and contact details from the child's medical record. This could be printed and faxed to the trial team in the same way as normal referral paperwork. In addition, it was noted in the patient's consultations notes that he or she had been referred to the trial. Many primary care clinicians made use of this facility, and feedback from them suggested that it made the referral process simpler and easier to use. Eleven of the 18 collaborator sites that had the potential to install the EMIS macro on their computer systems agreed to its installation.

The EMIS prompt was a specific patch written and installed remotely by EMIS to alert clinicians about the possible eligibility of children to the trial, when in a consultation with a patient. The prompt was the question 'Is this child eligible for PITCH?', which appeared on the computer screen in response to the clinician's entry of symptom or diagnosis codes for patients aged between 6 months and 6 years. Again, all 18 collaborator sites that had the potential for the EMIS prompt to be installed were contacted throughout the course of the recruitment period and all sites agreed to its installation.

Community recruitment strategy

It is clear from previous research[1] and our research nurses reports that many parents chose to manage their child's fever without seeking help from the NHS. This suggested that a large pool of potentially eligible children were being missed. In response to this, the community recruitment strategy was implemented in May 2006 (16 months into the recruitment period). It allowed children ill with a fever living within the recruitment area to enter the study directly from the community, without prior contact with the NHS. Parents were invited to contact the study team directly using a designated telephone hotline whenever their child was ill with a fever. During normal office hours, the study secretary would respond to calls, and at other times an answerphone message asked callers to leave their name and contact details and informed them that a member of the study team would contact them within 24 hours. The answerphone message also advised parents who were worried about their child's condition to seek advice from their GP, out-of-hours GP service, or NHS Direct.

When the study secretary answered a call, details of the call were logged in the trial ACCESS database. The secretary used a flowchart to ensure all calls were responded to effectively (see Appendix 8). Any parents calling who did not have potentially eligible children at that time or were calling for more information about the study were sent a trial promotional leaflet (Appendix 9) and a fridge magnet (Appendix 10) for future use. Once the caller had confirmed that the child was in the study age range, living in the recruitment area and had a fever, a disclaimer notice was read to the caller, explaining that telephoning the hotline was not a substitute for seeing a GP or telephoning NHS Direct. Callers were advised that if they were at all concerned about their child's condition they should contact their GP, out-of-hours GP service or NHS Direct as normal. The secretary checked that the caller was the child's parent or guardian and then asked for contact details, which were stored on a secure, electronic, database. It was explained that a research nurse would contact them within the next 4 hours, but that in the meantime they should continue to treat their child's illness as normal. Details of the call were

passed to the research nurse, who would contact the family as soon as possible. Outside office hours the research nurses were able to access the hotline remotely. This facility enabled them to continue to recruit at local NHS sites yet still be able to respond quickly to any community call messages. When returning calls the research nurses were careful to maintain confidentiality. Once the parents' identity of the potentially eligible child was confirmed, the research nurses used a structured nurse telephone triage form (Appendix 11) to assess whether the child's fever was due to a serious underlying illness so that eligibility could be established. The telephone triage was based on the fever algorithms used by NHS Direct and was checked for clinical validity by an experienced paediatric specialist registrar. Triage was conducted only by experienced, registered paediatric nurses. They checked that the parent had been told and understood the disclaimer notice and then conducted the telephone triage in three sections. First was the red section, designed to assess the child's vital signs – airway, breathing, circulation and consciousness level. This section also included questions related to the signs and symptoms of meningitis. Second was the amber section, designed to identify other important, but not generally life-threatening conditions that might require a medical consultation, for example dehydration or fever of more than 3 days' duration. At the end of the first two sections the research nurse would advise appropriately. Finally, the green section referred to the reassuring symptoms usually associated with minor illness, such as the presence of coryza or cough. The parent was then asked about any previous or ongoing medical problems including allergies. At this stage of the assessment, unless the parent had been advised to seek a clinical consultation, the research nurse explained the aims and design of the study. If the parent was happy to continue, a face-to-face meeting was arranged.

Trial promotion

A range of promotional items and activities were used to raise the profile of the trial. One hundred and thirty posters (Appendix 12), 1000 A5 poster flyers, 21,000 promotional leaflets (Appendix 9) and 6000 fridge magnets (Appendix 10) bearing the trial logo, basic eligibility criteria and the hotline telephone number were produced and distributed. Promotional leaflets and fridge magnets were handed out to parents of young children during the research nurses' visits to local recruitment strategy sites and in general day-to-day contacts. They were also posted out to parents who had contacted us via the hotline and remote fax referrals. Community venues were approached and asked to help promote the study. This promotional help was adapted to suit the individual site, and a database recording the details was developed. Each research nurse was responsible for a geographical area within the recruitment area and contacted libraries, day care services, cafes and pharmacies. Each venue was asked to display a poster, promotional leaflets and flyers. The contact details of the research nurse were given to these sites so that more promotional items could be requested if required up to the end of the recruitment period. Cooperating pharmacies were asked to give a promotional leaflet to anyone buying paediatric antipyretic medicines or collecting prescriptions that were dispensed for young children. The research nurses visited regularly to offer encouragement and serve as a reminder.

Health visitors were encouraged to promote the study among parents of the pre-school population. The research nurses visited health visitor-run child health and baby clinics attached to some of the larger GP practices, making use of the more relaxed atmosphere to explain the study to parents. Nurseries and pre-school groups were asked to hand out flyers when they issued parents with fee invoices. Some sites offered to mention the study in parent newsletters. Toddler groups were often happy for a research nurse or the trial co-ordinator to give a short, informal talk to parents about the trial. Often the research nurses would come across the same parents at their local GP practice, during a local recruitment strategy session, indicating that cross-coverage within the recruitment area was occurring. As well as displaying study material, the public libraries were happy for the research nurse to attend weekly 'parent and child' story sessions and promote the study face-to-face. In addition, promotional items were included in Bookstart reading packs, which are available to every toddler aged 15–35 months in the Bristol area. Bookstart is a national programme that encourages parents and carers to share and enjoy books with their children from an early age. The hotline number was also promoted using local newspaper (Appendix 13) and on local radio advertisements.

Other strategies adopted to improve recruitment rates

Throughout the recruitment period, several other strategies and methods were implemented to try to improve the recruitment rates to the

trial. These included strategies targeted at our sites and our team. For the sites, we sent monthly emails to encourage clinicians to refer to the trial. These emails varied each month and would typically include the importance of the trial and the reasons why it was being conducted, basic inclusion criteria, reminders on how to refer, an update on recruitment numbers and any other important news, for example new research nurses commencing employment with the trial. The team also provided helpful information to clinicians on how to introduce and discuss the trial within the clinical consultation and the promotion of clinical equipoise. Publications from the trial team[83,84] were also sent to each clinician by email and a summary of the trial was published in the local research collaborative newsletter. The trial team also developed a newsletter and recruitment league tables to encourage some competition between recruiting sites. Finally, towards the end of the recruitment period, an appeal letter to encourage a final 'push' on recruitment was sent to each clinician helping to recruit.

Feedback from these communications to clinicians provided us with excellent insight into clinicians' recruitment issues. Many said that they found the communications helpful reminders, and clinicians would highlight problems with recruitment. In response we organised practice meetings, gave clinicians an opportunity to express their concerns and discussed potential solutions. The main problems were confusion around eligibility and when and how to refer. Once these issues had been raised and dealt with, referrals often improved. Other examples of addressing clinicians' feedback was the modification of the reimbursement scheme to relate to each appropriate referral received. Originally, clinicians were reimbursed for every child randomised. However, we discovered that some clinicians were referring many children who were not eventually randomised. Some eventually became demotivated to refer, as they were not rewarded for their time and effort for referring. In response, we changed the reimbursement scheme to reflect each appropriate child referred and this boosted the number of referrals without, in the event, compromising the quality of referrals.

The trial team promoted and utilised good research nurse–site relationships to encourage referrals and recruitment. The research nurses visited sites to locally recruit children on regular days or at certain consultation sessions so that clinicians were aware of when the research nurses were recruiting.

There were continual efforts to increase recruitment by widening the number of sites and clinicians that could refer. Surgeries and sites that had expressed an interest in research were invited to collaborate throughout the recruitment period. Sites which were only recruiting through the local recruitment method were encouraged to use the remote recruitment method. We encouraged practice nurses, who often triage or treat children with minor illnesses, to help with remote recruitment, and this increased the referral rates. Other clinical staff were also encouraged to engage with the trial and help as much as they could, for example health visitors. Many health visitors handed out promotional leaflets and fridge magnets to parents.

Every research nurse–parent interaction was essential to recruitment success. A research nurse coming into contact with a potentially eligible child would communicate regularly with the family, even if the child was not eligible at that time. The research nurses and trial co-ordinator regularly reviewed the way in which they discussed the trial with parents to ensure that they maintained clinical equipoise, gave parents every opportunity to clarify queries or ask questions and broke down barriers to parental decline. Owing to the short time available to parents to assimilate the trial information and decide whether to participate, advance mailings from some GP surgeries were sent out to families with appropriately aged children. This prepared parents, giving them more time to consider the trial.

Finally, within the trial team, further activities occurred to try to maximise recruitment. The research nurses worked shift patterns in order to cover evenings and weekends, which facilitated more referrals from out-of-hours GP cooperatives. The trial team reviewed and analysed monthly recruitment figures from the three methods and acted on patterns or problems raised. The trial co-ordinator accompanied research nurses to observe their recruitment methods, resolve any problems or difficulties they had and reflect on their practice and communications with potentially eligible families. This dovetailed with the trial's collaboration with the QUARTET study (see below for more details).

Description of trial participation

Once a potentially eligible child was identified, a research nurse would arrange a visit, usually in the child's house, to explain the trial and fully assess

final eligibility. If the child was eligible this visit was termed the baseline visit. Follow-up visits occurred at 24 hours and 48 hours and a telephone follow-up took place on day 5.

Baseline visit

The purpose of the baseline visit was for the research nurse to confirm eligibility, collect baseline data and organise treatment allocation. The parent was given time to read the PIS and given an opportunity to ask questions. The child was assigned a case report form (CRF), on which all data and a unique enrolment number were recorded. Written informed consent was obtained from a parent. Once the research nurse had established that it was safe for the child to receive study medicines, she proceeded with the process of randomisation. The child was fitted with a datalogger (see below for more details and Appendix 21) that continuously recorded temperature and the nurse gave her the study medicines. The child's parents were asked to complete a symptom diary (see below for more details and Appendix 24) detailing the child's discomfort, appetite, sleep and activity levels as well as timings of administration of study medicines.

Twenty-four-hour follow-up visit

The purpose of the 24-hour visit was to assess how the child had been since the baseline visit and to address any early parental concerns or problems with the child or the study. In addition, the research nurse checked the study medicines, datalogger and symptom diary to ensure that data were collected accurately. All information was recorded in the child's CRF. The research nurse retrieved the datalogger to download the data collected from it.

Forty-eight-hour follow-up visit

The purpose of the 48-hour visit was to assess how the child had been since the 24-hour visit. In addition, the research nurse weighed the study medicines and retrieved the medicines and symptom diary to ensure data that were being collected accurately. All data were recorded in the child's CRF. Economic data were also collected during this visit (see below for more details).

Day 5 follow-up telephone call

The purpose of the follow-up telephone call was to assess the child, confirm any data queries with the parent and collect the final economic data. All data were recorded in the child's CRF. The research nurse thanked the parent and child for their involvement in the study.

Interventions

Study medicines

The intervention was the provision of, and advice to give, the study medicines for up to 48 hours. Consented children were randomised to receive either (a) paracetamol^{active} and ibuprofen^{placebo}, (b) paracetamol^{placebo} and ibuprofen^{active} or (c) paracetamol^{active} and ibuprofen^{active} as Figure 4 demonstrates.

Parents received two medicine bottles and were aware which was nominally paracetamol/placebo and which was ibuprofen/placebo. All liquid suspensions were sugar free and supplied in licensed containers with approved child-resistant caps.

Dose calculation

The dose of study medicines used was calculated by weight, as recommended by the Children's National Service Framework and the Royal Pharmaceutical Society for Great Britain in the BNFC. These were:

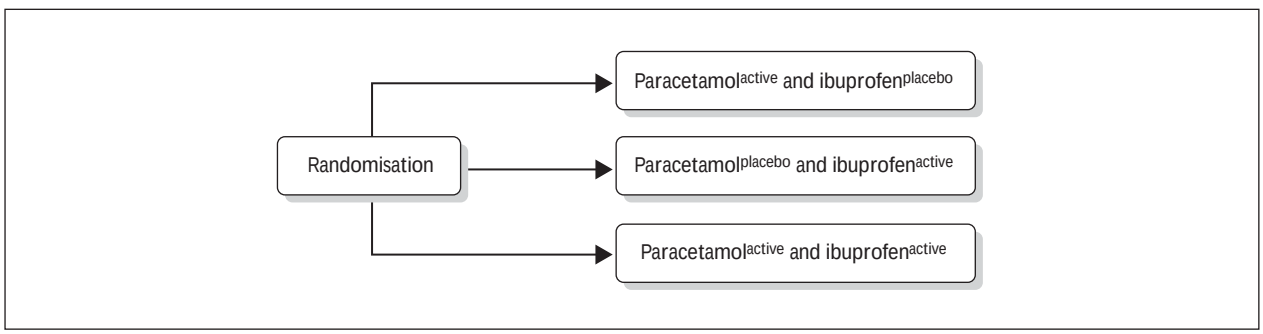


FIGURE 4 Treatment allocation.

- paracetamol 15 mg/kg repeated every 4–6 hours (maximum of four doses in 24 hours); and
- ibuprofen 10 mg/kg repeated every 6–8 hours (maximum of three doses in 24 hours).

This dosing regimen was chosen because it avoids differential dosing of heavier children compared with lighter children of the same age. The active medicine bottles contained the standard concentrations: 120 mg/5 ml of paracetamol and 100 mg/5 ml of ibuprofen. The volume of suspension per dose was calculated according to the required dose, which the research nurse first calculated to the nearest 0.1 ml, and then confirmed during the process of randomisation.

At the baseline visit and before randomisation, the research nurse weighed the child, undressed to one layer, without nappy or shoes, using scales approved for paediatric use (SECA, UK). The child's weight was recorded in the CRF to one decimal point. A standard operating procedure (SOP) was developed to estimate the child's weight if a child could not be weighed (see Appendix 14). The research nurses would abandon randomisation if the child's weight could not be established and they deemed administration of the study medicines to be unsafe. At the point of randomisation, the research nurse entered the child's weight (amongst other variables) and the telephone randomisation system used an algorithm to calculate the medicine volumes, rounded down to the nearest 0.5 ml (see Appendix 15). The research nurse checked that this dose corresponded to her calculation and noted this on the child's CRF. The dose for each medicine was also noted on the medicine bottles and on the patient participation card (Appendix 16).

Administration and timings

The research nurses handled, dispensed and administered the study medicines according to an SOP (see Appendix 17). After randomisation, and in the presence of the nurse, both study medicines (either paracetamol/placebo and ibuprofen/placebo) were given to the child. The first doses were timed to coincide with the child's next due dose of antipyretic, respectively 4–6 or 6–8 hours after paracetamol or ibuprofen. Suspensions were administered to the nearest 0.5 ml using 10-ml syringes marked at 0.5-ml increments. Parents were given 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.

The order in which the first medicine was administered was determined randomly (see below for details). The time that the medicines were swallowed was recorded using a personalised digital assistant (PDA; Palm, UK), was designated as time zero (t_0). This was used to determine all subsequent data collection times. The details of the administration (which medicine first, dose, volume, indication that the medicines were successfully swallowed/taken) were logged on the symptom diary by the research nurses. For the first 4 hours after administration of the study medicines, termed the 'efficacy period', no further medicine should have been given. From 4 to 24 hours, parents were asked to administer the medicines regularly ('proactive period'), i.e. paracetamol repeated every 4–6 hours and ibuprofen repeated every 6–8 hours. From 24 to 48 hours parents were asked to give the medicines as required ('reactive period') in response to the child's symptoms. Table 2 describes the intervention period. The light and dark grey squares represent the times when paracetamol or ibuprofen were to be administered respectively.

The medicine volumes to be given and the child's initials, enrolment number and date dispensed were written on the medicine bottles and storage box. At 48 hours, the study medicines were retrieved from the family and weighed. From 48 hours to the day 5 final follow-up, the parents were advised to use over-the-counter medications if needed. The research nurses also offered guidance to the parents regarding what to do in the event

TABLE 2 Use of the interventions during the first 24 hours

of medicine spillage or subsequent vomiting. In addition, all parents were given a standardised advice sheet (Appendix 18) regarding other cooling measures, such as appropriate clothing, ambient temperature and avoiding tepid sponging.

Pharmacovigilance

Adverse events

In accordance with the European Clinical Trial Directive 2001/20/EC, adverse events were defined as new or worsening of pre-existing symptoms. As this was a phase IV trial of medicines whose side effect and adverse event profiles are well described, we decided to record descriptions of adverse events but not to attribute causality during recruitment, though this would be possible at the end of the trial if needed. We informed the child's GP of a small group of adverse events that, although not defined as serious under the European legislation, might have implications for the child's future clinical care (see Appendix 19). The adverse events reported to the GP were:

- new onset of rash;
- angio-oedema;
- bronchospasm (or wheeze);
- bloody diarrhoea or haematuria.

In most instances, the child's parent would also be advised to consult their GP.

Serious adverse events

The trial complied with the various regulations overseeing and governing pharmacovigilance for investigational medicinal product trials.[61,85,86] An SOP was developed to ensure that serious adverse events (SAEs) were independently investigated and reported within required timeframes (Appendix 20). SAEs are defined by European legislation[61] as the development of an undesirable medical condition or the deterioration of an existing medical condition following or during exposure to an investigational medicinal product, whether or not considered causally related to that product, which results in one of the following:

- hospitalisation or prolongation of hospitalisation;
- immediately life-threatening illness;
- persistent or significant disability or incapacity; or
- death.

All SAEs were assessed for causality (Was it a reaction to a study or concomitant medicines?) and expectedness (Was the reaction a recognised adverse effect of the medication?). Depending on the answers to these questions, SAEs were classified as serious adverse reactions (SARs) or serious unexpected suspected adverse reactions (SUSARs). European regulations describe set time limits for the reporting of SARs and SUSARs depending on their outcome, and these were adhered to. In addition, the Trial Steering Committee (TSC) recommended that, in the case of all reported SAEs, participants' readiness to seek clinical advice from the NHS should be assessed, i.e. whether a participant's parent/guardian delayed or accelerated seeking clinical advice as a result of taking part in the trial. All initial and follow-up SAE documentation was reported to the trial Data Monitoring Safety Committee (DMSC), the TSC and the sponsor (NCCHTA). Any recommendations in response to SAE reports made by the DMSC and/or TSC were implemented. Annual safety reports, including details of any SAEs occurring within the year, were sent to the Bath Ethics Committee and the Medicines and Healthcare products Regulatory Agency (MHRA).

Outcomes

Primary outcomes

There were two primary outcomes:

1. the number of minutes without fever (below 37.2°C) in the 4 'efficacy' hours; and
2. the proportion of children scoring 'no discomfort' (normal) at 48 hours.

Secondary outcomes

Secondary outcomes were:

- the number of minutes from randomisation until the child's temperature first fell below the fever threshold of 37.2°C (known as 'fever clearance');
- the number of minutes spent without fever (temperature below 37.2°C) in the first 24 hours;
- the proportion of children scoring normal for discomfort, activity, appetite, sleep and mean temperature at 24 hours;
- the proportion of children scoring normal for discomfort, activity, appetite, sleep and mean temperature at 48 hours;
- the proportion of children scoring normal for discomfort, activity, appetite, sleep and mean temperature at day 5;

- adverse events; and
- costs to parents and the NHS compared with benefits as measured by the percentage of children 'recovered' at 48 hours and day 5.

Methods used to measure outcomes

Time without fever

The Omega precision temperature datalogger (OM-CP-RTDTEMP110; Omega Engineering Ltd, Manchester, UK) was used to measure and record the child's temperature every 30 seconds. This instrument, measuring approximately 5.5×4×1.5 cm, was placed 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 was attached by a short length of wire to a skin thermistor placed under the child's arm using skin-appropriate adhesive tape (see photograph in Appendix 21). The datalogger is accurate to within 0.05°C, with high resolution (the smallest detectable change in temperature distinguishable) to within 0.01°C.

The research nurse started the datalogger with a PDA to ensure that recording of times was consistent with the administration of the study medicines and the symptom diary (see Appendix 22 for the SOP). The research nurses also used an SOP to attach the datalogger to the child just prior to randomisation (Appendix 23). Parents were shown how to reattach the datalogger and were encouraged to keep it attached for the first 24 hours. They were asked to periodically check that the skin thermistor was in place and to make a note in the symptom diary of any known detachment. Output from the logger was exported in ASCII file format, compatible with most statistical software packages. The research nurses checked the output file, annotated the start and end times and exported the data for analysis.

Symptom diary

At the time of the study, there was no validated method available to measure fever-associated symptoms in children. Therefore, in order to measure the fever-associated symptoms, a symptom diary (Appendix 24) was devised for use by both the research nurses and the carers of randomised children. This was presented in such a way as to maximise ease of use yet minimise the risk of data loss, data errors and inconsistencies. Prospective recording of symptom diary entries is notoriously difficult to achieve, with studies commonly failing to report data due to the level of incompleteness, and various methods have been utilised to improve the yield of data.

Process of development

An initial version of the symptom diary was developed to include all the required variables, and this was presented to a number of parents with children in the trial age range for comments on content and presentation. Two families piloted completion of the symptom diary to help identify inconsistencies and impediments to successful use. From the feedback, a revised version of the symptom diary was resubmitted for comment and a final version created. Further amendment was subsequently required to force a disassociation between the recording of the time of medications and the timing of recording the child's discomfort level, as after the initial dose these, by definition, would not always coincide. To reinforce this, the times of the next due doses were written clearly on the front of the diary, reinforcing the dosing schedule differences between the two medicines. The symptom diary was adapted further, during the course of the trial, to maximise its user-friendliness. The symptom diary was a shared (professional and parent) document, demonstrating to parents its importance to the study team and the importance of parental input. Outcomes known to be important to parents were included as these were likely to have a significant impact on perception of symptom severity.

Variables recorded in the symptom diary

Temperature

The data from the dataloggers covered the first 24 hours and therefore addressed the primary outcome. In addition, axillary digital thermometry was used at 4, 16, 24 and 48 hours and day 5 as a back-up value in the event of datalogger failure/non-compliance.

Discomfort

This scale was based on behavioural pain scores and was specifically worded to promote consistency in response.[87] Other pain scoring methods, such as using face scales, are specific to the child, requiring a common state or pain source for between-child comparisons. Given the generic nature of the symptom being studied and the wide range of likely diagnoses leading to this, such specific scoring is less valuable than scales using a combination of more detailed recordings such as facial expression and response to stimuli. However, these tools were considered overly complicated for

use in this context. By ensuring that variables were relevant and easily understood, it was anticipated that parents' understanding and appropriate use would be optimal.

Activity, appetite and sleeping
Parental monitoring of a child's recovery is directly influenced by the child's activity levels at the time. A pyrexial child who is laughing and running around is less likely to receive close monitoring or antipyretic therapy than one who is inactive and uninterested in his or her surroundings. This may influence both antipyretic use and other symptom recording and was therefore included as a potential confounding variable. In addition to giving a measure of well-being, appetite may reflect the tolerability of the drugs in question and potential adverse effects. By including this variable in the symptom diary, there was no suggestion that this was an anticipated side effect, thus avoiding reporting bias. A child's sleep pattern is known to be important to parents and would assist in the interpretation of the data regarding subsequent or missed doses and the potential additional effects of combining drugs.

Medicine administration and other information
After the first doses of the two medicines, the administration pattern was directly controlled by the parents. To assist in the interpretation of symptom and temperature recordings after the first 4 hours, a detailed log was required of any study medicines given. Considerable effort was taken to simplify this aspect of symptom diary completion, with due dose times in the first 24 hours completed by the study nurse in advance and a space for parents left to indicate the actual time of dosing. Whilst allowing for presenting symptoms and initial diagnosis, it was important to have documented any events or symptoms that may reflect unwanted drug effects. Health service contact was documented to be confident that parents did not delay seeking medical advice, to the possible detriment of their child's health, through inclusion in the study. In addition, deviance from the protocol through external influences or advice could be documented.

Using the symptom diary
The child's name, carer's name, enrolment and randomisation number, child's diagnosis and symptoms, any adverse events, other cooling interventions and health service contacts were recorded on one side. Dose administration timings, standard digital axillary thermometry, discomfort, activity, appetite and sleep were recorded on another side. Discomfort, activity, appetite and sleep were measured using ordered categorical scales. Temperature was recorded to the nearest 0.1°C using the O-Temp III thermometer, (OMRON, UK) supplied by the study. The symptom diary was explained to the parents in a standardised manner (see Appendix 25). The research nurse and parents completed the first set of entries on the symptom diary as the first dose of study medicines were given. This was to ensure that parents/carers were taught how to complete the symptom diary, what information to include in each section and that parents were confident using it. Parents were instructed to enter the value representing the child's state at the time of recording, or during the previous 10 minutes if this was more representative of their state at the time. The symptom diary was completed at 2, 4 and 16 hours after the first administration of study medicines, then 8-hourly until 48 hours had elapsed. The research nurse supported the completion at the 24- and 48-hour visits, validating their perception of the child's state with the parent's. This provided a crude, readily applied, mechanism for ensuring the validity of between-child comparisons for data not recorded by the research nurse.

Sample size

In the original protocol the target difference for the time spent without fever in the first 4 hours was 30 minutes (with an assumed standard deviation of 80 minutes[82]), and that for the binary outcome of scoring 'normal' on the discomfort scale at 48 hours was 60% versus 75% [equivalent to an odds ratio (OR) of 2.0]. To detect the latter comparison with 90% power at a two-sided alpha of 0.027 (allowing for multiple comparisons between the combined therapy and each of the two single-therapy groups[88]) required a total sample size of 747. Recruitment difficulties led to the alternative recruitment methods, namely the 'remote' and 'community' approaches, and a reduced achievable target sample size. Using a revised standard deviation of 50 minutes based on an analysis of the first 50 outcome measures obtained irrespective of randomisation group, a sample size of 180 conferred 80% power to maintain the original target difference for time without fever with the same two-sided alpha of 0.027. Moreover, attrition and missing thermometry data were at that point both known to be minimal. However, sensitivity to differences in the binary discomfort outcome was reduced considerably, with ORs of just over 4 now

detectable with 80% power. The trial was therefore not adequately powered to detect either the original target OR for binary outcomes or, indeed, ORs considered to be plausible.

Randomisation

Sequence generation

The randomisation sequence was generated via a remote, automated telephone service provided by the Health Services Research Unit at the University of Aberdeen. Calls were made to the service via a freephone number. Research nurses responded to a series of questions to confirm the child's eligibility. Eligible children were randomised with a block size of six and stratified according to five minimisation variables, selected on their potential to modify the intervention effectiveness: age (6–17 months versus 18–71 months), fever severity (37.8–38.9°C versus 39–41°C), symptom diary discomfort category ('normal'/'not quite normal' versus 'some distress'/'very distressed'), prior fever duration (≤ 24 hours versus > 24 hours) and current antibiotic use (yes versus no). Responses were made by either speaking or by keying numbers on the telephone keypad.

Allocation concealment

The study medicines were provided by Pfizer Ltd and sent to DHP Ltd, a manufacturer of clinical trials medicines. DHP was aware of the randomisation procedure and the company was asked to supply the study medicines to the trial fully concealed. The active and placebo treatments were decanted into medicine bottles by DHP and shipped to the pharmacy of the United Bristol Hospitals Trust (UBHT). The study medicines were stored in the pharmacy until research nurses required them for randomisation. Pharmacy staff were unaware of treatment allocation.

Study medicines were provided in a white cardboard pack containing the two bottles, one of paracetamol/placebo and one of ibuprofen/placebo suspensions. The identity of the next treatment allocation was concealed from research nurses by the fact that they carried at least one unopened box of six medicine packs during any randomisation visit. Each research nurse was allocated a unique trial identity code for the telephone randomisation system and the system was aware of the unopened medicine packs held by each nurse at any one time. Randomisation could not occur if a research nurse did not have the minimum number of packs logged with the system. After inputting participant information required for randomisation, the research nurses were informed which pack to give to the child. The system also instructed the research nurse which medicine should be given first (determined randomly), the volume for each medicine, rounded down to the nearest 0.5 ml, and a randomisation number. The randomisation number was unique to the medicine pack in the research nurse's possession.

Implementation

Once a child had been determined to be eligible, the research nurse obtained written informed consent from the parent or legal guardian. The children were deemed to be too young to be competent to give consent. Nevertheless, the co-operation of the child was necessary for successful participation and so a child-centred approach to recruitment was taken, taking care to obtain the child's 'assent'. The research nurse then enrolled the child and assigned a unique enrolment number. This enrolment number was used as the child's identification number throughout the study.

Blinding

The parents, principal investigator, trial co-ordinator, research nurses and project administrator were all blinded to the study medicines allocated to randomised children throughout the recruitment and analysis periods. All external members (TSC, DMSC) of the trial were also blinded. The trial statistician was aware of group identity but remained blinded to the treatment allocation.

Unblinding the study medicines

Unblinding of the allocated treatments was available for clinicians responsible for trial children, and this was available 24 hours a day. Requests for unblinding were accepted only from such clinicians and the treatment code broken only in medical situations in which management of the child necessitated knowledge of the treatment. At the baseline visit, parents of children were given a card with information about unblinding procedures. In addition, the participant's GP was also faxed a letter detailing unblinding procedures as soon as possible after randomisation.

The UBHT pharmacy was responsible for the unblinding process. SOPs were used by the

pharmacy (Appendix 26) and the trial team to ensure that the process of unblinding was consistent (Appendix 27). Along with storing the study medicines, the pharmacy also kept two sets of unblinding codes, with scratch-off sections for each randomisation number, revealing the treatment allocated. One set of the unblinding cards was kept in the pharmacy (for normal working hours) and a second set in the on-call pharmacist's bag (for out-of-hours). A third set was kept in the trial investigator site file in the trial office. In the event of unblinding, the fewest possible number of people were informed of treatment allocation and parents were encouraged to continue trial participation.

Statistical methods

Primary analyses

All data were analysed using STATA. Descriptive statistics were obtained for the three randomisation groups to characterise recruited children and to assess baseline comparability. In accordance with CONSORT guidelines,[89] all comparative analyses were conducted on an intention-to-treat basis. The primary comparisons were the combined therapy versus each of the two single treatments, with Dunnett's adjustment for multiple comparisons ($\alpha = 0.027$).[88] The comparison between the single treatments was a secondary comparison, using the correspondingly more conservative Tukey adjustment.[88] All comparisons were conducted using linear or logistic regression depending on the outcome variable and were adjusted for minimisation variables as binary factors, apart from baseline temperature as a continuous variable and baseline discomfort in four categories (see Table 4). Regression models for time without fever were conducted using the proportion of valid time (temperatures between 33°C and 45°C) under the fever threshold as the outcome variable, with results converted into hours or minutes for presentational purposes. These models were weighted according to the number of time points in the relevant time interval contributing valid data on temperature.

Secondary analyses

All secondary outcome comparisons were analysed using linear or logistic regression depending on the outcome variable. Further secondary analyses included additional adjustment in these regression models for any factors demonstrating potentially influential baseline imbalance, and pre-planned exploratory subgroup analyses of any differential effects of the combined compared with single therapies across the following categories of children: age (6–17 months versus 18–71 months), fever severity (37.8–38.9°C versus 39–41°C), symptom diary discomfort category ('normal'/'not quite normal' versus 'some distress'/'very distressed'), current antibiotic use (yes versus no) and diagnosis of otitis media (yes versus no).

Mean temperature by treatment group

To present the time without fever data graphically, we produced a graph showing children's mean temperatures by treatment group. These were calculated every 15 minutes from recordings within the valid temperature range (i.e. between 33°C and 45°C).

Numbers needed to treat

We chose not to present the time without fever data as a number needed to treat (NNT) for two reasons. First, because outcome data need to be dichotomised in order to produce a NNT, we would have had to identify a 'minimum treatment effect' considered worthwhile, expressed as the absolute number of minutes without fever in the first 4 and 24 hours. This could not have been the same as our target difference in time spent without fever between treatments (30 minutes in the first 4 hours) and therefore would mean that the data were being presented in a different manner to the primary outcome. Also, expressing NNTs in the absence of a clear 'usual treatment' group is awkward, e.g. 'the number of children in whom ibuprofen should be added to paracetamol for one child to benefit'.

Economic evaluation

Study design

We adopted two perspectives for the economic evaluation: the NHS, and the parents/carers. We included all relevant resources used during the 5 days following randomisation. Costs to the NHS included practice-based consultations with a doctor or nurse; telephone consultations; visits to a WIC; contacts with NHS Direct; out-of-hours care; visits to an accident and emergency department; inpatient hospital care; ambulance use; and prescribed medication. From the perspective of the parents and carers, the relevant direct costs included travel to healthcare facilities for visits associated with the child's fever; over-the counter

medication purchased; extra care for dependants required because of the child's illness; and loss of earnings as a result of the child's illness.

The economic analysis was conducted at 48 hours and at 5 days. A range of benefits was measured at these time points, including temperature, discomfort, activity, appetite and sleep. In order to retain maximum information about cost and outcomes, we conducted a cost–consequences analysis, comparing cost from both perspectives with all outcomes at both time points. We also combined the outcomes to provide an indication of whether the child had 'recovered' at 48 hours. This was based on parents reporting that the child was 'normal' with respect to discomfort, activity, appetite, and sleep and having a temperature less than 37.2°C. Thus 'recovered' is, in effect, 'returned to normal for that child'. We used this outcome in a cost-effectiveness analysis at 48 hours to compare cost with the proportion of children who had 'returned to normal for that child' in each group.

Data collection and unit costs

Participant data on resource use were collected from the parents during the 5 days following randomisation. The research nurse collected data on resource use during scheduled contacts; face-to-face at 48 hours and by telephone at day 5. The unit costs are given in Table 3. Primary care contacts were valued as described by Curtis and Netten,[90] and we used the NHS tariff[91] and Department of Health reference costs[92] for secondary care and ambulance services. Visits to the WIC and contact with NHS Direct were valued using information from published national evaluations.[93,94] For prescribed medication, we used costs reported in the British National Formulary,[95] and the Automobile Association schedule of motoring costs[96] was used for travel by car. Parents who reported loss of income were asked how many days of work had been affected, and this was valued using a national wage rate.[97] We took a realistic stance on the cost of the study medicines and costed as though parents had bought these over the counter. We costed these medicines according to the dosing regimen in the study, i.e. dosing by weight rather than by age. All resources were valued in pounds sterling at 2006 prices, using an appropriate inflation index where necessary.[90]

TABLE 3 Resources and unit costs used for the economic evaluation

	Unit cost (£)
Primary care[90]	
General practitioner	
At the surgery	21.00
Telephone	23.00
Practice nurse	8.00
Health visitor	24.83
Out-of-hours[98]	
Nurse telephone	12.00
Doctor telephone	34.50
Doctor face-to-face	31.50
Walk-in centre[93]	29.81
NHS Direct[94]	18.55
Accident and emergency[91]	71.00
Inpatient stays[91]	
Pneumonia	1063.00
Bronchiolitis URTI	942.00
Upper respiratory tract infection	550.00
Ambulance[92]	132.90
Study medicines[a]	
Paracetamol (Calpol 100 ml)	2.45
Ibuprofen (Neurofen 100 ml)	4.13
Mileage[96]	0.49
Lost income per day[97]	94.80

a Mean cost reported by parents buying these over the counter between 48 hours and 5 days.

Data analysis

All analyses were carried out using Microsoft EXCEL and STATA 9. We estimated frequencies of resource use by patient group and mean cost per patient, by group. We excluded inpatient care and use of ambulances in the base-case analysis, as these are unusual in a primary care population and likely to affect the results in an unrepresentative way. NHS data were complete for 154 (99%) children at 48 hours and 150 (96%) at day 5. Personal costs were reported by 143 (92%) parents at 48 hours and 130 (83%) at day 5. Bootstrapping (1000 replicates) was used to estimate cost-effectiveness planes and cost-effectiveness acceptability curves to indicate the

level of uncertainty around the point estimates of the incremental cost-effectiveness ratios. It was not necessary to discount the costs and outcomes, as the time horizon of the study was 5 days.

Sensitivity analysis

We tested the robustness of our results against three possible areas of subjectivity. First, we re-estimated the cost per patient from both perspectives if the study medicines had been prescribed rather than purchased over the counter. Second, we investigated the effect on the results if dosing had been by age rather than weight. Third, we estimated the cost of hospitalisations.

Qualitative process study

Study objective 3 was to use qualitative methods to optimise the trial process and explore parents' beliefs about the use of antipyretic medicines. It was our original intention that the trial co-ordinator would conduct these interviews once the trial was successfully recruiting. However, recruitment remained problematic, requiring the addition of the remote and community methods, and diverting resources away from the qualitative studies.

To address the qualitative aspect of the trial's objectives, at least in part, the PITCH team collaborated with a Medical Research Council (MRC)-funded study called QUARTET (Qualitative Research to Improve Recruitment to Randomised Controlled Trials) run at the University of Bristol. The aim of this study was to investigate whether qualitative research methods could be used to increase trial recruitment rates and simultaneously ensure that children receive a well-balanced explanation of the trial, thereby improving the trial process. Specifically, QUARTET focused on how recruiters provided verbal information about the trial to potential children and, from their collaboration with multiple trials, developed general guidelines for good practice. In relation to the PITCH trial, the QUARTET team focused on how the research nurses provided information to the children's parents.

The data collected from the QUARTET team included information collected during face-to-face interviews with some members of the trial team, namely the principal investigator, the trial co-ordinator and four research nurses. Ten research nurse–parent telephone calls about trial participation, involving three research nurses, were recorded, with parental consent. Finally, observations of local recruitment at two GP practices with two research nurses were also recorded. The QUARTET team analysed these data using qualitative methods in conjunction with up-to-date recruitment CONSORT figures. At two points during the recruitment period, the QUARTET team provided feedback based on these analyses to inform the trial team.

Feedback to the trial team first occurred in November 2006, 22 months into the recruitment period, and overall the feedback was highly positive. The investigators found that the team members were competent, hard-working and strongly committed to seeing that the trial completed successfully, and that they believed that the trial aims were important both clinically and socially. The investigators recognised that, within the team, low recruitment rates were a cause for concern and that proactive strategies to address this had occurred. Analysis of the recruitment figures found that in a large proportion of cases the children of parents approached for possible inclusion were ineligible from the outset because of the absence of fever. It was noted that this difficulty was being countered by employing multiple recruitment strategies. The rate of refusal to participate among parents whose children had a fever and were assumed to be eligible on other criteria was lower. The report concluded that it was encouraging to note that only a minority of 'remote' parents decided against participating after being contacted by a study nurse about the trial, possibly due to the endorsement of the trial participation by the child's clinician. Within the trial team, the QUARTET investigators found that the research nurses reflected regularly on their experiences in an effort to communicate the trial information to parents effectively. It was clear from the recordings of recruiter–parent telephone conversations that they implemented good practice; they provided a balanced explanation of the trial, checks to see how parents felt about the trial, addressed concerns and possible refusals and were approachable and friendly. The QUARTET team recommended that recruiters approach all possible parents, irrespective of previous disappointing experiences with certain groups. It was also observed that asking parents directly to participate was within the rights of the team but, similarly, it was within the parents' rights to decline if asked. These recommendations were welcomed by the trial team, discussed and implemented.

The QUARTET team organised a feedback workshop in April 2007 to suggest ways in which the research nurses could fine-tune their practice for the last month of recruitment. The final feedback to the trial occurred in May 2007, detailing the feedback from the workshop and an update on the interim report. Finally, the research nurses' perspectives on involvement with QUARTET was also reported. Again, overall the investigators found that the research nurses were dedicated, hard-working and committed to the success of the trial. They commented that all the research nurses were effective communicators and no substantive problems with information provision to parents were found. The workshop addressed the minor issues previously identified, namely making decisions about parents' willingness to participate and the issue of not directly asking parents to participate. Further minor issues were identified, for example sympathising with parents and judging whether to make a home visit to potentially eligible children. Examples of good practice were also identified, as was implementation of the previous report's recommendations. Finally, it was reported that the research nurses and other trial members felt that their interaction with the QUARTET study had made a difference and that the reflection process, feedback, analysis and discussions generated from hearing their parent–recruiter recordings during the workshop had helped.

Natural history of fever

As with the qualitative studies, it had been our intention to recruit febrile children whose parents did not want to use the PITCH study medicines into an observational study to investigate symptom duration and complications. Full research governance and ethics approvals were received for this study, but, due to the trial recruitment challenges, we prioritised resources to the trial.

Nonetheless, we will present the data from all children in the study to provide information regarding symptom duration, treatments and complications. Symptom definitions such as 'fever' or 'cough' are preferred to disease definitions in the research of acute conditions in primary care,[100] because of the inconsistency with which disease labels are used.[101] For consistency, we used the same definition of the 'recovered child' as with the economic analyses (see above), i.e. parents reporting that the child was 'normal' with respect to discomfort, activity, appetite and sleep and having a temperature less than 37.2°C or 'returned to normal for that child'. In addition, we recorded the number of children treated with antibiotics subsequent to randomisation and the number admitted to hospital.

Data management

Data collection

All baseline, 24-hour, 48-hour and day 5 data were collected in the participant's CRF, which was identified by their enrolment and randomisation numbers. The research nurses collected all written data and clarified any queries with parents prior to the child's exit from the trial. Time without fever data (via the datalogger) were retrieved at the 24-hour visit and downloaded using specialist Omega software by the research nurses as soon as possible after the visit. It was securely saved and a back-up copy taken.

Data entry

The project administrators entered baseline, follow-up and symptom diary data into the trial ACCESS database. This was set up so that each section of the CRF was replicated as ACCESS forms for ease of data entry. Data entry was conducted throughout the trial. A 'query sheet' was created for each CRF detailing any aspect of data about which the administrators were uncertain, with an associated SOP (see Appendix 28). The trial co-ordinator and research nurses periodically checked the query sheets and resolved problems so that data could be entered accurately.

Data quality assurance

Data collection deviations

A number of quality assurance processes were developed throughout the trial. Any data collection deviations from the standard methods were documented by the research nurses. The trial co-ordinator reviewed these and clarified description of the deviations and resultant activity. Review of data collection deviations was carried out monthly for participant and trial implications and processes were put in place to minimise the risk of these deviations recurring. The TSC reviewed all deviations.

Data entry quality checks

Data entry was completed by three administrators. To ensure that data were entered accurately and consistently by the three administrators, an SOP

was developed (see Appendix 29). Any queries that the administrators came across while entering data were logged on the data query sheet to bring to the trial co-ordinator's attention for resolution. These logged sheets were stored within the CRF.

A process of double entry was constructed to assess agreement and correct primary outcome disagreements. Two administrators entered a random selection of 15 CRFs. All baseline data as well as date of birth, date of study entry, gender, age, temperature, time temperature taken, fever duration, current antibiotic use, nurse's hydration assessment, baseline discomfort scale data and 48-hour discomfort levels were re-entered and checked against the original CRF.

Data storage

According to MRC and NHS guidelines, CRF data are stored in locked offices and the CRFs scanned for electronic archiving until participating children have reached the age of 21. Thermometry data are kept on a secure server.

Chapter 3
Results

Participants

Letters were sent from the PITCH study office to 68 primary care sites in the Bristol area inviting them to participate in local and/or remote recruitment. Replies were received from 44 sites and those that expressed were sent an information pack was sent. A total of 35 sites agreed to take part in local or remote recruitment. These sites consisted of one WIC, one children's emergency department, the Avon, Gloucester and Wiltshire NHS Direct, two GP out-of-hours co-operatives and 30 general practices. The first participant was recruited on 17 January 2005 and the last participant completed the study on the 22 May 2007. Early recruitment analysis showed that recruiting children locally yielded a low randomisation rate. Therefore, the remote and community strategies were started in May 2005 and May 2006 respectively. All children randomised to the study were within the correct age range, pyrexial and met all other inclusion criteria. No children withdrew from the study.

The flow of children through the study is shown in Figure 5. It shows the three recruitment methods, the overall numbers ineligible, the numbers for whom eligibility was unknown and that 156 children were randomised. It also shows the very low data attrition rates with respect to the two primary outcomes, time without fever and discomfort.

Local recruitment

Figure 6 shows that total of 3746 research nurse invitations were issued during local recruitment. Of these, 3042 children were known to be ineligible (I), mainly because they were not sufficiently pyrexial (2669). Forty-one potentially eligible children were admitted to hospital, 30 children had parents who did not have a sufficient understanding of English to give informed consent and seven children were living outside the Bristol area. Other potential children were missed because their parents were called through to visit their GP while research nurses were giving information to other parents in the waiting room or because they left the site before the research nurse could make contact. In these cases eligibility was unknown (U). Of the 1288 potential children who were pyrexial, 417 potential children declined. The principal reasons for decline were the commitment required being too great (163) and concerns about the study medicines (79), usually because the parent wanted to use both medicines. Forty-six children had an eligibility status of unknown (U) as they were missed at the site. The total number of children randomised to the trial via local recruitment was 46.

Remote recruitment

Figure 7 shows that a total of 641 children were referred from sites by fax during the course of the study. Of these, 259 children were excluded on the basis that they were not sufficiently pyrexial and 83 children were excluded as they failed to meet other inclusion criteria, including 17 children who were outside the age range of the study, 11 children who were admitted to hospital, five children who had cardiac disease and three children who had renal disease. The study team was unable to make contact with 77 children, and parents of 136 children declined to take part in the study when contacted. The main reason cited for declining to take part was the study time/commitment involved in taking part in the trial and that parents wanted to administer both medicines to children. A total of 83 children were randomised via remote recruitment.

Community recruitment

Figure 8 shows that a total of 128 calls were received via the community hotline. Of children referred in this way, 37 were excluded because they were apyrexial or were missed due to the study team being unable to make contact. Following the triage process and a home visit, a further 36 children were excluded on the basis of not being sufficiently pyrexial. Seven children declined due to bad timing/study commitment (4) or because of concerns about the study medicines (3). In the case of the last three children, the parents declined to participate because they wanted to use both paracetamol and ibuprofen. Overall, 27 children were randomised via community recruitment.

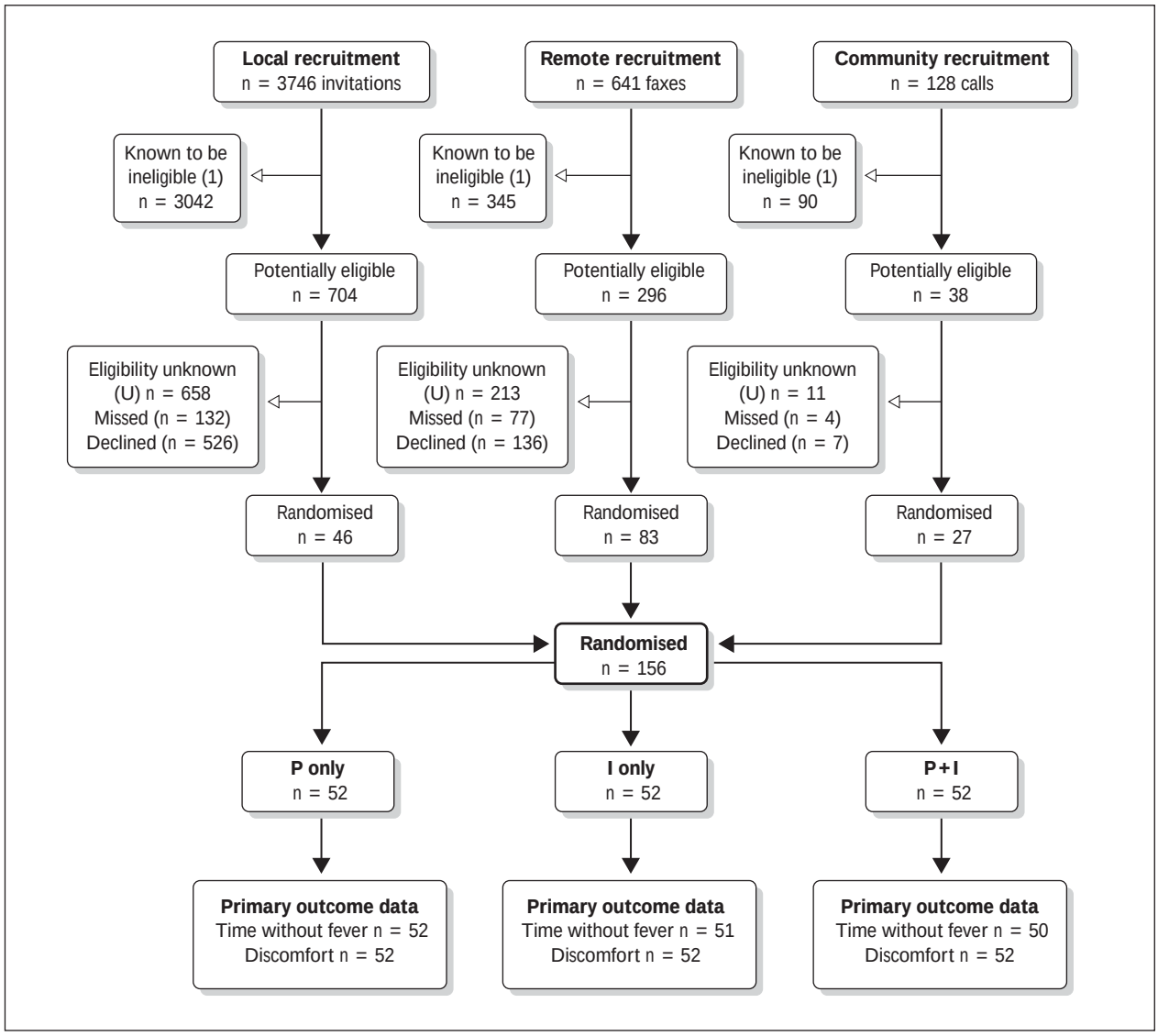


FIGURE 5 Overall flow of children through the study.

Numbers analysed – sample size

A total of 156 children were recruited to the trial. Numbers analysed in each group for the time without fever outcome were 52, 51 and 50 in the paracetamol, ibuprofen and combined medicine groups respectively. The number analysed in each group for the discomfort primary outcome was 52. Thus, children were omitted from analyses only if none of the data required were available, and as these were so few in number the influence of missing data on the intention-to-treat analyses was negligible. For example, where the logger was faulty, or the temperature probe had dislodged from the child's underarm and had recorded implausibly high or low temperatures (as discussed in Chapter 4), the readings were excluded from the analysis.

Baseline data

The three treatment groups had similar baseline characteristics, as shown in Table 4. The majority of the children included in the study were of white ethnicity. Children taking part in the study were of average weight for their age, and there were similar numbers of children in each age category. The majority of children were not on antibiotic treatment at the baseline visit, had not received ibuprofen in the 8 hours prior to randomisation,

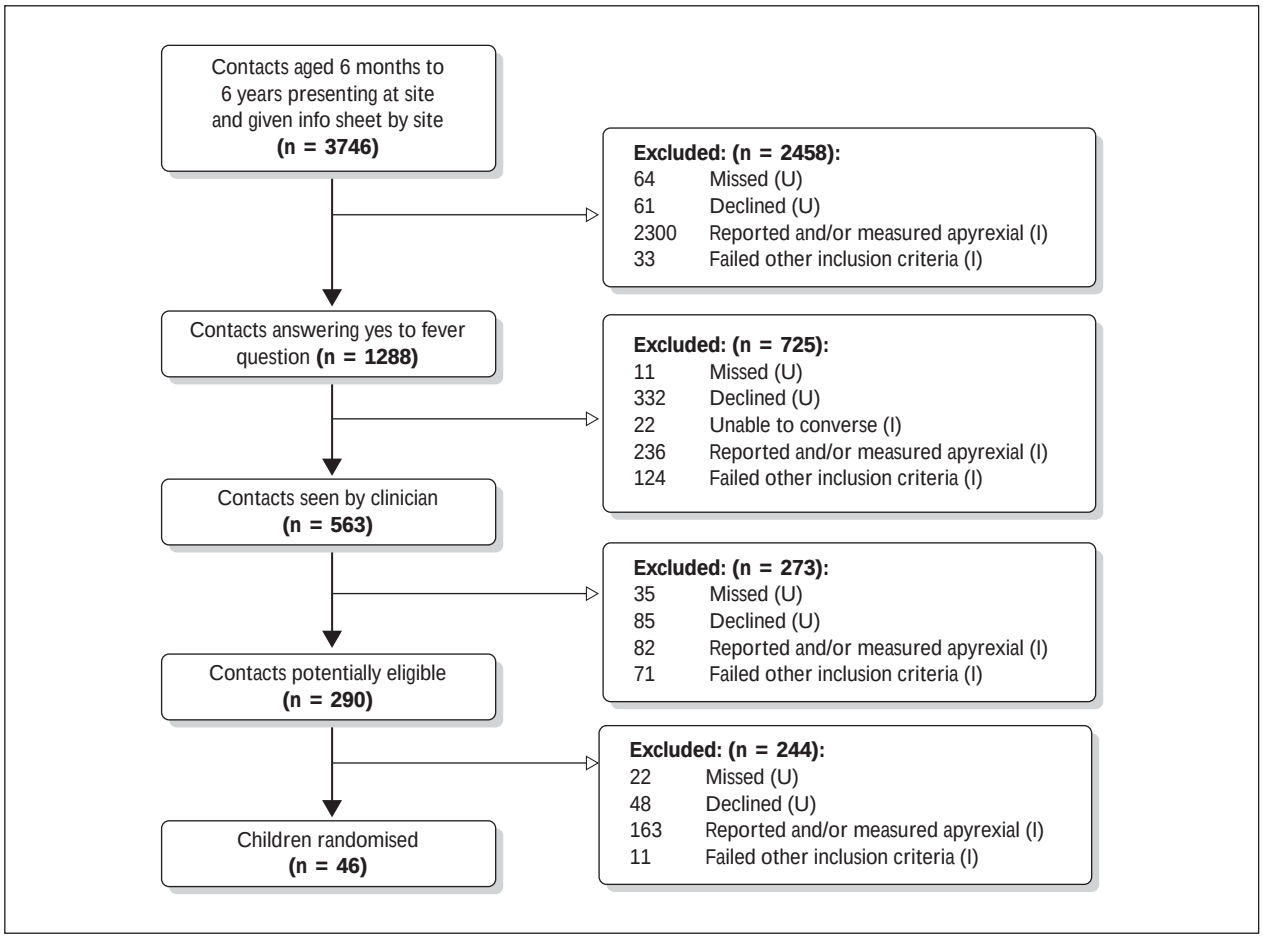


FIGURE 6 Flow of children through local recruitment. U, eligibility unknown; I, ineligible.

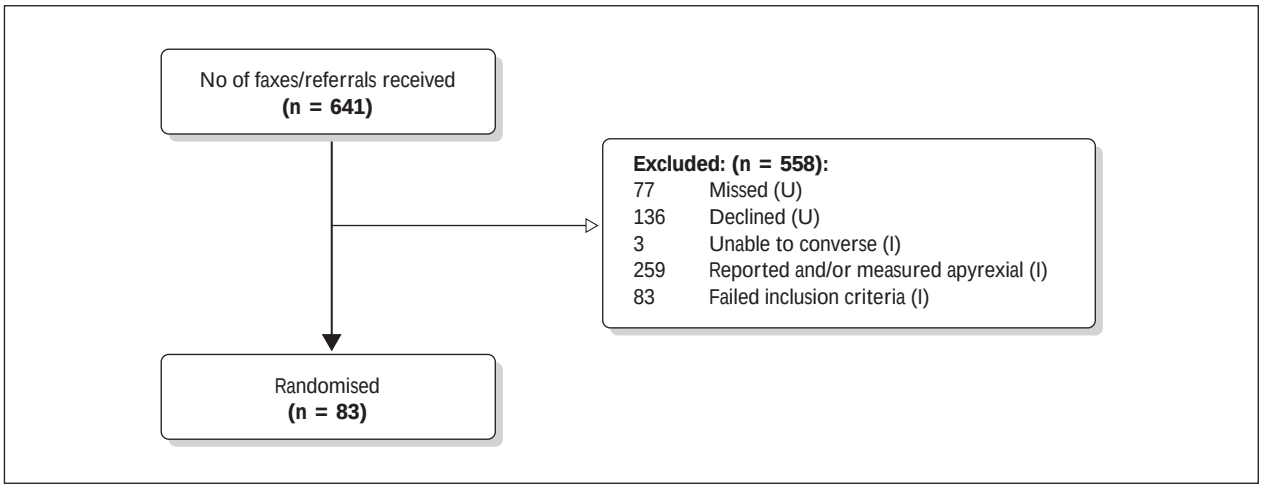


FIGURE 7 Flow of children through remote recruitment. U, eligibility unknown; I, ineligible.

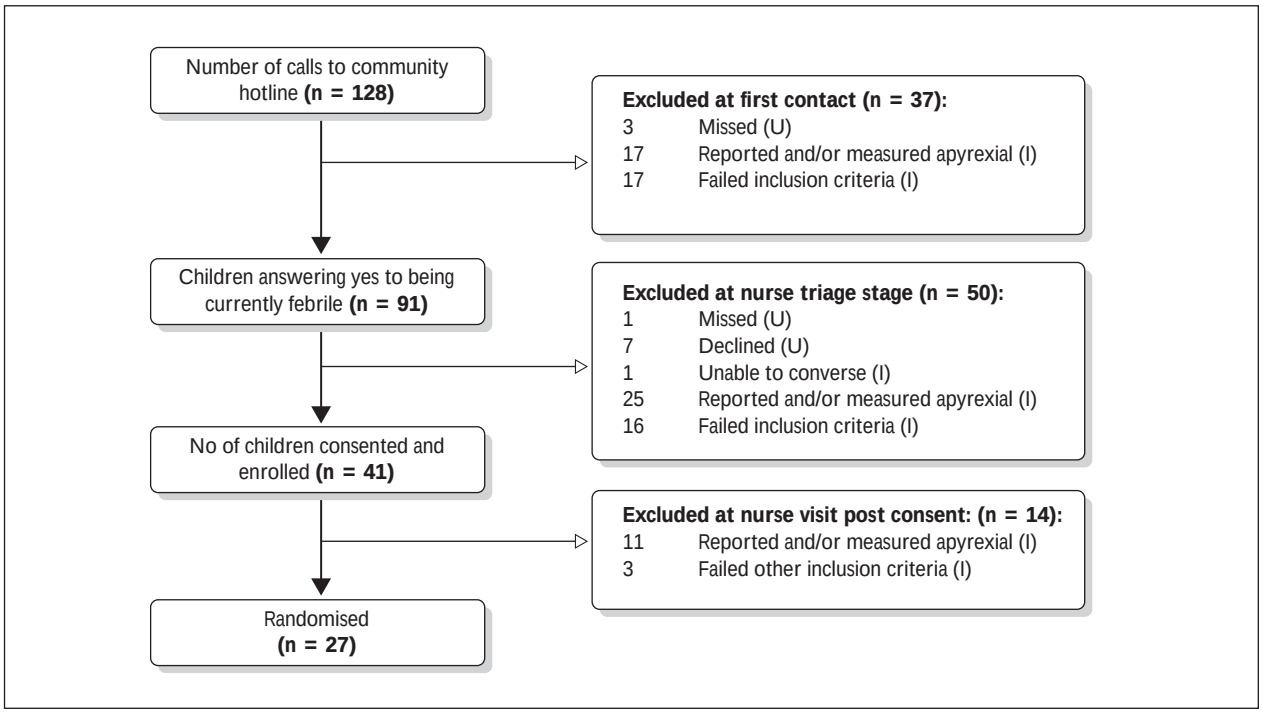


FIGURE 8 Flow of children through community recruitment. U, eligibility unknown; I, ineligible.

had been pyrexial for over 24 hours and had not had a previous febrile convulsion. Around one-third of children (equally distributed across treatment arms) had received paracetamol in the 4–6 hours prior to randomisation. Most children were recorded as having some discomfort, or disruption to their activity, sleep or appetite. At baseline, the proportion of children with a discomfort level of 'not quite normal' was 60%, 52% and 58% in the paracetamol, ibuprofen and paracetamol and ibuprofen groups respectively. Similarly, 34%, 35% and 27% of children in the paracetamol, ibuprofen and combined treatment group, respectively, reported discomfort levels of 'some pain/distress'. The potentially influential between-group differences were gender, recruitment method and baseline activity. Although we thought it unlikely they would greatly influence the primary comparisons, we controlled for them in secondary analyses.

Primary outcomes

Time without fever

The median time between randomisation and giving the first dose of study drug was 8 minutes for paracetamol plus ibuprofen and 9 minutes for paracetamol and for ibuprofen. For the primary outcome of time without fever in the first 4 hours, the mean number of valid minutes (temperature > 33°C and < 45°C) for paracetamol, ibuprofen and both medicine groups was 219, 211 and 202 respectively. Children receiving both medicines spent longer under the fever threshold than those given paracetamol (171 minutes compared with 116 minutes; Table 5). Similarly, children in the ibuprofen treatment group spent longer under the fever threshold than those allocated to the paracetamol treatment group (157 minutes compared with 116 minutes; Table 5). Table 6 shows the comparative analyses of the primary outcome data. It shows that in the first 4 hours children given both medicines were apyrexial for about 1 hour longer than those given paracetamol ($p < 0.001$). Table 6 also shows strong evidence of a benefit for ibuprofen compared with paracetamol ($p < 0.001$), with about 40 additional minutes spent without fever. Moreover, both point estimates exceed the 30-minute target difference, as does the lower confidence limit for the primary comparison.

Discomfort at 48 hours

Table 5 shows that there was no obvious difference in discomfort at the primary 48-hour end point. By this time, the majority of the children had recovered, with 65% (34), 71% (37) and 69% (36)

TABLE 4 Baseline characteristics

Baseline characteristic	Paracetamol (n = 52)	Ibuprofen (n = 52)	Paracetamol and ibuprofen (n = 52)
Gender			
Male	26 (50%)	37 (71%)	25 (48%)
Female	26 (50%)	15 (29%)	27 (52%)
Weight (kg)	13.04±4.16	13.43±3.91	12.63±3.30
Age (months)	28.70±17.69	28.09±17.42	25.06±13.36
Age[a]			
6–17 months	20 (38%)	18 (35%)	19 (37%)
18–71 months	32 (62%)	34 (65%)	33 (63%)
Baseline temperature (°C)	38.60 ± 0.56	38.58 ± 0.56	38.56 ± 0.60
Temperature (°C)[a]			
37.8–38.9	37 (71%)	37 (71%)	39 (75%)
39–41	15 (29%)	15 (29%)	13 (25%)
Discomfort[a]			
'No discomfort'	3 (6%)	5 (9%)	5 (9%)
'Not quite normal'	31 (60%)	27 (52%)	30 (58%)
'Some pain/distress'	18 (34%)	18 (35%)	14 (27%)
'Crying/very distressed'	0 (0%)	2 (4%)	3 (6%)
Fever duration[a]			
≤24 hours	18 (35%)	19 (37%)	19 (37%)
> 24 hours	34 (65%)	33 (63%)	33 (63%)
Antibiotic use[a]			
Yes	14 (27%)	15 (29%)	17 (33%)
No	38 (73%)	37 (71%)	35 (67%)
Paracetamol use 4–6 hours prior to randomisation			
Yes	20 (38%)	17 (33%)	20 (38%)
No	32 (62%)	35 (67%)	32 (62%)
Ibuprofen use 6 to 8 hours prior to randomisation			
Yes	4 (8%)	2 (4%)	3 (6%)
No	48 (92%)	50 (96%)	49 (94%)
Activity			
'Normal'	3 (6%)	4 (8%)	4 (8%)
'Quiet longer than usual'	12 (23%)	18 (35%)	23 (45%)
'Hardly moving about'	31 (60%)	19 (36%)	19 (36%)
'Not moving about willingly'	6 (11%)	11 (21%)	6 (11%)
Appetite			
'Normal'	5 (10%)	3 (6%)	4 (8%)
'Eating less than normal'	12 (23%)	14 (27%	10 (19%)
'Eating much less than normal'	35 (67%)	33 (63%)	36 (69%)
'Vomiting/refusing food/drink'	0 (0%)	2 (4%)	2 (4%)

TABLE 4 Baseline characteristics (continued)

Baseline characteristic	Paracetamol (n = 52)	Ibuprofen (n = 52)	Paracetamol and ibuprofen (n = 52)
Sleep			
'Normal'	8 (15%)	3 (6%)	4 (8%)
'More than usual'	20 (38%)	21 (40%)	20 (38%)
'more disturbed than usual'	9 (17%)	15 (29%)	10 (19%)
'A lot more disturbed than usual'	15 (29%)	13 (25%)	18 (35%)
Recruitment method			
Local	17 (33%)	18 (35%)	10 (19%)
Remote	27 (52%)	26 (50%)	31 (60%)
Community	8 (15%)	8 (15%)	11 (21%)
Ethnicity			
White	47 (90%)	7 (90%)	44 (85%)
Other	5 (10%)	5 (10%)	8 (15%)
Diagnosis			
Otitis media	7 (14%)	11 (20%)	8 (15%)
Respiratory tract infection	12 (23%)	15 (28%)	17 (33%)
Non-specific viral illness	21 (40%)	20 (37%)	16 (31%)
Other	12 (23%)	8 (15%)	11 (21%)
Previous febrile convulsion			
Yes	2 (4%)	1 (2%)	2 (4%)
No	50 (96%)	51 (98%)	50 (96%)
Asthma			
Yes	9 (17%)	4 (8%)	6 (12%)
No	43 (83%)	48 (92%)	46 (88%)

a Minimisation criteria.

being recorded as having no discomfort or as 'normal' for discomfort in paracetamol, ibuprofen and both medicine groups respectively. Table 6 shows that there was no difference between treatment groups, although the low power is reflected in the wide confidence limits and high p-values when both treatments were compared with paracetamol alone (0.49–3.56, $p > 0.7$) and ibuprofen alone (0.32–2.43, $p > 0.8$), and ibuprofen alone was compared with paracetamol alone (0.53–4.26, $p > 0.5$). There was a suggestion that the proportion of children reported as being 'normal' was higher in the ibuprofen group than in the paracetamol group [71% (37) compared with 65% (34)], but again this difference could have occurred by chance.

Secondary outcomes

Time until first apyrexial (fever clearance)

Table 5 shows that the pattern of times until the fever was first cleared is consistent with the primary time without fever outcome. It took over 1 hour (71 minutes) for the temperature of children given paracetamol to first fall below 37.2°C compared with 45 minutes for children given both medicines. Table 7 shows that, on average, children in the paracetamol and ibuprofen group became apyrexial 24 minutes faster than children in the paracetamol group ($p = 0.025$), and that children given ibuprofen became apyrexial 27 minutes faster than those given paracetamol ($p = 0.015$).

TABLE 5 Descriptive statistics of the outcomes: mean (standard deviation, SD) or number (percentage)

Outcome	Paracetamol (n = 52)	Ibuprofen (n = 52)	Paracetamol and ibuprofen (n = 52)
Primary outcomes			
Time without fever in first 4 hours[a]	116.2 (65.0)	157.2 (57.6)	171.1 (40.8)
No discomfort at 48 hours[b]	34 (65%)	37 (71%)	36 (69%)
Secondary outcomes < 24 hours			
Time until first fever clearance (minutes)[c]	71.0 (69.1)	42.2 (33.5)	45.5 (34.3)
Time without fever in first 24 hours[a]	940.3 (362.9)	1055.5 (328.3)	1217.4 (237.6)
No discomfort[b]	22 (44%)	36 (69%)	29 (56%)
Normal activity[b]	20 (40%)	20 (58%)	23 (48%)
Normal appetite[b]	10 (21%)	14 (27%)	14 (29%)
Normal sleep[b]	17 (37%)	13 (50%)	20 (37%)
Recovered child[d]	4 (8%)	9 (17%)	7 (13%)
Secondary outcomes at 48 hours			
Mean temperature (°C)[e]	36.4 (0.89)	36.4 (0.85)	36.6 (1.01)
Normal activity[b]	31 (60%)	37 (73%)	28 (54%)
Normal appetite[b]	21 (41%)	22 (44%)	21 (41%)
Normal sleep[b]	27 (52%)	31 (61%)	25 (48%)
Recovered child[d]	15 (29%)	14 (27%)	12 (23%)
Secondary outcomes at day 5			
Mean temperature (°C)[f]	36.2 (0.93)	36.1 (0.78)	36.0 (0.66)
No discomfort[b]	43 (88%)	38 (81%)	38 (76%)
Normal activity[b]	44 (90%)	39 (85%)	37 (73%)
Normal sleep[b]	31 (62%)	25 (50%)	27 (53%)
Normal appetite[b]	29 (58%)	29 (59%)	32 (62%)
Recovered child[e]	21 (40%)	17 (33%)	19 (37%)

a Mean (SD) number of minutes spent below 37.2°C in the first 4/24 hours after randomisation, using the number of valid 30-second interval points from the datalogger; unknown for zero, one and two children in the paracetamol, ibuprofen and paracetamol plus ibuprofen groups, respectively, by 4 hours, and for zero, two and two children, respectively, by 24 hours.
b No discomfort/normal activity: the number (%) of children reported at the relevant time to be 'well' (i.e. 'normal' as opposed to the other three categories given in Table 4); denominators vary slightly due to missing data (in almost all cases fewer than four children).
c Time from baseline until the child's temperature first fell below 37.2°C; unknown for five children altogether (zero, two and three in the paracetamol, ibuprofen and paracetamol plus ibuprofen groups respectively) and right censored at 240 minutes for three children.
d A recovered child or a child whose behaviour 'returned to normal for that child' is defined as a child categorised as 'normal' for discomfort, activity, appetite and sleep and who had a temperature reading of < 37.2°C.
e Measured by a research nurse; unknown for one, five and two children in the paracetamol, ibuprofen and paracetamol plus ibuprofen groups respectively.
f Measured by a parent; unknown for four, seven and three children the paracetamol, ibuprofen and paracetamol plus ibuprofen groups respectively.

TABLE 6 Regression models for the primary outcomes adjusting for minimisation

	Primary comparisons		Secondary comparison
Outcome	**Paracetamol plus ibuprofen vs paracetamol**	**Paracetamol plus ibuprofen vs ibuprofen**	**Ibuprofen vs paracetamol**
Time without fever in first 4 hours[a,b]			
Adjusted difference (minutes)	55.3	16.3	39.0
95% confidence interval	33.1 to 77.5[c]	–7.0 to 39.4[c]	15.9 to 61.0[d]
p-Value	< 0.001[c]	0.2[c]	< 0.001[d]
No discomfort at 48 hours[e]			
Adjusted odds ratio	1.33	0.89	1.50
95% confidence interval	0.49 to 3.56[c]	0.32 to 2.43c[d]	0.53 to 4.26[d]
p-Value	0.7[c]	>0.8[c]	>0.5[d]

a Weighted by number of time points in the first 4 hours contributing valid data on temperature.
b Positive differences indicate additional minutes below 37.2°C for the first named treatment group compared with the comparator.
c Primary comparisons after applying Dunnett's correction (approximate p-values obtained using extrapolation from limited published figures;[88] uncorrected p-values were < 0.001 and 0.11 for temperature, 0.53 and 0.79 for discomfort).
d Secondary comparison after applying Tukey's correction (p-values obtained using interpolation from extensive published figures;[88] were < 0.001 for temperature, 0.37 for discomfort).
e The odds of being 'well' compared with being 'not well'.

Time without fever in the first 24 hours

For time without fever, the mean number of valid minutes (temperature > 33°C and < 45°C) for paracetamol, ibuprofen and both medicine groups was, respectively, 1078, 1028 and 1051 over 24 hours. Table 5 shows that in the first 24 hours children in the paracetamol group spent on average just over 15.5 hours without fever. Time without fever increased to just over 17.5 hours for children in the ibuprofen treatment group and to just over 20 hours for those children in the paracetamol and ibuprofen treatment group. The comparative analyses in Table 7 show strong evidence of a treatment effect, with the combined treatment group spending an average of 4.5 hours more time without fever in the first 24 hours than those in the paracetamol treatment group ($p < 0.001$). Children allocated to both medicines spent an average of 2.5 hours longer without fever than those given ibuprofen ($p = 0.008$). There was no treatment effect when comparing paracetamol with ibuprofen, with children allocated to the ibuprofen groups spending on average 1.9 hours longer without fever; however, the wide confidence interval, which crosses the null, indicates that the difference could have been in favour of paracetamol, i.e. children allocated to the paracetamol-only treatment group could have spent 0.2 hours longer without a fever.

Symptom diary data at 24 hours

More children in the ibuprofen group were recorded as having no discomfort with, for example, 69% (37) scoring normal for discomfort compared with 56% (36) in the both medicines group and 44% (34) in the paracetamol group. Comparative analyses in Table 7 shows that there was no evidence of treatment effects, except for the comparison between paracetamol and ibuprofen, which suggests that more children in the ibuprofen group reported 'normal' discomfort levels ($p = 0.042$). However, this finding needs to be interpreted with caution given the number of comparisons involved in this analysis.

Symptom diary data at 48 hours

Table 5 shows that the proportions of children's symptoms that returned to normal was higher in the ibuprofen group than in the other treatment groups, but comparative analyses shown in Table 8 show that there was no evidence of any treatment effects.

Symptom diary data at day 5

By day 5 the majority of children were apyrexial. Table 9 shows that there was no difference in mean temperature between treatment groups, as measured by the parent. The majority of

TABLE 7 Regression models for secondary outcomes up to 24 hours adjusting for minimisation

	Primary comparisons		Secondary comparison
Outcome	**Paracetamol plus ibuprofen vs paracetamol**	**Paracetamol plus ibuprofen vs ibuprofen**	**Paracetamol plus ibuprofen vs paracetamol**
Time until first fever clearance[a]			
Adjusted difference (minutes)	–23.5	3.0	–26.6
95% confidence interval	–44.8 to –2.2[b]	–18.3 to 24.4[b]	–48.9 to –4.2[c]
p-Value	0.025[b]	> 0.8[b]	0.015[c]
Time without fever in first 24 hours[d]			
Adjusted difference (hours)	4.4	2.5	1.9
95% confidence interval	2.4 to 6.3[b]	0.6 to 4.4[b]	–0.2 to 4.0[c]
p-Value	< 0.001[b]	0.008[b]	0.076[c]
No discomfort at 24 hours[e]			
Adjusted odds ratio	1.54	0.53	2.88
95% confidence interval	0.60 to 3.94[b]	0.21 to 1.38[b]	1.03 to 8.06[c]
p-Value	0.4[b]	0.3[b]	0.042[c]
Normal activity at 24 hours[e]			
Adjusted odds ratio	1.07	0.59	1.80
95% confidence interval	0.45 to 2.95[b]	0.26 to 1.68[b]	0.6 to 4.7[c]
p-Value	0.8[b]	0.3[b]	0.4[c]
Normal appetite at 24 hours[e]			
Adjusted odds ratio	1.46	0.99	1.48
95% confidence interval	0.5 to 4.07[b]	0.4 to 2.9[b]	0.4 to 4.1[c]
p-Value	0.5[b]	> 0.5	> 0.5[c]
Normal sleep at 24 hours[e]			
Adjusted odds ratio	0.85	0.52	1.63
95% confidence interval	–1.8 to 3.51[b]	0.4 to 3.05[b]	0.4 to 3.8[c]
p-Value	0.19[b]	> 0.5	> 0.5[c]

a Negative differences indicate that the first named treatment group has a shorter mean fever clearance time than the comparator group.
b Primary comparisons after applying Dunnett's correction (uncorrected p-values were 0.016 and 0.75 for fever clearance, < 0.001 and 0.005 for time without fever, 0.31 and 0.15 for discomfort, 0.74 and 0.33 for activity, 0.77 and 0.88 for appetite and 0.47 and 0.86 for sleep).
c Secondary comparison after applying Tukey's correction (uncorrected p-values were 0.006 for fever clearance, 0.033 for time without fever, 0.02 for discomfort, 0.19 for activity, 0.62 for appetite and 0.58 for sleep).
d Weighted by number of time points in the first 24 hours contributing valid data on temperature; positive differences indicate additional minutes below 37.2°C for the first named treatment group compared with for the comparator.
e The odds of being 'well' compared with being 'not well'.

children had not yet returned to normal in terms of appetite and sleep, however, but comparative analyses shown in Table 9 indicate that there was no evidence of any treatment differences. A repeated measures logistic regression analysis of all nine discomfort levels recorded over the 5 days was carried out to investigate any differences between groups over time, and none was found (data not shown).

TABLE 8 Regression models for the secondary outcomes at 48 hours adjusting for minimisation

	Primary comparisons		Secondary comparison
Outcome	**Paracetamol plus ibuprofen vs paracetamol**	**Paracetamol plus ibuprofen vs ibuprofen**	**Paracetamol plus ibuprofen vs paracetamol**
Mean temperature at 48 hours[a]			
Adjusted difference (°c)	0.21	0.23	–0.02
95% confidence interval	–0.20 to 0.61[b]	–0.18 to 0.64[b]	–0.46 to 0.41[c]
p-Value	0.4[b]	0.3[b]	> 0.9[c]
Normal activity at 48 hours[d]			
Adjusted odds ratio	0.67	0.40	1.68
95% confidence interval	0.26 to 1.70[b]	0.13 to 1.20[b]	0.60 to 4.67[c]
p-Value	0.5[b]	0.12[b]	0.47[c]
Normal appetite at 48 hours[d]			
Adjusted odds ratio	1.08	0.78	1.39
95% confidence interval	0.41 to 2.84[b]	0.30 to 2.01[b]	0.50 to 3.82[c]
p-Value	> 0.9[b]	0.7[b]	> 0.5[c]
Normal sleep at 48 hours[d]			
Adjusted odds ratio	0.84	0.56	1.49
95% confidence interval	0.34 to 2.07[b]	0.22 to 1.40[b]	0.57 to 3.92[c]
p-Value	0.9[b]	0.3[b]	> 0.5[c]

a Positive differences indicate that the first named treatment group has a higher mean temperature than the comparator group.
b Primary comparisons after applying Dunnett's correction (uncorrected p-values were 0.27 and 0.22 for temperature, 0.34 and 0.039 for activity, 0.86 and 0.56 for appetite, 0.66 and 0.16 for sleep).
c Secondary comparison after applying Tukey's correction (uncorrected p-values were 0.90 for temperature, 0.24 for activity, 0.45 for appetite, 0.33 for sleep).
d The odds of being 'well' compared with being 'not well'.

Adjusting for baseline imbalances

The only potentially influential between-group differences were differences in gender, recruitment method and baseline activity. To take these into account, all regression models were adjusted for these imbalances by way of secondary analysis, and in no case did this affect the results of the regression model.

Planned subgroup analyses

We conducted a pre-planned subgroup analysis employing appropriate interaction terms in the regression models to ascertain any differential effects of the combined compared with single therapies across the following baseline categories: temperature, discomfort, fever duration,antibiotic use, age and a diagnosis of otitis media. The subgroup analyses were carried out on fewer patients than expected and lacked statistical power. Table 10 presents p-values from subgroup analyses for the primary outcomes, which were mostly > 0.2. However, in relation to time without fever in the first 4 hours, these exploratory analyses suggest greater effects for combined therapy in children aged over 18 months (p = 0.14) and those with fever duration of at least 24 hours (p = 0.19). Insufficient numbers of children were diagnosed with otitis media to ascertain any differential effects of the combined compared with single therapies.

Mean temperature by treatment group over 24 hours

Figure 9 shows the mean temperature every 15 minutes by treatment group. The graph

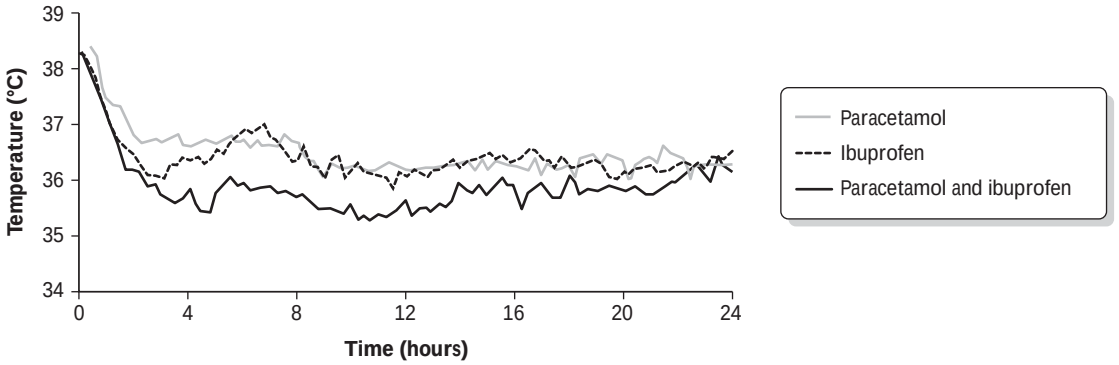
TABLE 9 Regression models for the secondary outcomes at day 5 adjusting for minimisation

	Primary comparisons		Secondary comparison
Outcome	**Paracetamol plus ibuprofen vs paracetamol**	**Paracetamol plus ibuprofen vs ibuprofen**	**Paracetamol plus ibuprofen vs paracetamol**
Mean temperature at day 5[a]			
Adjusted difference (°C)	–0.14	–0.08	–0.06
95% confidence interval	–0.51 to 0.22	–0.45 to 0.28	–0.45 to 0.34[b]
p-Value	0.5	0.7	> 0.7[d]
No discomfort at day 5[c]			
Adjusted odds ratio	0.45	0.75	0.60
95% confidence interval	0.13 to 1.59[d]	0.24 to 2.34[d]	0.15 to 2.39[b]
p-Value	0.3[d]	0.7[d]	> 0.5[b]
Normal activity at day 5[c]			
Adjusted odds ratio	0.30	0.45	0.66
95% confidence interval	0.08 to 1.10[d]	0.14 to 1.49[d]	0.15 to 2.99[b]
p-Value	0.1[d]	0.3[d]	> 0.5[b]
Normal appetite at day 5[c]			
Adjusted odds ratio	1.16	1.07	1.10
95% confidence interval	0.45 to 2.94[d]	0.42 to 2.73[d]	0.40 to 2.91[b]
p-Value	> 0.9[d]	> 0.9[d]	> 0.9[b]
Normal sleep at day 5[c]			
Adjusted odds ratio	0.64	1.09	0.59
95% confidence interval	0.25 to 1.62[d]	0.44 to 2.71[d]	0.17 to 1.35[b]
p-Value	0.4[d]	> 0.9[d]	0.42[b]

a Negative differences indicate that the first named treatment group has a lower mean temperature than the comparator group.
b Secondary comparison after applying Tukey's correction (uncorrected p-values were 0.73 for temperature, 0.39 for discomfort, 0.53 for activity, 0.86 for appetite, 0.20 for sleep).
b The odds of being 'well' compared with being 'not well'.
d Primary comparisons after applying Dunnett's correction (uncorrected p-values were 0.39 and 0.61 for temperature, 0.16 and 0.58 for discomfort, 0.041 and 0.14 for activity, 0.73 and 0.87 for appetite, 0.29 and 0.83 for sleep).

TABLE 10 Planned subgroup analyses

Subgroup	Time without fever in first 4 hours (p-value)	Discomfort at 48 hours (p-value)
Temperature	0.77	0.29
Discomfort	0.19	0.85
Fever duration	0.19	0.82
Antibiotic use	0.23	0.92
Age	0.14	0.52
Otitis media	0.43	–



Treatment group	Percentage of children recording temperatures > 37.2°C at different time points (hours)												
	0	2	4	6	8	10	12	14	16	18	20	22	24
P	81[a]	36	29	25	19	25	19	19	17	15	14	12	12
I	85[a]	15	15	29	12	13	10	12	15	6	8	12	13
P&I	75[a]	9	2	10	13	5	6	12	6	8	2	6	10

FIGURE 9 Mean temperatures over 24 hours measured by treatment group. aAll children recorded temperatures of > 37.2°C at baseline eligibility assessment, as measured by standard digital axillary thermometry. Delays between this measure and medicine dosing (the median number of minutes between randomisation and giving the first dose of study drug was 8 for paracetamol plus ibuprofen and 9 for paracetamol and for ibuprofen) and differences between digital and data logger thermometry methods mean that, for some children (n = 19), the data logger temperature measured < 37.2°C.

is consistent with the tabulated results in demonstrating that ibuprofen and both medicines reduced children's temperatures faster and for longer than paracetamol in the first 4 hours, and that both medicines were superior to either monotherapy in reducing mean temperatures over 24 hours. The mean temperatures seen in Figure 9 are lower than expected. To counter the possibility that for the combined group this may be due to a liberal range of valid temperatures, allowing inclusion of implausibly low temperatures (for example, if the axillary probe had become partially detached), we carried out a sensitivity analysis excluding temperatures below 33.5°C, 34°C, 34.5°C and 35°C (see Figure 10 and Figure 11). These analyses raised the lowest mean temperatures between 4 and 24 hours, but not the relative positions of the treatment means, showing that these low temperature recordings were equally distributed across the treatment arms. We looked in detail at the small number of children who were reported to be 'cold to touch' during the course of the study. Parents of three children in the ibuprofen group and two children in the combined treatment group reported 'cold' as an adverse event (see Table 11). One (with pneumonia) had a temperature of 37.5°C at the time and the others had parent-measured temperatures of 36.1°C, 33.5°C, 35.9°C and 35.3°C. These events were all recorded within the first 4 hours of the study, and within 2 hours all temperatures had risen to over 36°C.

Adverse events

Adverse events were recorded at 24 hours, 48 hours and at day 5. An adverse event was defined in accordance with the European Clinical Trials Directive 2001/20/EC as a new symptom or a worsening of a pre-existing symptom. Overall, 62% of children experienced one or more adverse events. Table 11 shows that the most common adverse events recorded were diarrhoea and vomiting, and that these were equally distributed across treatment groups.

Serious adverse events

Five children were admitted to hospital because of serious adverse events (SAEs) during the course of their study involvement: one in the paracetamol group, three in the ibuprofen group and one in the combined treatment group.

SAE1

This child was admitted to hospital and treatment allocation unblinded at the request of the on-call paediatrician. A chest radiograph confirmed right upper lobe consolidation consistent with a right upper lobe pneumonia. The child was prescribed amoxicillin and discharged after an overnight hospital stay. The child stayed in the study until day 5 and none of the study team were unblinded. Two independent clinicians assessed the SAE and decided that the SAE was not caused by study participation or the study medication.

SAE2

This child was admitted to hospital with a suspected lower lobe pneumonia. The diagnosis was confirmed and the child was discharged from hospital after an overnight stay and was prescribed oral penicillin. The child continued with the trial to day 5. Two independent clinicians assessed the SAE and decided that the SAE was not caused by study participation or the study medication.

SAE3

The child was hospitalised and referred to a respiratory registrar with a presumed lower respiratory tract infection secondary to bronchoscopy. The child was diagnosed as having bronchiolitis and was monitored and discharged after 3 days in hospital. The child continued with the study to day 5. Two independent clinicians assessed the SAE notes and decided that the SAE was not caused by study participation or the study medication.

SAE4

The child was hospitalised with a suspected severe upper respiratory tract infection or Henoch–Schönlein purpura. The patient was diagnosed with viral/streptococcal upper respiratory tract infection. The child continued with the study to day 5. Two independent clinicians assessed the SAE and decided that the SAE was not caused by study participation or the study medication.

SAE5

The child was hospitalised and diagnosed as having bronchiolitis. The child was discharged after two nights in hospital. The child continued with the study to day 5. Two independent clinicians assessed the SAE and decided that the SAE was not caused by study participation or the study medication.

Economic evaluation

Resource use

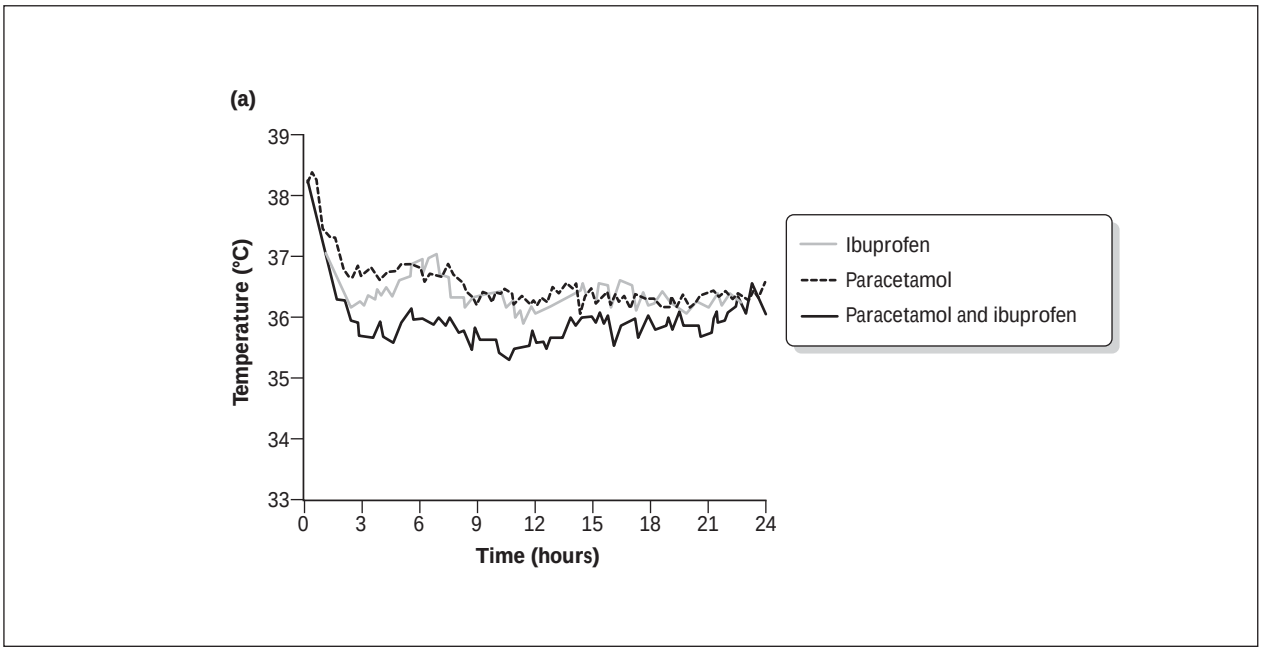
The mean resource use per child over the 5-day follow-up period is given in Table 12. Eighty per cent of children (123) had no primary care contacts, with the remaining 30 having a mean number of contacts of just fewer than 3. The majority of these (52%) were face-to-face at the surgery, 14 (16%) were with an out-of-hours service, and the rest were either telephone consultations or with a variety of other primary care providers such as walk-in centres or NHS Direct. Children receiving paracetamol had the fewest face-to-face consultations though most overall, but there was no significant difference in the total use of primary care across the three groups. Thirty-six prescriptions were issued (excluding two for medicines that had been provided in the study). Most (81%) were for antibiotics. One hundred and thirteen over-the-counter preparations were purchased for 46 children. Sixty-two (55%) were paracetamol or ibuprofen; 29 (47%) of these were bought in the first 48-hour period when study medicines were provided, of which 24 (83%) of these were for the active ingredient being provided. Five children spent some time in hospital. Ninety-two days of work were lost due to the illness though only 48 (31%) parents reported having time off, of whom 21 (44%) reported a direct loss of earnings. Nine (6%) parents incurred out-of-pocket expenses for sibling or other dependant care because of the child's illness.

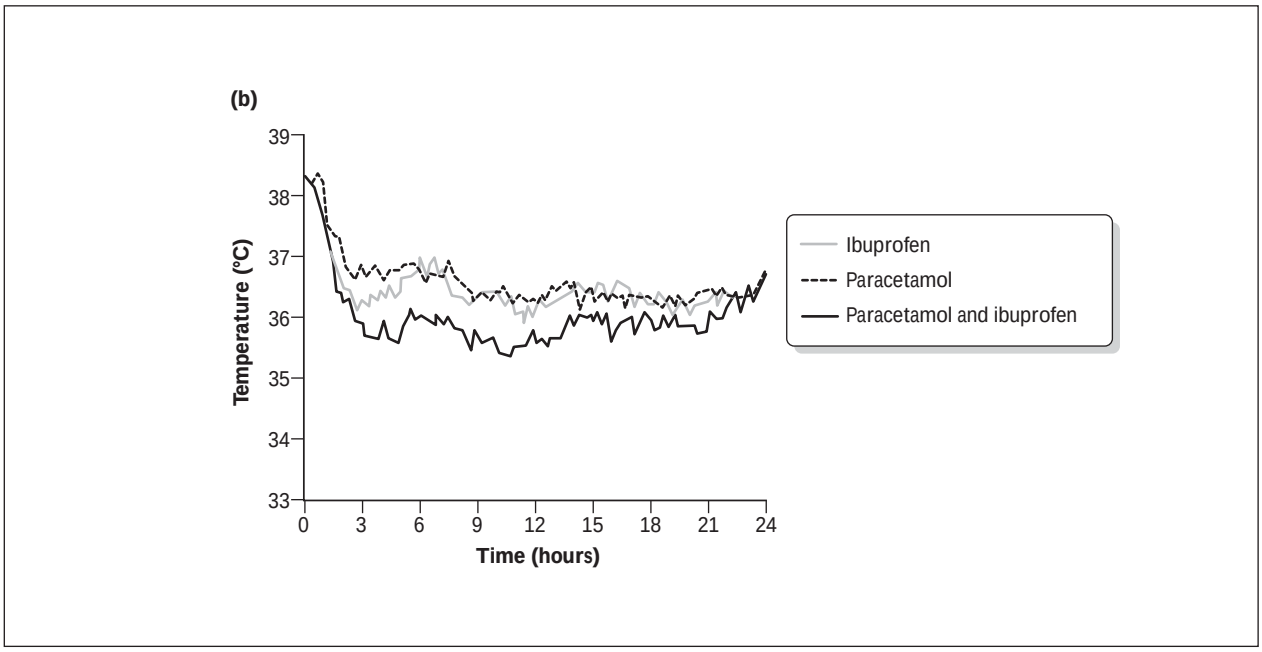
Cost analysis

The mean cost per patient, by group, at 48 hours and day 5 is given in Table 13. Around 60% of all NHS costs are accounted for by GP appointments, and accident and emergency was the second largest contributor. Personal costs were dominated by loss of income. At 48 hours the combined therapy was cheaper than both monotherapies from the NHS perspective, though most expensive from the point of view of parents. By day 5, this group remained cheapest to the NHS and was also cheapest for the parents; the greater expenditure on medication was offset by lower travel costs (because of less health service use) and less time off work.

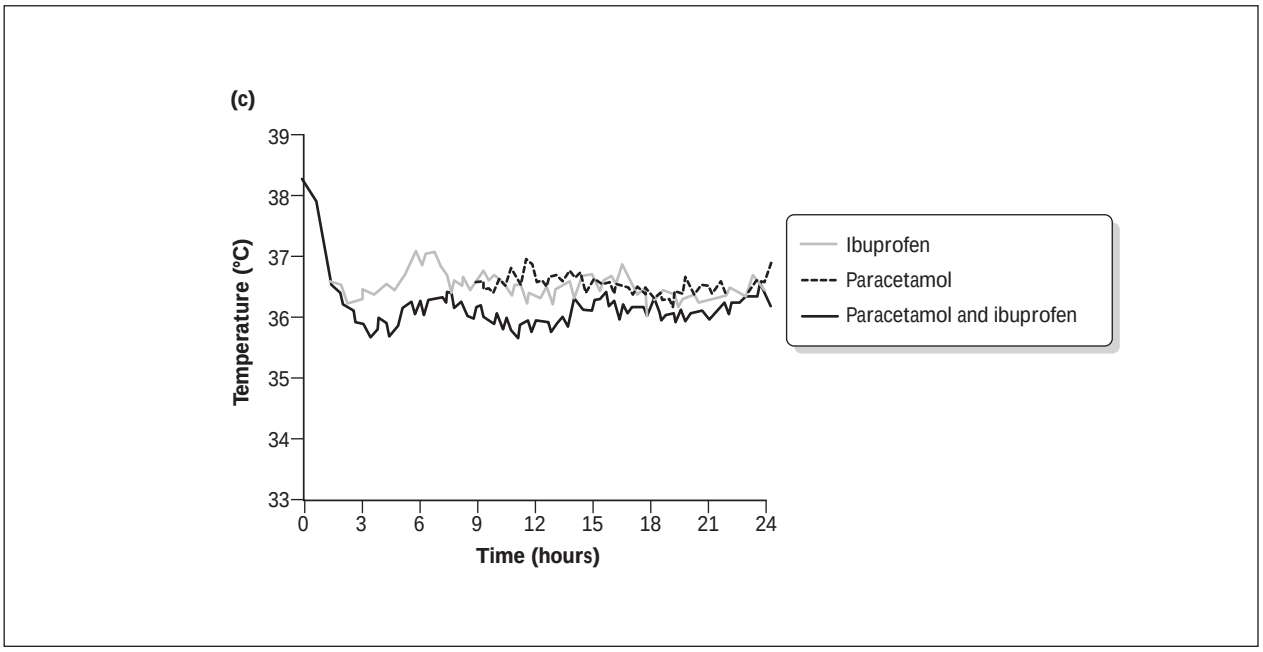
Cost-effectiveness analysis at 48 hours

In Table 14 we show the incremental costs and benefits at 48 hours. Cost is expressed as incremental mean cost per child by group; benefits





are expressed as the proportion of children in each group returning to 'normal for that child' (based on combining temperature, discomfort, activity, appetite and sleep). The incremental cost-effectiveness ratios (ICERs), comparing each treatment group with each of the other two, are expressed as cost per extra child returning to 'normal for that child'. From the perspective of the NHS, the dual therapy is cheaper but less effective than either of the two monotherapies, and paracetamol alone is more expensive but more effective than ibuprofen alone. The ICERs all fall in the south-west quadrant of the cost-effectiveness plane. From the parent perspective, paracetamol and ibuprofen together is more expensive and less effective than either of the single treatments.



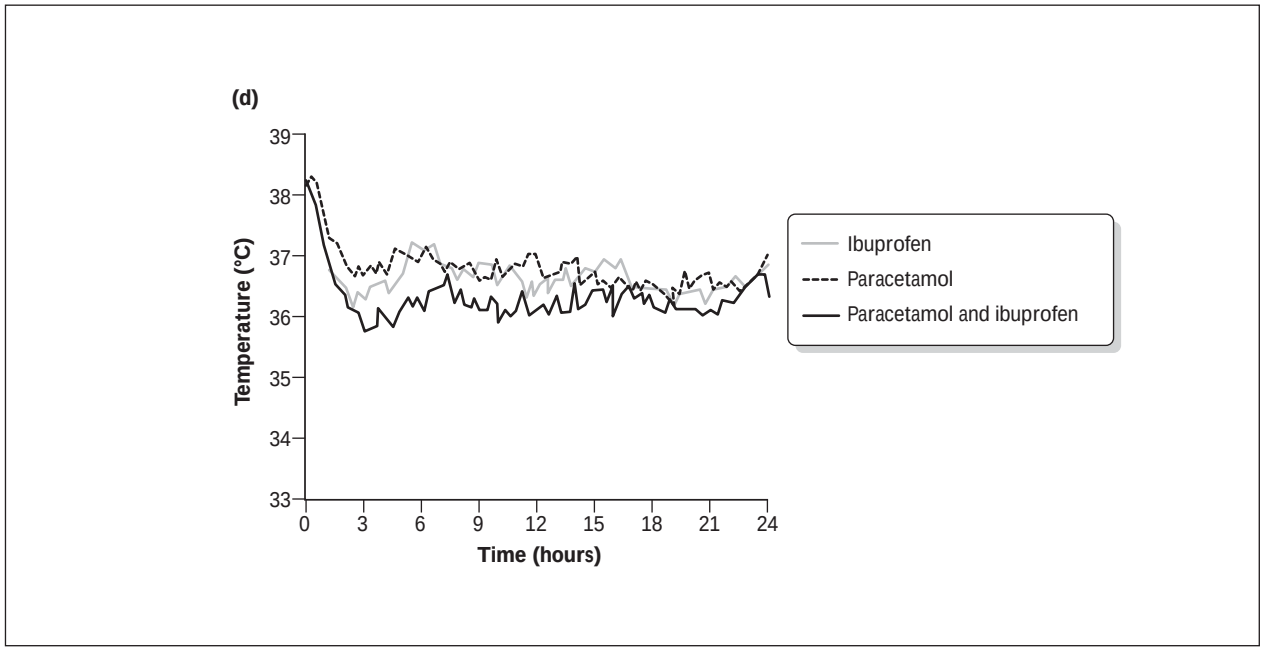
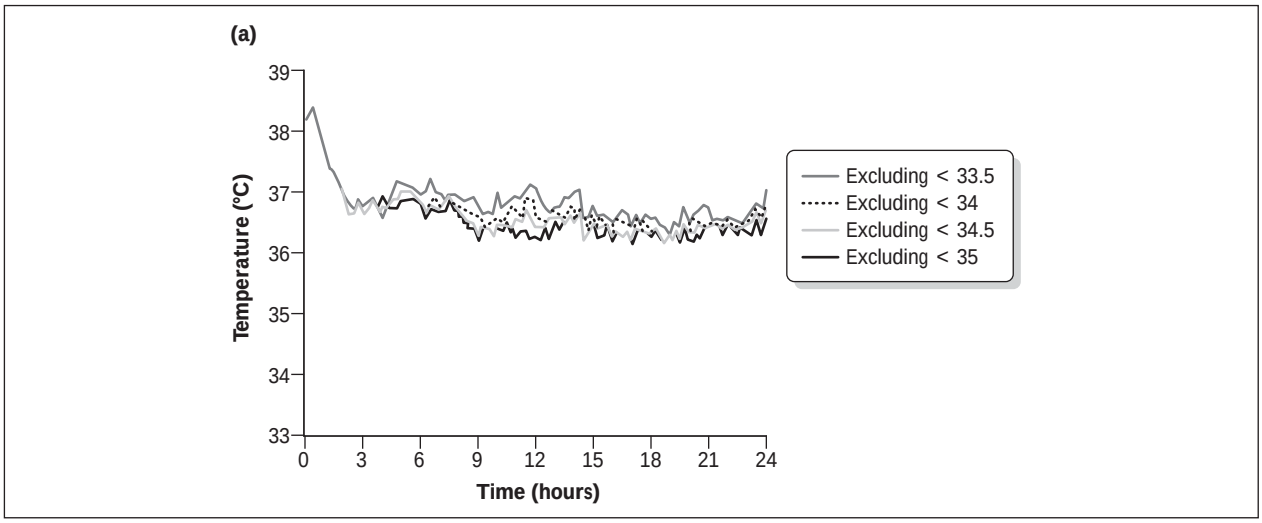
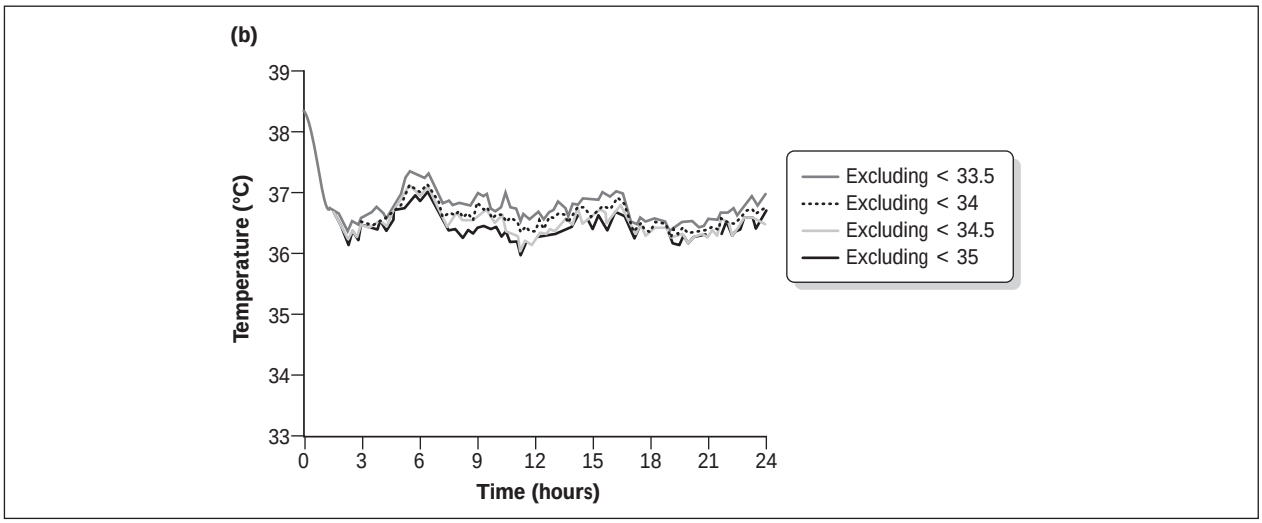


FIGURE 10 Mean temperatures over 24 hours discarding temperatures below different levels. (a) Temperatures below 35.5°C disregarded. (b) Temperatures below 34.0°C disregarded. (c) Temperarures below 34.5°C disregarded. (d) Temperatures below 35.0°C disregarded.

Ibuprofen alone is cheaper but less effective than paracetamol alone. The level of uncertainty around the ICERs is shown by the bootstrapped replications shown on the cost-effectiveness planes in Figure 12. All replications fall in all four quadrants for all comparisons, suggesting that there is little evidence that any treatment choice is more cost-effective than any other. This is reinforced by the cost-effectiveness acceptability curves in Figure 13, in which the probability of one treatment being more cost-effective than another is shown. None of these probabilities reaches 50%.





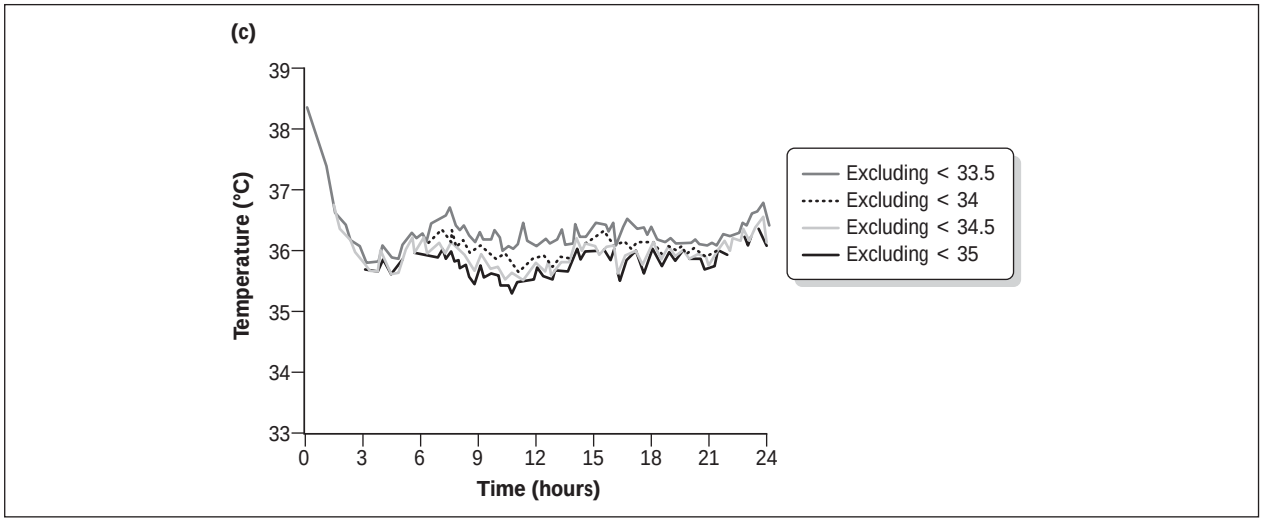


FIGURE 11 Treatment group mean temperatures disregarding temperatures below different levels. (a) Paracetamol treatment group. (b) Ibuprofen treatment group. (c) Paracetamol and ibuprofen treatment group.

TABLE 11 Adverse events experienced by children (number of children)

Adverse effect	Paracetamol	Ibuprofen	Paracetamol plus ibuprofen
Diarrhoea	10	9	12
Vomiting	6	3	2
Rash	2	2	1
Cough	2	0	1
Cold to touch	0	3	2

Cost consequences: 48 hours and day 5

In Table 15 we compare the costs and outcomes of each treatment regime with each of the other two. This includes cost to the NHS and to parents of all five outcomes of temperature, discomfort, activity, appetite and sleep at both time points of 48 hours and 5 days. Temperature is expressed as the difference in mean temperature between the groups over the time period; discomfort, activity, appetite, and sleep are expressed as odds ratios of 'normal' compared with 'not normal'. The proportion of children per group who returned to 'normal for that child' is also given.

At 48 hours ibuprofen alone outperforms paracetamol alone on all outcomes separately (though not when combined) and is cheaper to parents and the NHS. It also performs well against the combined therapy, though it is slightly more expensive to the NHS. There is no clear pattern in the comparison of the combined therapy with paracetamol alone. At 5 days the combined therapy is more favourable than either monotherapy in terms of cost and temperature, though less so for the other outcomes. There is no evidence of a difference between the two single treatments. The confidence intervals around the incremental costs and outcomes indicate only weak evidence in support of these results.

Sensitivity analysis

Table 16 gives the results of the sensitivity analysis. If the study medicines had been prescribed, rather than bought over the counter, costs to the NHS increase, but by less than the associated decrease in parent costs. The increase in NHS costs is greatest for the combined therapy group though this is still the cheapest treatment option for the NHS at day 5. Parents of 45 children (29%) would have used fewer bottles of medicine if they had dosed by age (as per the instructions on the bottle) rather than by weight (as in this study). Around half (51%) were in the paracetamol only group though the cost impact is greatest in the combined therapy group because of having to purchase two medicines, and because ibuprofen is more expensive than paracetamol.

Secondary care costs include inpatient care, ambulance use and travel cost for families. These are estimated at day 5 only as the episodes of care generally spanned the whole period. Of the five children who received secondary care, one was in the paracetamol only group, one in the combined treatment group, and three were in the ibuprofen only group. This is reflected in the cost estimates, which increase by about £20 per hospitalised child per group (i.e. about £1000 per hospitalisation). There is no evidence that any of these adverse events were related to the medication the child received, and the combined therapy remains the most attractive choice for the NHS and parents.

Natural history of fever

Table 4 shows that 37% of children were diagnosed with a 'non-specific viral infection', 28% with a respiratory tract infection, 16% with otitis media and 20% with 'other' diagnoses. As expected, Table 5 and Table 17 show that fever and associated symptoms resolve in increasing numbers of children with time. Overall, 26% of children 'recovered' (or were back to 'normal for that child') by 48 hours and 36% by day 5. Discomfort and activity levels normalised before sleep or appetite. Table 17 also shows that increasing numbers of children were being treated with antibiotics as the study progressed, with the highest proportion (45%) being seen at day 5. By this time only a few (8%) were being treated with over-the-counter antipyretics.

TABLE 12 Mean resource use per episode per patient: day 5 follow-up

Item of resource use	Paracetamol		Ibuprofen		Paracetamol and Ibuprofen	
	n	Mean number (SD)	n	Mean number (SD)	n	Mean number (SD)
Primary care consultations at the surgery	51	0.235 (0.513)	50	0.300 (0.505)	52	0.423 (0.605)
Primary care telephone consultations	52	0.077 (0.269)	50	0.060 (0.240)	52	0.038 (0.194)
Out-of-hours consultations	52	0.154 (0.500)	50	0.100 (0.100)	52	0.058 (0.196)
Other primary care consultations	52	0.192 (0.192)	50	–	52	0.039 (0.196)
Prescribed medication (number of items)	52	0.269 (0.564)	50	0.240 (0.517)	52	0.192 (0.444)
Over-the-counter medication (number of items)	52	0.442 (0.725)	50	0.360 (0.631)	52	0.519 (0.852)
Accident and emergency visits	51	0.039 (0.196)	50	0.100 (0.416)	52	0.038 (0.194)
Inpatient hospital stays (number of nights)	51	0.020 (0.140)	49	0.122 (0.600)	52	0.077 (0.555)
Ambulance use (number of journeys)	51	–	50	0.060 (0.314)	52	0.019 (0.139)
Days off work (number of days)	52	0.596 (1.116)	49	0.768 (1.439)	52	0.442 (0.802)
Loss of income (proportion of parents incurring a cost)	52	0.096 (0.298)	52	0.192 (0.398)	52	0.115 (0.323)
Child care cost (proportion of parents incurring a cost)	52	0.038 (0.194)	52	0.077 (0.269)	52	0.058 (0.235)

SD, standard deviation.

TABLE 13 Mean (SD) cost per patient (£), by group at 48 hours and 5 days

	48 hours			Day 5		
	Paracetamol alone	Ibuprofen alone	Paracetamol plus ibuprofen	Paracetamol alone	Ibuprofen alone	Paracetamol plus ibuprofen
NHS costs	**n = 51**	**n = 52**	**n = 51**	**n = 50**	**n = 49**	**n = 51**
Primary care doctor consultations	6.15 (15.41)	3.99 (10.67)	6.48 (13.36)	12.10 (28.30)	10.38 (18.17)	10.23 (14.67)
Primary care nurse consultations	0.00 (0.00)	0.15 (1.11)	0.00 (0.00)	0.58 (4.09)	0.16 (1.14)	0.00 (0.00)
Other primary care consultations	2.03 (7.29)	0.00 (0.00)	0.00 (0.00)	3.55 (9.37)	0.00 (0.00)	0.36 (2.60)
Total primary care cost	8.18 (17.26)	4.14 (11.16)	6.48 (13.36)	16.23 (34.11)	10.54 (18.42)	10.59 (15.16)
Accident and emergency	2.78 (13.92)	4.10 (21.84)	1.39 (9.94)	2.84 (14.05)	7.24 (29.86)	2.78 (13.92)
Prescribed medication	0.37 (1.00)	0.25 (0.85)	0.29 (0.86)	0.56(1.27)	0.58 (1.43)	0.55 (1.63)
Total NHS cost	11.33 (23.18)	8.49 (29.13)	8.16 (16.36)	19.63 (38.11)	18.36 (40.26)	13.92 (23.17)
Parental costs	n **= 47**	n **= 49**	n **= 47**	n **= 45**	n **= 42**	n **= 43**
Travel cost	0.31 (1.04)	0.02 (0.08)	0.21 (0.74)	0.70 (1.56)	0.29 (0.77)	0.35 (0.89)
Over-the-counter medication	2.52 (0.29)	4.13 (0.00)	6.75 (0.68)	3.69 (1.61)	4.74 (1.44)	8.03 (2.36)
Other out-of-pocket expenditure	21.03 (62.18)	16.44 (58.50)	18.10 (51.64)	21.97 (63.41)	24.83 (90.81)	15.64 (46.74)
Total parental costs	23.86 (62.20)	20.60 (58.52)	25.07 (51.60)	26.35 (63.37)	29.90 (90.68)	24.02 (46.36)

SD, standard deviation.

TABLE 14 Cost-effectiveness at 48 hours: incremental mean costs and benefits

	Paracetamol alone	Ibuprofen alone	Paracetamol plus ibuprofen	Paracetamol plus ibuprofen vs paracetamol alone	Paracetamol plus ibuprofen vs ibuprofen alone	Ibuprofen alone vs paracetamol alone
NHS perspective (n = 154)						
Mean (SD) total cost (£)	11.33 (23.18)	8.49 (29.13)	8.16 (16.36)			
Incremental cost (95% CI) (£)				–3.16 (–11.05 to 4.72)	–0.33 (–9.59 to 8.93)	–2.84 (–13.14 to 7.46)
Proportion (SD) of children returning to 'normal for that child'[a]	0.275 (0.451)	0.269 (0.448)	0.235 (0.428)			
Incremental benefit (95% CI)				–0.039 (–0.212 to 0.134)	–0.034 (–0.205 to 0.137)	–0.005 (–0.181 to 0.170)
Cost per extra child returning to 'normal for that child'				£80.70	£9.62	£537.65
Parent perspective (n = 143)						
Mean (SD) total cost (£)	23.86 (62.20)	20.60 (58.52)	25.07 (51.60)			
Incremental cost (95% CI) (£)				1.20 (–22.20 to 24.60)	4.47 (–17.90 to 26.90)	–3.27 (–27.70 to 21.20)
Proportion (SD) of children returning to 'normal for that child'[a]	0.298 (0.462)	0.286 (0.456)	0.234 (0.428)			
Incremental benefit (95% CI)				–0.064 (–0.246, 0.119)	–0.052 (–0.231, 0.128)	–0.012 (–0.198, 0.174)
Cost per extra child returning to 'normal for that child'				£–18.87	£–86.55	£268.78

CI, confidence interval; SD, standard deviation.
a Based on complete cases: proportions vary by perspective due to missing data.

As described, there were five children (3%) admitted to hospital, two with pneumonia, two bronchiolitis and one with a severe but unidentified 'viral illness'. No child was admitted with meningitis and none died.

Other results

Blinding

The success of blinding was assessed at the 48-hour nurse visit, when parents were asked to guess treatment allocation. Taking any 'I don't know' responses to either medicine as failure to guess correctly, 16 (31%), 17 (33%) and 9 (17%) of participants in the paracetamol, ibuprofen and combined treatment groups, respectively, guessed their allocation correctly, compared with the 33% expected by chance. Excluding all 'I don't know' responses, increased these percentages to 50% of 32, 53% of 32 and 43% of 21 parents respectively.

Medicine tolerability

Parents were asked to record how each dose of medicine was swallowed by the child. All children

TABLE 15 Cost consequences matrix: incremental costs and outcomes at 48 hours and day 5

	48 hours			Day 5		
	Paracetamol plus ibuprofen vs paracetamol alone	Paracetamol plus ibuprofen vs ibuprofen alone	Ibuprofen alone vs paracetamol alone	Paracetamol plus Ibuprofen vs paracetamol alone	Paracetamol plus ibuprofen vs ibuprofen alone	Ibuprofen alone vs paracetamol alone
Incremental mean (95% CI) cost per patient (£)						
NHS costs	–3.16 (–11.0 to 4.7)	–0.33 (–9.6, 8.9)	–2.84 (–13.1 to 7.5)	–5.71 (–18.1 to 6.7)	–4.44 (–17.4 to 8.5)	–1.27 (–16.9 to 14.4)
Personal costs	1.20 (–22.2 to 24.6)	4.47 (–17.9, 26.9)	–3.27 (–27.7 to 21.2)	–2.33 (–26.0 to 21.3)	–5.88 (–36.8 to 25.1)	3.55 (–29.6 to 36.7)
Outcomes						
Temperature: adjusted difference in mean temperature (°C)	0.21 (–0.20 to 0.61)	0.23 (–0.18 to 0.64)	–0.02 (–0.46 to 0.41)	–0.14 (–0.51 to 0.22)	–0.08 (–0.45 to 0.28)	–0.06 (–0.45 to 0.34)
Discomfort: odds ratio of 'well' compared with 'unwell'	1.33 (0.49 to 3.56)	0.89 (0.32 to 2.43)	1.50 (0.53, 4.26)	0.45 (0.13 to 1.59)	0.75 (0.24 to 2.34)	0.60 (0.15 to 2.39)
Activity: odds ratio of 'well/normal' compared with 'unwell/not normal'	0.67 (0.26 to 1.70)	0.40 (0.13 to 1.20)	1.68 (0.60 to 4.67)	0.30 (0.08 to 1.10)	0.45 (0.14 to 1.49)	0.66 (0.15 to 2.99)
Appetite: odds ratio of 'well/normal' compared with 'unwell/not normal'	1.08 (0.41 to 2.84)	0.80 (0.30 to 2.01)	1.39 (0.50 to 3.82)	1.16 (0.45 to 2.94)	1.07 (0.42 to 2.73)	1.10 (0.40 to 2.91)
Sleep: odds ratio of 'well/normal' compared with 'unwell/not normal'	0.84 (0.34 to 2.07)	0.56 (0.22 to 1.40)	1.49 (0.**57** to 3.92)	0.64 (0.25 to 1.62)	1.09 (0.44 to 2.71)	0.59 (0.17 to 1.35)
Difference (95% CI) in proportion of children returning to 'normal for that child' (n = 156)	–0.06 (–0.23 to 0.11)	–0.04 (–0.22 to 0.13)	–0.02 (–0.20 to 0.16)	–0.04 (–0.23 to 0.15)	0.04 (–0.15 to 0.23)	–0.08 (–0.27 to 0.11)

CI, confidence interval.

received their first dose of medication in the presence of the research nurse at the baseline visit. Table 18 shows that the trial medicines were tolerated well by the children and there was no difference in tolerability between the placebo or active medicines.

Relationship between temperature and discomfort

Given our lack of power to determine treatment effects on fever-associated symptoms, we conducted an exploratory analysis to investigate the relationship between temperature and discomfort, using a repeated measures regression analysis. Table 19 shows that children recording higher mean temperatures (standard nurse- or parent-measured digital axillary thermometry) also recorded higher levels of discomfort across the nine symptom diary time points when both were measured. Across all time points, children who had no discomfort compared with 'not quite normal', 'some pain/distress' and 'crying/very distressed' had mean temperatures of 36.4°C, 37.2°C, 38.1°C and 38.3°C respectively. Table 20 shows that the difference in temperature (adjusted for treatment, age, use of antibiotics and fever duration) across all time points was associated with different discomfort categorisations and that higher levels of discomfort are associated with higher temperatures.

Using the symptom diary

Acceptability

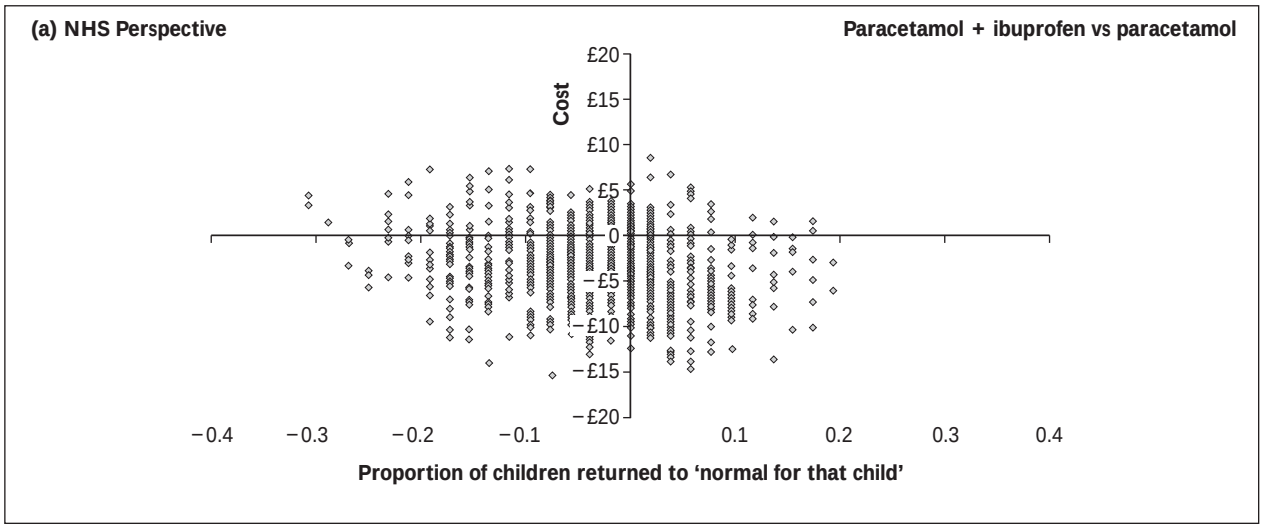
The symptom diary proved very acceptable to parents, reflecting in large part the time and

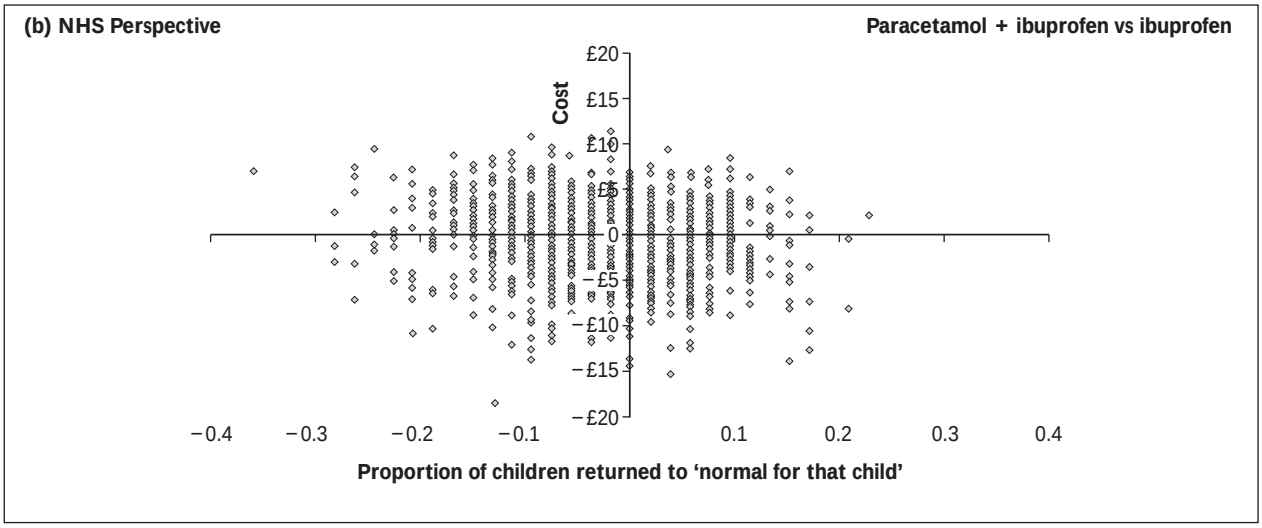
DOI: 10.3310/hta13270

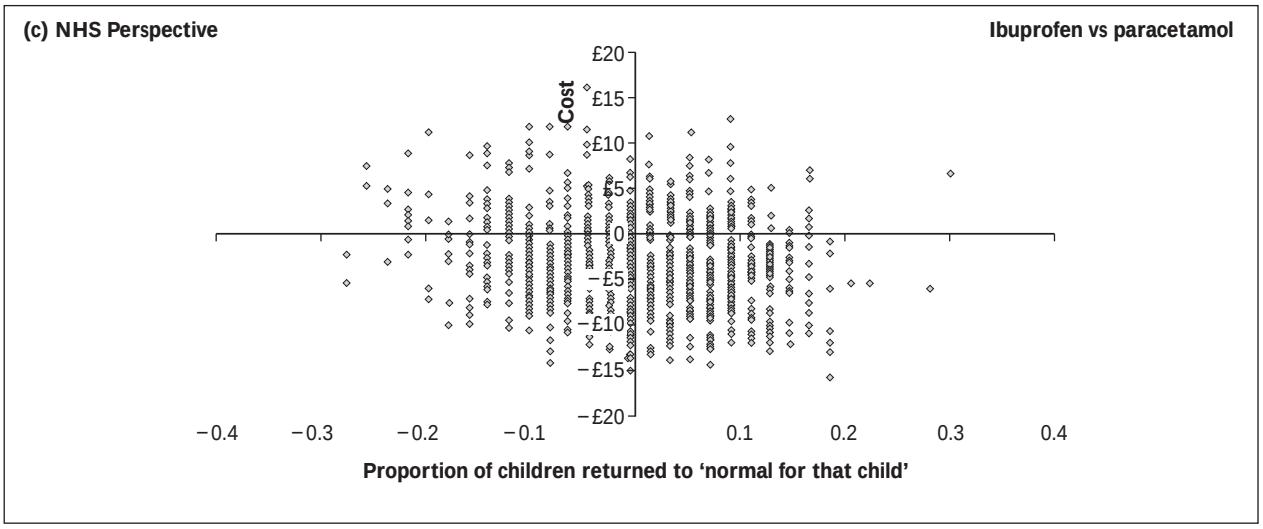
TABLE 16 Sensitivity analysis

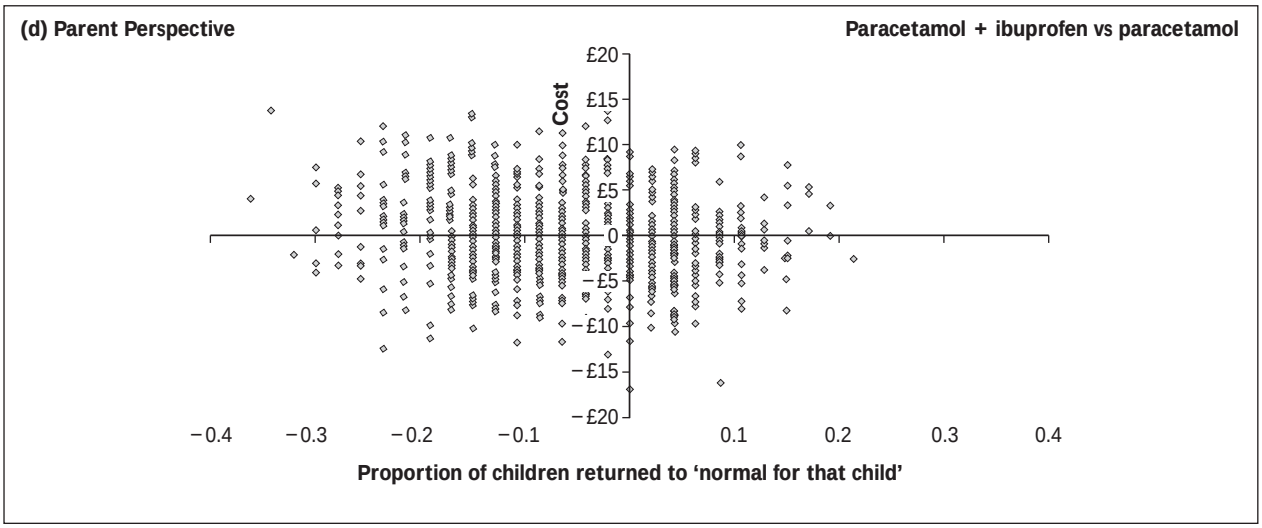
Different scenarios	Mean (SD) cost (£)			Incremental NHS cost and change from base case		
If study medicines had been prescribed	**Paracetamol**	**Ibuprofen**	**Paracetamol plus ibuprofen**	**Paracetamol**	**Ibuprofen**	**Paracetamol and ibuprofen**
For 0–48 days						
NHS costs	11.69 (22.98)	11.18 (29.13)	11.27 (16.36)	–0.42 (+2.74)	0.09 (+0.42)	–0.52 (+2.32)
Parental costs	21.88 (62.09)	16.87 (59.89)	19.30 (51.39)	–2.58 (–3.78)	2.43 (–2.04)	–5.01 (–1.74)
For 0–5 days						
NHS costs	20.00 (37.99)	20.92 (39.87)	17.02 (23.18)	–2.98 (+2.73)	–3.91 (+0.53)	0.92 (+2.20)
Parental costs	22.88 (63.27)	25.28 (90.81)	16.14 (46.68)	–6.73 (–4.13)	–9.14 (–2.48)	2.40 (–1.65)
If dose by age						
Parental costs for 0–5 days	25.36 (63.27)	29.41 (90.81)	22.75 (46.68)	–2.60 (–0.28)	–6.66 (–0.78)	4.05 (+0.50)
Including secondary care costs						
NHS costs for 0–5 days	40.89 (164.8)	78.64 (268.3)	35.19 (168.6)	–5.70 (+0.01)	–43.45 (–39.01)	37.75 (+39.02)
Parental costs for 0–5 days	26.89 (63.23)	31.21 (90.6)	24.28 (46.3)	–2.60 (–0.27)	–6.92 (0.26)	4.35 (+0.30)

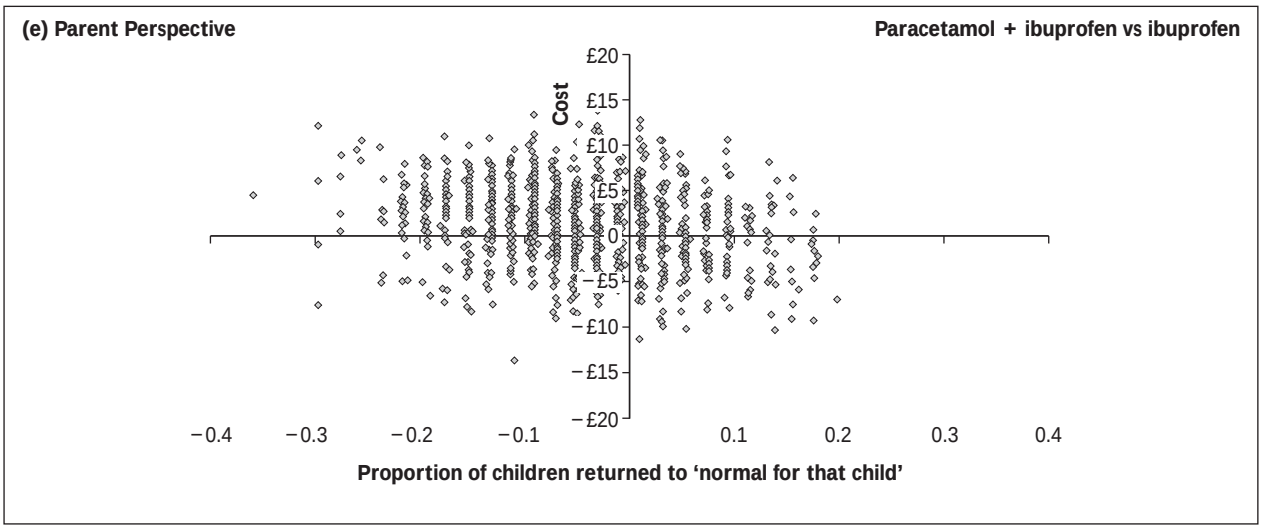
CI, confidence interval; SD, standard deviation.


(a) NHS Perspective
Paracetamol + ibuprofen vs paracetamol
Cost
£20
£15
£10
£5
0
−£5
−£10
−£15
−£20
−0.4
−0.3
−0.2
−0.1
0.1
0.2
0.3
0.4
Proportion of children returned to 'normal for that child'


(b) NHS Perspective
Paracetamol + ibuprofen vs ibuprofen
Cost
£20
£15
£10
£5
0
−£5
−£10
−£15
−£20
−0.4
−0.3
−0.2
−0.1
0.1
0.2
0.3
0.4
Proportion of children returned to 'normal for that child'


(c) NHS Perspective
Ibuprofen vs paracetamol
Cost
£20
£15
£10
£5
0
−£5
−£10
−£15
−£20
−0.4
−0.3
−0.2
−0.1
0.1
0.2
0.3
0.4
Proportion of children returned to 'normal for that child'





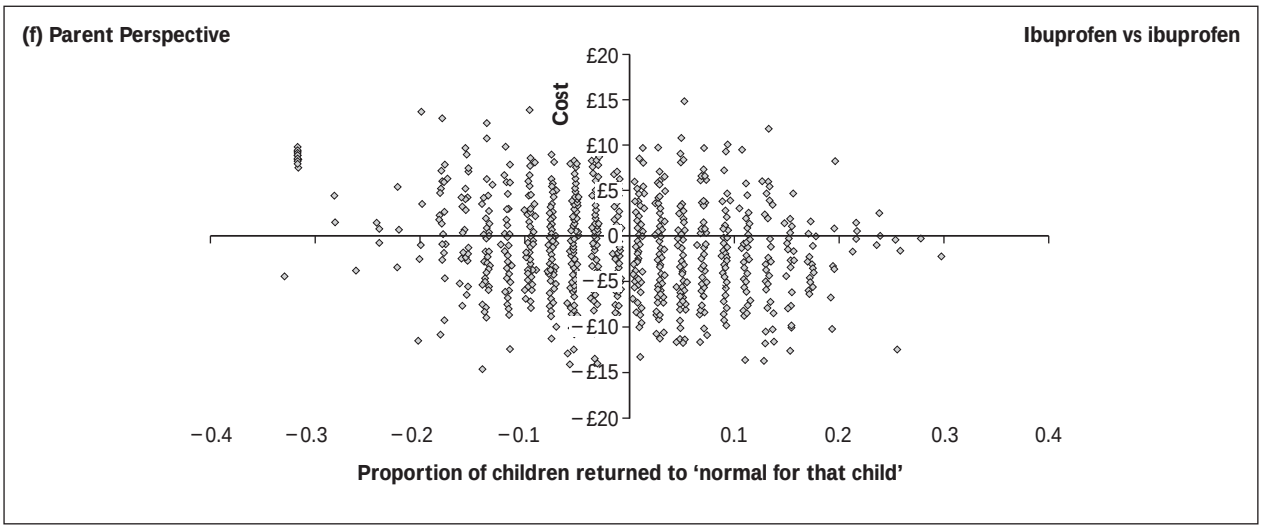


FIGURE 12 Cost-effectiveness planes comparing cost with proportion children 'normal' at 48 hours.

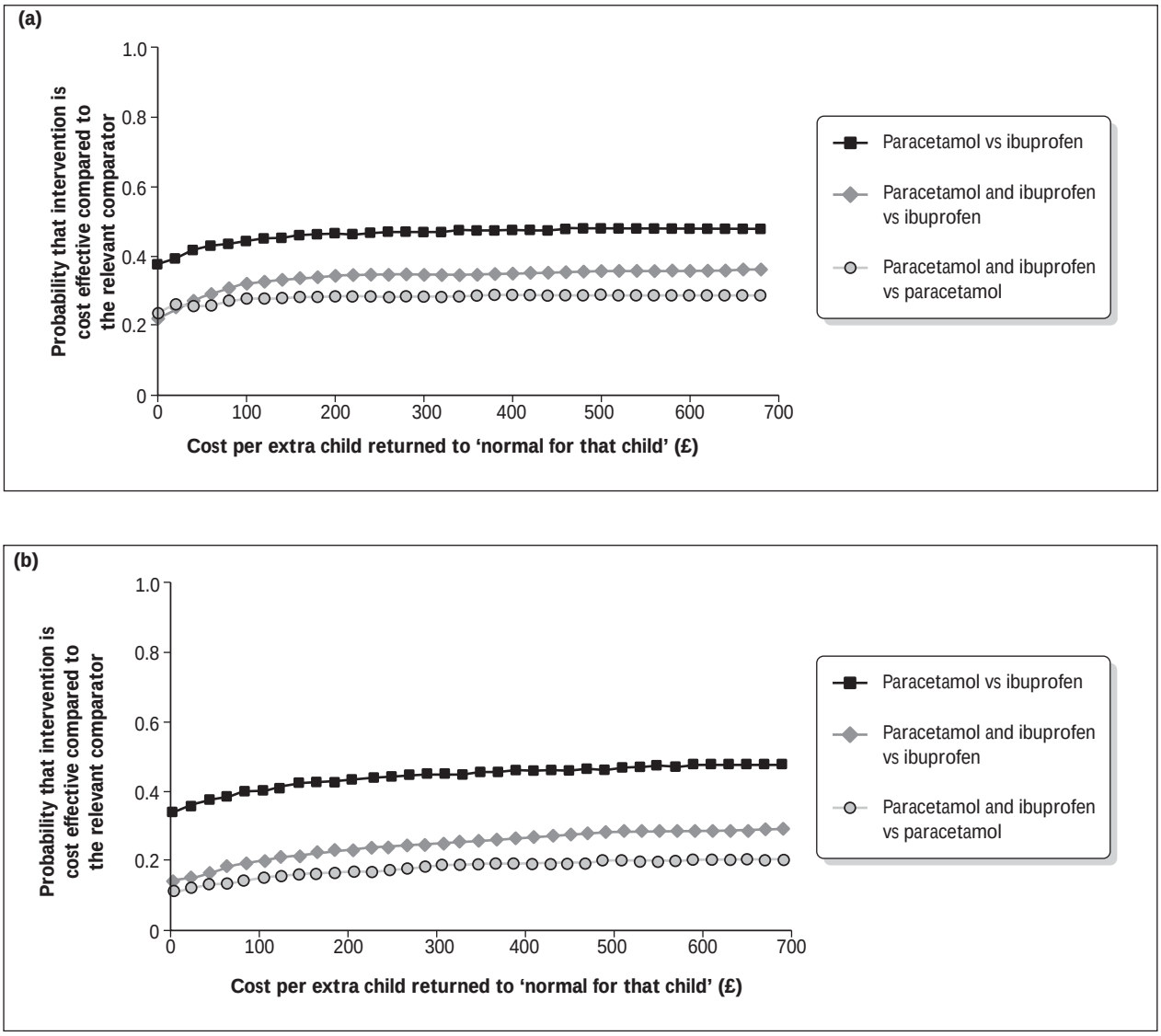


FIGURE 13 Cost-effectiveness acceptability curves for NHS and parent perspectives at 48 hours. (a) NHS perspective. (b) Parent perspective

TABLE 17 Treatment and recovery experience of all children

	Paracetamol	Ibuprofen	Paracetamol plus ibuprofen	Total (%)
Recovered (n) at 24 hours	4	9	7	20 (13%)
Recovered (n) at 48 hours	15	14	12	41 (26%)
Recovered (n) at day 5	21	17	19	57 (36%)
Antibiotic use (n)				
At baseline	14	15	17	46 (29%)
At 24 hours	24	14	15	53 (35%)
At 48 hours	21	19	20	60 (38%)
At day 5	23	23	24	70 (45%)
Antipyretic (n) use at day 5	4	5	3	12 (8%)

TABLE 18 Medicine tolerability

How easy first dose of medicine swallowed	Paracetamol (n)	Ibuprofen (n)	Paracetamol plus ibuprofen (n)
Paracetamol			
Easy	40	43	42
OK	10	7	9
Difficult	2	2	1
Ibuprofen			
Easy	36	41	37
OK	11	8	10
Difficult	5	3	5

TABLE 19 Mean temperature (°C) at nine time points by discomfort level

	Symptom diary time points (hours)								
Discomfort category	**0**	**2**	**4**	**16**	**24**	**32**	**40**	**48**	**Day 5**
'No discomfort'	38.3	36.7	36.4	36.3	36.3	36.4	36.3	36.3	36.1
'Not quite normal'	38.5	36.6	36.9	36.9	36.6	36.9	36.8	36.8	36.3
'Some pain/distress'	38.8	37.1	38.0	37.9	38.2	37.5	36.7	37.3	38.1
'Crying/very distressed'	38.4	36.8	38.1	37.9	39.5	38.2	38.5	-	38.5

TABLE 20 Regression model for the relationship between mean temperature and discomfort at symptom diary time points

	Comparison of discomfort scale categories		
Outcome	**'Not quite normal' vs 'no discomfort'**	**'Some pain/distress' vs 'no discomfort'**	**'Crying/very distressed' vs 'no discomfort'**
Adjusted difference (°C)	0.83	1.73	1.95
95% confidence interval	0.55–1.07	1.36–1.96	1.40–2.34

trouble taken to ensure that parents understood what it was for and how to complete it correctly. The study nurses became adept at identifying families in which completion was likely to be problematic unless explanations were repeated and measures taken to overcome problems – for example tailoring how the times were presented (for data purposes 24-hour clock, for parental purposes writing day and time in full if necessary).

Symptom diary – missing data

The missing data were evenly distributed across each arm of the trial and were minimal at the key time points of 4, 24 and 48 hours, with, respectively, 1%, 0.6% and 1.1% of data points being missing at these times. Although the majority of symptoms entries were completed, additional entries such as GP visits and other measures taken to cool the child were more likely than the symptom levels to be left blank until the nurse visited. Owing to the limited time delay (visits at 24 and 48 hours) these could be completed with reasonable certainty. Parents occasionally found it difficult to decide which category best described their child's symptoms, a common problem when applying scales such as these in any situation, but the nurses were able to help explain the scales.

Value of the symptom diary as a monitoring device

The symptom diary proved invaluable during the study as a means of detecting protocol deviations,

especially with respect to the administration of the study drugs. Moreover, parents found the diaries useful and reassuring for monitoring their child's recovery. Most importantly, over frequent dosing was detected, a problem that is likely to occur in practice when both drugs are being used by parents. By monitoring entries on a frequent basis, such errors could be detected early (within 24 hours) and the opportunity taken to educate the parents about the dosing and to prevent dosing exceeding safe limits. This was as important for the family's use of these drugs after the study as it was for the integrity of the data. Such events were uncommon, but serve as a reminder of how complicated dosing regimes are open to misinterpretation even when highly regulated and well supported.

The data in Table 21 illustrates two points. First, in the first 24 hours, parents administered the minimum intended doses of paracetamol or placebo (four doses) to 42–65% of children and of ibuprofen or placebo (three doses) to 71–75% of children. This suggests that three times daily dosing is superior or more likely to be adhered to than four times daily dosing and may have contributed towards greater ibuprofen efficacy. This pattern was unaltered if the cut-off of 24 hours is brought forward by 20 minutes to ensure that the last included dose is likely to have had some antipyretic effect.

The second point is that, despite clear spoken and written direction regarding maximum dosing recommendations, a proportion of parents were administering significantly more than the recommended maximum number of doses (four paracetamol, three ibuprofen) in 24 hours, in some cases by an additional two doses. The overuse of these drugs may be even worse in the community, where parents who are advised to alternate the drugs struggle without close supervision to use the different dosing regimes correctly.

TABLE 21 Doses of paracetamol, ibuprofen or placebo given in the first 24 hours

	Within 24 hours			
Doses given	**Paracetamol**	**Ibuprofen**	**Paracetamol plus ibuprofen**	**Total**
Paracetamol				
First dose	52	52[a]	52	156
Second dose	52	49[a]	51	152
Third dose	48	44[a]	47	139
Fourth dose	34	24[a]	22	80
Fifth dose	6	3[a]	4	13
Total doses	192	172	176	
Percentage of children receiving four doses of paracetamol	65.4	46.2	42.3	
Ibuprofen				
First dose	52[b]	52	52	156
Second dose	51[b]	48	50	149
Third dose	38[b]	39	37	114
Fourth dose	7[b]	4	7	18
Fifth dose	–	–	2	2
Total doses	148	143	148	
Percentage of children receiving three doses of ibuprofen	73.1	75.0	71.2	

a Placebo ibuprofen.
b Placebo paracetamol.

Protocol deviations

Delayed 48 hour and day 5 follow-up contacts

Owing to bank holidays, staff sickness or working parents, the 24-hour and 48-hour visits were replaced by telephone calls in the case of two and 39 children respectively. The day 5 follow-up telephone call was carried out retrospectively in nine cases, but no later than 7 days after randomisation. When a visit or follow-up call was carried out after the designated time, the parent completed the symptom diary retrospectively.

Unblinding

Four children were unblinded from the trial medication during the study. One was unblinded following a request from the child's GP because the child's parent wanted to know what medication the child had received as the child's condition had deteriorated. One was unblinded following a parent request, as there was concern as the child was vomiting and had a high temperature. Both of these cases of unblinding occurred within the first few months of the trial and, as the study progressed, there were fewer requests. Two children were unblinded during the course of an SAE. In both cases unblinding was requested by hospital clinicians. In the case of these children, all of the research team remained blind to the treatment group and in one case all of the research team was unblinded.

Intervention withdrawals

One child stopped receiving the study medicines at 24 hours as the parent wanted to administer paracetamol. However, the parent completed data collection up to the follow-up telephone call at day 5.

Data quality

Data quality was assessed by double data entry according to the data quality SOP (see Appendix 28). There was a 2% overall disagreement error rate on all symptom diary data entries and a 1% error rate for CRF data entries. Disagreement for selected baseline and all primary outcome data was overcome by referring to the CRF.

Chapter 4
Discussion and conclusions

Clinical effectiveness

Summary of main results

We found strong evidence of faster and more prolonged time without fever in the first 4 hours favouring the use of both medicines and ibuprofen over paracetamol. In the first 24 hours, there was strong evidence of more time without fever favouring the use of both medicines over either monotherapy. There was a suggestion that ibuprofen might be the most effective treatment for reducing fever-associated symptoms, particularly at 24 hours, but we found no evidence of differences in fever-associated discomfort at 48 hours or at any other secondary time point. There appeared to be no difference between treatment groups in the frequency of adverse effects or the tolerability of the medicines. Despite the research nurse supervision, a number of children received more than the recommended number of medicine doses in 24 hours.

Comparison with previous research

As summarised in Chapter 1, we are aware of four studies that have investigated the relative effectiveness of two versus one antipyretic medicines.[48–51] To our knowledge, our study was the first to compare the effects of two antipyretics versus single-agent antipyretics using maximum licensed doses over a 48-hour period in children recruited from and managed in the community. This study is one of only two studies[50] to investigate the treatment effect of two medicines on fever-associated discomfort. Previous studies have recruited from secondary care,[48–51] investigated the effects of single doses[49,51] and not used continuous thermometry. To our knowledge, continuous thermometry has been used only once previously for 4 hours in a trial comparing paracetamol with physical methods.[82]

The finding that ibuprofen is more effective than paracetamol in the first 4 hours is consistent with the literature.[46] We are not surprised that the antipyretic activity of ibuprofen develops faster (by 27 minutes) than that of paracetamol, even though previous studies have shown that time to maximum antipyresis is lower for paracetamol than for ibuprofen (133 versus 183 minutes respectively).[32] This is because other studies measured time to maximum reductions in temperatures, not the more clinically meaningful time to achieving antipyresis.

Strengths and weaknesses

The main strengths of our study are its internal validity (concealed randomisation, blinding of children, nurses and investigators to allocation and minimal data attrition) and the use of continuous thermometry for 24 hours to generate the time without fever outcome. As discussed on p.10, the duration of continuous thermometry was long enough to enable a fair comparison between antipyretic agents with differing times to maximum antipyretic effect and to measure the effects of multiple doses.[32]

We are aware of five potential weaknesses. First, there was no placebo-only group, our data cannot inform the decision regarding whether or not to use antipyretics. Our design was deliberate as we did not think parents would be willing to allow children to participate in a trial with a placebo-only group. Indeed, 81% of parents exiting the PITCH study said that this was the case. That said, three previous studies have shown that both paracetamol and ibuprofen are more effective than placebo,[45,44,102] and one that paracetamol is more effective than unwrapping for the relief of fever.[82]

Second, the recruited sample did not give sufficient power to detect plausible treatment effects for discomfort. However, an exploratory analysis did show an association between discomfort and temperature, suggesting that, with adequate power, the effects on symptoms might have followed those of temperature.

Third, an axillary temperature of 37.8°C might not be regarded as denoting fever. As there is no agreed definition of fever or how to measure temperature,[13] temperature selection was to some extent arbitrary. For example, a lack of agreement between temperature measured using different thermometer types and at different sites means

that an axillary temperature of 37.8°C could represent a rectal temperature of as high as 39.7°C.[103] Temperature is such a dynamic variable that, although many children did not meet our criterion for temperature before randomisation, most were already being treated for a febrile illness and their parents and doctors thought that treatment with up to two drugs was warranted. The mean temperature at baseline was 38.5°C (Table 5), a temperature at which 90% of doctors and 70% of nurses would recommend treatment,[19] and most of the children were unwell with febrile illness affecting their comfort, appetite, activity and sleep.

Fourth, the success of blinding was assessed at the 48-hour nurse visit by asking parents to guess which drugs were active. Overall, the 153 parents who responded were not able to guess treatment, but the 83 who expressed a definite opinion did identify allocation more often than would be expected by chance. Although we carried out blinded taste tests and volunteers could not distinguish placebo from active drugs, some parents may have been better able to do so because they had more time to compare study drugs with known products in the home as well as observing their children's responses to treatment. Although this could have influenced the parental recording of the discomfort outcome, we do not see how it could influence the outcome of time without fever.

Finally, given the recruitment challenges, it is possible that our sample was not representative of the general population. For example, we do not know how the possibility of receiving either or both medicines affected parental consent for children with more or less severe illnesses, or of those with prior preferences for medicine type. However, given that most difficulties were due to children being insufficiently pyrexial, we do not believe the randomised children are likely to differ substantially from the general population.

Clinical implications of this research

For health-care professionals and parents

It is good practice for parents, nurses and doctors who have made the decision to treat young children unwell with fever to use the minimum number of medicines.[22] While other studies have shown that paracetamol is superior to placebo,[44,45,102] our study suggests that parents wishing to provide faster and more prolonged fever relief in the first 4 hours should use ibuprofen in preference to paracetamol. Similarly, where symptoms are expected to last at least 24 hours (the majority of children with fever), parents wanting to maximise the time without fever should consider the relative risks (inadvertently exceeding the maximum recommended dose) and benefits (an additional 2.5 or 4.4 hours without fever) of alternating both medicines in preference to using ibuprofen or paracetamol alone. Pragmatically, although our trial design does not specifically address this, we speculate that, if a child remains unwell after a first dose of ibuprofen, subsequent alternation of both medicines for 24 hours will be more effective than either monotherapy. This is supported by the Nabulsi study,[51] which complements the evidence from our study in two ways. First, the medicine doses used were the same and, second, it randomised children receiving ibuprofen at baseline to receive paracetamol or placebo at 4 hours. Its results were consistent with PITCH, finding that more children receiving paracetamol were afebrile between 6 and 8 hours than in the placebo group. However, the complexity of using two medicines over a 24-hour period is more likely to lead to inadvertently exceeding the maximum recommended dose and, conversely, the simpler thrice-daily dosing of ibuprofen may contribute to its superiority over paracetamol. Irrespective of how doses are determined, we believe that, to minimise inadvertently exceeding the maximum recommended dose, multiple blank charts for parents to record when and how much medicines have been given should be supplied with all medicines.

Comments about the intervention

These medicines are usually dosed by age in the community in the UK, though in other countries (e.g. the US) the medicine bottles contain dosing advice by both age and weight. However, we recognise that calculating medicine doses by weight means that our results inform primary and secondary care practice more than that in the home. We decided against a 'dose by age' regimen for two reasons. First, 'dose by weight' calculations have been advocated in the Children's National Service Framework[79] because they are more appropriate than 'dose by age', particularly for children at the extremes of weight and close to age boundaries, who could be receiving as much as 50% more or less paracetamol and 100% more ibuprofen (see Figure 2 and Figure 3). Thus, we wanted to avoid under/overdosing children who were heavy/light for their age. Second, given this and the dose presentations in the BNFC,[37] we believe that more medicines for children will be administered by weight in the future. However,

we think that two steps are needed before parents can routinely use weight to determine dose in the home. First, studies should investigate the safety implications of any differences between estimates of children's weights measured by parents using domestic scales (or recently recorded weights in parent-held children's health records) and those measured by professionals using paediatric scales. Second, manufacturers and suppliers of antipyretics should consider routinely including dose by weight tables and have investigated the accuracy with which they are followed by parents.

The pragmatism of the intervention changed with time, moving from the efficacy end of the spectrum in the first 4 hours, when parents were observed to give their children the first medicine doses, to effectiveness in the second 24 hours, when the medicines were used unobserved in response to the child's symptoms. This could, in part, explain the lack of observed effects on discomfort and the other fever-associated symptoms at 48 hours. Our data also show that a higher proportion of children received the full three doses of ibuprofen than received the maximum four doses of paracetamol, which could have contributed to the superior effectiveness of the former.

Minimising adverse effects

None of the five SAEs recorded in our trial was related to the trial medicines or study design. For parents to use the interventions safely, we recommend that the same exclusion criteria as in the trial are followed. All children should be screened for medicine intolerances or allergies, and clinicians will need to give individualised advice regarding medicine suitability for children with underlying medical conditions that could be worsened by the medicines.[33,34] Recent case reports of children given NSAIDs, many of whom were fluid depleted and went on to develop renal failure, highlight the concerns about giving ibuprofen to dehydrated children.[65,68] Fortunately, 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. Nonetheless, there are particular concerns about possible interactions between paracetamol and ibuprofen, because ibuprofen inhibits the production of glutathione in the kidney, which detoxifies renal paracetamol metabolites.[69] Thus, ibuprofen should not routinely be given in the community to children with clinical features of dehydration or those weighing less than 7 kg.[34] We did not exclude children with asthma as there is good evidence that ibuprofen is no more likely to exacerbate asthma than paracetamol,[73] although more care may be needed for ibuprofen-naive children with asthma.

Guideline development

We agree with the NICE fever guidelines that antipyretics should be used only when children have fever associated with other symptoms,[22] although further research is needed to establish the effectiveness of antipyretics for the relief of these symptoms. However, we believe that the guidance regarding the use of two medicines need not be so cautious now that there is good evidence of superiority for two medicines over one for increasing time without fever over 24 hours.

Cost-effectiveness

Summary of main results

The results of the economic analysis, which assumed that patients bought all study medicines over the counter, indicate that the combined therapy was cheaper than either paracetamol or ibuprofen from the NHS perspective. It was the most expensive option for parents at 48 hours, but by day 5 this treatment regime was also cheapest for parents because lower travel costs and less time off work compensated for the greater expenditure on medication.

Comparison with existing literature

Although there are no published economic evaluations comparing single and dual therapy for childhood fever, we can assess the face validity of the results of our economic analysis by looking at the cost of illness. In this study, the mean cost of an episode of illness over 5 days was £38 to the NHS (allowing for the cost of the initial consultation) and £27 to parents and carers. A recent cost of illness analysis estimated the cost of an episode of childhood cough to be £25 to the NHS and £15 to parents.[104] Fever resulted in greater use of health-care resources across the board, the difference being most marked in the use of accident and emergency and out-of-hours care, the purchase of over-the-counter medication and the effect on parental time off work.

Strengths, weaknesses and implications

The economic evaluation benefited from being part of a well-conducted randomised controlled

trial. Data collection and entry were carried out in a thorough way and checked rigorously. The data quality was also enhanced by the method of collection, i.e. the research nurses dealing with the parents face-to-face or by telephone. Using this method, any misunderstandings or ambiguities could be resolved immediately and thus reduce the number of missing items or spurious entries.

Owing to the recruitment challenges, we were unable to achieve our original target sample size. This impacted on interpretation of the cost data and some of the outcome data as the study was eventually powered to detect clinical differences solely in the time spent without fever. This outcome was measured at 4 hours and 24 hours, but cost data were not collected for this short time period. We were underpowered with respect to the outcomes measured or reported at 48 hours and 5 days, when cost data were collected.

The cost-effectiveness analysis, conducted at 48 hours, was based on a combined measure of temperature, discomfort, activity, appetite and sleep, which we defined as 'recovered' (normal for that child). As these outcomes were affected by the lack of power, our choice of outcome for the cost-effectiveness analysis limits its value. None of the comparisons were able to demonstrate evidence of differences between the groups in terms of cost-effectiveness, and it is therefore difficult to draw strong conclusions from this analysis.

The economic evaluation was intended to enhance the clinical study by taking a longer-term view and providing information about costs and benefits over the whole episode of illness. This time point was chosen as it was anticipated that by day 5 most children would have 'recovered'. In fact, this was not the case; using our strict definition only 36% children had 'recovered' at this point, mainly because appetite and sleep had not 'returned to normal for that child'. It would seem that disruption of eating and sleeping patterns following an illness lasts longer than we originally hypothesised. However, it is unlikely that these effects would result in significant further use of health care as nearly 90% children had a normal temperature and no discomfort at this point. The ultimate cost of the episode of illness is unlikely to be affected to any great extent.

The sensitivity analysis indicates the effect of our baseline assumptions on the results. The result looking at dosing by age should be interpreted with caution as the effectiveness results are for dosing by weight, which may well have greater effectiveness than dosing by age. However, the cost estimates may be closer to the real-life scenario in which parents buy over-the-counter medication and follow the dosing regime given.

The main study was designed to detect clinical differences, and none of the cost comparisons were able to demonstrate evidence of differences between the groups. It is therefore difficult to draw meaningful conclusions from the results, though we may regard them as indicative. A further weakness is that, although we were able to estimate the direct cost to parents of time off work, the data did not allow us to assign a societal value to that lost productivity. The economic evaluation provides no evidence to detract from the clinical implications. Indeed, though imprecise, the data suggest that two medicines are likely to be less costly than either one to both parents and the NHS.

Qualitative studies

Lessons from collaboration with the QUARTET study

Although the original qualitative study could not be completed, collaboration with the QUARTET study provided valuable conclusions from their observations of communication with parents. Analysis of the recruitment figures established that clinician endorsement of the trial was important to parents and encouraged them to participate. Information delivery during local recruitment was identified by the QUARTET study as a potential area for improvement. Ensuring that the research nurses approached all parents, even those that they thought could be challenging to engage with, was recommended. QUARTET also highlighted that nurses had a right to ask parents to participate and were not asking them for a 'favour'. The QUARTET study concluded that overall the trial team worked well together, worked efficiently and harmoniously and communicated extremely well.

Natural history of fever

Our data show that by 48 hours one-quarter, and by day 5 around one-third, of children with fever, the majority of whom were seen in primary care, were symptom free. Nearly half were taking antibiotics by day 5, and most were no longer using antipyretics. Three per cent required hospital admission. There are no other UK-based studies investigating the natural history of fever in children

presenting to primary care with which to compare our data. One US cohort of children with fever aged up to 3 months recruited by office-based paediatricians found that 36% were admitted to hospital.[105] The higher rates of more severe illness compared with our study are likely to be due to a different illness spectrum presenting to paediatricians as opposed to primary care clinicians and the younger age group. A large study of children aged up to 16 years presenting with any acute, non-trauma-related illness to primary care in Belgium[106] found that 0.8% were admitted to hospital. In a study of pre-school children with acute cough presenting to UK primary care, we found that 2% required hospital admission.[107] The proportion of children recovered at day 5 from the same cohort was around 20%.[108] Parents and clinicians should be aware that, overall, fever is a relatively short-lived symptom, but may have more serious prognostic implications than other common symptom presentations. Specific information regarding symptom duration and the potential for hospitalisation may help set realistic parental expectations.

Recruitment challenges

Summary of main challenges

Recruitment remained a challenge throughout the recruiting period. One of the main challenges lay with the nature of fever itself. Fever in children is often short-lived, a highly incident symptom of many illnesses, and in the UK its duration is usually actively curtailed by parents, who wish to use antipyretics. This had a twofold impact on parents and the research team. For parents, there was only a small amount of time to take on board the trial information and make a decision about participating. Often, parents declined early on during discussions due to being unable to take in the information needed to make an informed decision. Their ability to decide could also have been clouded by anxiety about their child's illness. For the research nurses, only a small window of opportunity existed to agree a visit time with parents, to ensure that children could receive medicines safely and to randomise the child because, often, children's fever subsided quickly.

A lack of clinical equipoise in relation to the trial's objectives was also evident. Many parents had strong feelings that using both medicines was best for their child and they did not want to participate in a trial that could not guarantee this. Parents often felt that using just one medicine was not enough and making use of both confirmed that they were doing the best they could for their child during their illness. Their lack of clinical equipoise and prolific use of antipyretics was sometimes supported by their GP or other health care professionals, which created a barrier to recruitment that was difficult to overcome.

Finally, motivating clinicians to refer was difficult for a variety of reasons. Often, clinicians had little time when in consultation with parents; some were unsure of how to introduce the trial and some simply forgot. Having clinician support for participation was key to helping improve rates, as endorsement for the trial by their GP appeared to be important to parents. Recruitment sites and their staff were important to the trial, and their support for the trial's need and their practical support by providing referrals and was crucial. Often 'research fatigue' was a problem; many sites were recruiting to several trials, and keeping PITCH in their minds was challenging.

Summary of main solutions to these challenges

As previously discussed, continued review and reflection of recruitment rates and problems enabled the team to address issues and provide workable solutions. One of the major solutions to recruitment was the introduction of the community recruitment strategy. This addressed several problems, the first of which was the effective removal of parental decline. Only those families that had an interest in the trial, took the time to call the hotline and request further information or participated. Second, this route enabled parents who had expressed an interest in the trial previously, but whose children were not sufficiently pyrexial, to re-enter of their own accord without the need to contact the NHS or their GP. This maximised the number of potentially eligible children coming into contact with the trial. Third, due to the unpredictability of fever, and in combination with the research nurses being available 7 days a week, the community strategy allowed parents to contact the trial at any time and at the start of their child's illness. This enabled the small window of opportunity to participate to be widened, which maximised participation.

Further strategies to address the main barriers to recruitment were implemented throughout the recruitment period. Restricting referrals to GPs

only was abandoned and recruitment broadened to include practice and/or triage nurses; this proved to be successful. Nurses were often more frequent referrers of potentially eligible children than GPs. Letters from their GP surgery informing them that they could be asked to participate gave parents more time to consider this and also served as an endorsement of the trial by the GP. Clinicians were kept abreast of eligibility criteria and were regularly reminded of how they could engage with potentially eligible families and communicate the trial to them. Much effort was put into making referrals easier for clinicians and to remind them to refer regularly. Issues of clinical equipoise were addressed with clinicians and parents on a regular basis to encourage consideration to participate. Communication with parents and clinicians was key to addressing this problem and other reasons not to participate or refer.

Lessons learned from the recruitment process

On reflection of the recruitment period and practices, many lessons were learnt about the way in which recruitment was conducted, carried out and improved. Improvements to the recruitment rates occurred over the course of the trial, and the conclusions drawn from these experiences has implications for future trials. These are discussed below.

Monitoring and addressing recruitment issues promptly

Addressing the issue of recruitment challenges was important in order to identify problems to recruitment. The original recruitment target of 807 children was ambitious using the one 'local' recruitment strategy, even though the recruitment period was long in duration. It was quickly established that further strategies were needed in order to maximise recruitment, and the remote and community methods were developed and implemented. Monthly reviews of recruitment rates and the act of reflecting on recruitment practices established the issues that needed to be rectified. Once problems were identified, the team proposed and discussed potential solutions in order to ensure that the correct decision was being made. Monitoring of those solutions was crucial to establish their effectiveness. Facing up to recruitment challenges rather than overlooking them is essential to improving rates throughout the recruitment period.

Tailoring recruitment strategies to the trial aims

The three strategies worked well with the nature of the illness investigated. Fever is an unpredictable symptom of illness, rather than an illness in its own right, and because of the numerous illnesses that can induce fever there are naturally numerous ways in which fever can be noticed, dealt with and managed in the community. Having several strategies to 'capture' these ways maximised the possibility of contact with pyrexial children. Each of the strategies has its own strengths and weaknesses; local recruitment was labour intensive, but fostered excellent relationships with collaborating sites. Remote recruitment was less labour intensive on the trial team, but relied heavily on clinicians engaging with families and referring regularly. The community strategy reduced the number of parental declines and captured potential children not reached via their GP, but was resource intensive and required promotion. However, it appears that the interdependent nature of these three strategies helped to saturate the pool of potential children and served as a reminder to those who had had contact previously.

Dedicated recruiting staff

Employing experienced paediatric research nurses who had experience of and could take a degree of clinical responsibility for the illness/fever was essential. Because the fever was short lived, having several research nurses available 7 days a week and at various times of the day enabled them to capture as many feverish children as possible. The research nurses empathised well with parents, were confident in communicating with them and their children, had experience about their concerns and could reassure them appropriately. Overall, effective communication between research nurses and parents was vital and developed a bond of trust between nurses and those parents who eventually participated in the trial.

Effective communication within the trial team and with collaborators

Communication was key to improving recruitment rates across the whole trial. Engaging with recruitment sites on a regular basis and developing close working relationships with them kept the trial in their minds and improved referrals. Regular problem solving, for example, making referring to the trial simpler and more user-friendly and breaking down barriers to referring, gave clinicians confidence to refer more easily and readily.

Informing clinicians of the importance of the trial helped motivate them to support the trial, and their endorsement was important to parents. Addressing parental concerns and establishing the real reason for declining, rather than accepting a possible disguised reason, ensured that parents had every opportunity to participate and, furthermore, enabled the team to rectify barriers to recruitment.

Reflecting on the recruitment problems encountered with this trial and possible lessons for other trials suggests that detailed and realistic recruitment plans and targets from the outset is essential, particularly for unpredictable illnesses or symptoms. The three 'hot recruitment' strategies working simultaneously helped to improve recruitment rates by being interdependent and tailored to the trial aims and where the illness/symptom was mostly managed. The employment of dedicated paediatric research nurses was essential to the success of this trial. Effective communication within the trial team, and with parents and clinicians, and reflection on recruitment rates and practices were major factors in improving recruitment.

Comparison with the literature

Recruitment remained a challenge through the recruitment period. It is difficult to know whether a 'cold recruitment' strategy would have been more successful. To our knowledge, trials investigating combined treatments for fever in children to date have been conducted in emergency secondary care departments (where consecutive children presenting with fevers have been recruited) or 'hot recruitment' was conducted via clinician referral.[48–52] Recruitment rates were lower than anticipated, but in line with the experience of other paediatric randomised controlled trials. A review of trials from 1982 to 1996 found that 24% of single-centre studies recruited fewer than 25 children, 54% recruited fewer than 40 children, 73% recruited fewer than 60 children and 87% recruited fewer than 100 children.[109] Overall, research evidence regarding recruitment rates is lacking. Many studies tend to suggest that recruitment is generally rather poor. For example, a review of 333 cancer trials completing recruitment between 1971 and 2000 found that less than half (48%) reached or exceeded their recruitment target, only 19% recruited at least 75% of their target and 20% recruited less than 25% of their target.[110] Furthermore, there is little evidence-based practice regarding recruitment strategies employed, even though a wide range of interventions are often utilised.[111] A recent study[112] concluded that establishing good relationships with practices, simplifying referrals and offering enhanced care to participants were effective methods of improving recruitment rates. These conclusions are closely linked to the experiences of this trial. Generally, the literature concludes that there is a lack of sufficient reporting of recruitment rates and practices and evidence to inform researchers on recruitment strategies that work best.

Consent

A review of randomised controlled trials published in the Archives of Disease in Childhood from 1982 to 1996 found that consent rates were not reported in 45% of trials. In studies in which consent rates were reported, the rate was reported to be 100% in a very high proportion [111/137 (81%)] of studies. Consent rates varied with the study setting: of those that reported the rate, the consent rate was 100% in 51/57 (90%) inpatient studies, 51/65 (78%) outpatient studies and 9/15 (60%) community studies.[109]

Conclusions

Clinical

Doctors, nurses and parents wishing to use medicines to treat young children who are unwell with fever should be advised to use ibuprofen first and to consider the relative risks and benefits of using ibuprofen plus paracetamol over either one. Pragmatically, we speculate that, if a child remains unwell after a first dose of ibuprofen, subsequent use of both medicines will be more effective than either monotherapy. To guarantee effectiveness, doses should be calculated by weight. We recommend that dose times are recorded carefully to avoid accidentally exceeding the maximum recommended dose and that, to minimise this risk, manufacturers should supply multiple blank charts for parents to record when and how much medicines have been given.

Cost

The economic analysis does not conflict with the clinical results and although imprecise, shows that over the whole period of the episode of illness, treating children with both medicines could result in less use of other health care resources than either of the single therapies. This results in lower

costs to the NHS and to parents because of less travel and time off work.

Research

Further research is needed for 'dose by weight' regimens to be used safely in the community. Studies should investigate the dose implications of differences between estimates of children's weights measured by parents using domestic scales (or recently recorded weights in parent held children's health records) and those measured by professionals using paediatric scales. Further adequately powered research is also needed to investigate the relative effectiveness of two versus one medicine for discomfort and other fever-associated symptoms and to improve the precision of the cost-effectiveness estimates.

Acknowledgements

We are extremely grateful to staff at the Avon, Gloucestershire and Wiltshire NHS Direct, the Bristol GP practices (see full list below), the South Bristol Walk-in Centre, the Bristol Royal Hospital for Children's Emergency Department and the children and parents whose participation made this study possible. We are indebted to the South West Medicines for Children Local Research Network (MRCN); the research nurse team of Wendy Horseman, Joy Farrimond, Becky Powell, Sheila Shatford, Paula Richards and Vicky Payne (MCRN), Wendy Patterson (trial co-ordinator), Susan Doohan and Stephanie Burke (project administrators), Dr Knut Schroeder, Dr Marjorie Weiss, Dr Ian Higginson and Professor Alan Emond (co-applicants), and Kate Pitcher (data entry and quality). We thank Dr Will Christian (nurse triage documentation) and Dr Tim Kenny for permission to reproduce the Patient UK 'Fever in Children' parent information leaflet. Finally, our thanks to the Trial Steering Committee and Data Monitoring and Safety Committee members for their expertise and support. For the duration of the trial, A.H. held a postdoctoral award from the National Coordinating Centre for Research Capacity Development (NCCRCD), Department of Health. The views and opinions expressed in this report do not necessarily reflect those of the NIHR Health Technology Assessment, NCCRCD or the Department of Health. The active medicines and matched placebos were purchased from Pfizer Ltd and DHP Investigational Medicinal Products respectively. Neither had any other role in the trial design, analysis or writing of the report.

GPs practices which referred to the PITCH trial were Horfield Health Centre, Gloucester Road Medical Centre, Whiteladies Health Centre, Montpelier Health Centre, Southmead & Henbury Family Practice, Bradgate Surgery, Gaywood House Surgery, The Malago Surgery, Lawrence Hill Health Centre, The Merrywood Practice, St George Health Centre, Monks Park Surgery, The Lennard Surgery, Grange Road Surgery, Kingswood Health Centre, Woodside Practice (Brooklea Health Centre), The Wedmore Practice, Stoke Gifford Medical Centre, Hillview Family Practice, Lodgeside Surgery, Hanham Surgery, The Stokes Medical Centre, Dr Robertson and Dr Bonnett (The Surgery), Seymour Medical Practice, Willow Tree Surgery, Elm Lodge Surgery and the Wellspring Surgery.

Contribution of authors

A.D.H. had the original idea for the study. A.D.H., A.A.M., S.H., M.F. and T.J.P. designed the trial, drafted the protocol and were responsible for its ongoing conduct. N.M.R. and C.C. were responsible for day-to-day trial management. C.C., A.A.M., S.H. and T.J.P. analysed the data. All authors were involved in data interpretation, drafting the report and have approved the final version.

Publications

Hollinghurst S, Redmond, N Costelloe C, Montgomary A, Fletcher M, Peters TJ, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): economic evaluation of a randomised controlled trial. BMJ 2008;**337**:a1490.

Hay AD, Costerlloe C, Redmond NM, Montgomery AA, Fletcher M, Hollinghurst, S, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial BMJ 2008; **337**:a1302.

References

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**:367–74.

2. Kai J. What worries parents when their preschool children are acutely ill, and why: a qualitative study. BMJ 1996;**313**:983–6.

3. Blumenthal I. What parents think of fever. Fam Pract 1998;**15**:513–18.

4. Impicciatore P, Nannini S, Pandolfini C, Bonati M. Mothers' knowledge of, attitudes toward, and management of fever in preschool children in Italy. Prev Med 1998;**27**:268–73.

5. Munro J, Nicholl J, O'Cathain A, Knowles E. Impact of NHS direct on demand for immediate care: observational study. BMJ 2000;**321**:150–3.

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**:399–402.

7. Management of childhood fever. Lancet 1991;**338**:1049–50.

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**:280–9.

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

10. National Assembly for Wales. Headline Statistics Wales. National Assemby for Wales; 2003. URL: www.wales.gov.uk/keypubstatisticsforwales/content/publication/health/2003/sdr33-2003/sdr33-2003-chems-g-o.xls

11. Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. Am J Med 2001;**111**:304–15.

12. Dinarello CA, Wolff SM. The role of interleukin-1 in disease. N Engl J Med 1993;**328**:106–13.

13. Michael MS, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004;**22**:551–6.

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

15. Morley CJ, Hewson PH, Thornton AJ, Cole TJ. Axillary and rectal temperature measurements in infants. Arch Dis Child 1992;**67**:122–5.

16. 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**:1875.

17. Kai J. Parents' perceptions of taking babies' rectal temperature. BMJ 1993; **307**:660–2.

18. Hay AD, Peters TJ, Wilson AD, Fahey T. The use of infrared thermometry for the detection of fever. Br J Gen Pract 2004; **54**:448–50.

19. Sarrell M, Cohen HA, Kahan E. Physicians', nurses', and parents' attitudes to and knowledge about fever in early childhood. Patient Education & Counseling 2002; **46**:61–65.

20. Sydenham T. Methodus curandi fibres. 1666.

21. Kluger MJ. Fever revisited. Pediatrics 1992;**90**:846–50.

22. NICE. Feverish illness in children. Assessment and initial management in children younger than 5 years. London: NICE; 2007.

23. Schmitt BD. Fever phobia: misconceptions of parents about fevers. Am J Dis Child 1980;**134**:176–81.

24. Betz MG, Grunfeld AF. 'Fever phobia' in the emergency department: a survey of children's caregivers. Eur J Emerg Med 2006;**13**:129–33.

25. Crocetti M, Moghbeli N, Serwint J. Fever phobia revisited: have parental misconceptions about fever changed in 20 Years? Pediatrics 2001;**107**:1241–6.

26. Rylance GW, Woods CG, Cullen RE, Rylance ME. Use of drugs by children. BMJ 1988;**297**:445–7.

27. Kai J. Parents' difficulties and information needs in coping with acute illness in preschool children: a qualitative study. BMJ 1996;**313**:987–90.

28. Wikipedia. Paracetamol. 2007.

29. Calixto JB, Beirith A, Ferreira J, Santos AR, Filho VC, Yunes RA. Naturally occurring antinociceptive substances from plants. Phytother Res 2000;**14**:401–18.

30. International Ibuprofen Foundation. The story of ibuprofen. 2007. URL: www.ibuprofen-foundation.com

31. Adcock Ingram Limited. Lotem suspension. South African Electronic Package Inserts (2004, cited 13 November 2007). URL: http://home.intekom.com/pharm/adcock/lotemsyr.html.

32. 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**:181–9.

33. Electronic Medicines Compendium. Summary of Product Characteristics for Calpol Sugar free Infant Suspension; 2004. URL: www.medicines.org.uk. Accessed July 2004.

34. Electronic Medicines Compendium. Summary of Product Characteristics Calprofen; 2004. Accessed July 2004.

35. Mackowiak PA, Plaisance KI. Benefits and risks of antipyretic therapy. Ann NY Acad Sci 1998;**856**:214–23.

36. Schwartz JI, Chan CC, Mukhopadhyay S, McBride KJ, Jones TM, Adcock S, et al. Cyclooxygenase-2 inhibition by rofecoxib reverses naturally occurring fever in humans. Clin Pharmacol Ther 1999;**65**:653–60.

37. BNF for Children. London: BMJ Publishing Group; 2007.

38. Lagerlov P, Helseth S, Holager T. Childhood illnesses and the use of paracetamol (acetaminophen): a qualitative study of parents' management of common childhood illnesses. Fam Pract 2003;**20**:717–23.

39. Mayoral CE, Marino RV, Rosenfeld W, Greensher J. Alternating antipyretics: is this an alternative? Pediatrics 2000;**105**:1009–12.

40. Havinga W. Time to counter 'fever phobia'. Br J Gen Pract 2003;**53**:253.

41. Hay AD, Stephens P. Do antipyretics prevent febrile convulsions in young children? South West Society for Academic Primary Care Conference, Torquay, 2007.

42. Meremikwu M, Oyo-Ita A. Physical methods for treating fever in children. Cochrane Database of Systematic Reviews 2003;**2**:CD004264.

43. Meremkwu M, Oyo-Ita A. Paracetamol for treating fever in children (Cochrane Review). Cochrane Library, Issue 1, 2003: Update Software 2002.

44. Walson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. Clin Pharmacol Ther 1989;**46**:9–17.

45. 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**:803–11.

46. Goldman RD, Ko K, Linett LJ, Scolnik D. Antipyretic efficacy and safety of ibuprofen and acetaminophen in children. Ann Pharmacother 2004;**38**:146–50.

47. 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**:521–6.

48. Lal A, Gomber S, Talukdar B. Antipyretic effects of nimesulide, paracetamol and ibuprofen-paracetamol. Indian J Pediatr 2000;**67**:865–70.

49. Erlewyn-Lajeunesse MDS, Coppens K, Hunt LP, Chinnick PJ, Davies P, Higginson IM et al. Randomised controlled trial of combined paracetamol and ibuprofen for fever. Arch Dis Child 2006;**91**:414–16.

50. Sarrell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. Arch Pediatr Adolesc Med 2006;**160**:197–202.

51. Nabulsi MM, Tamim H, Mahfoud Z, Itani M, Sabra R, Chamseddine F, et al. Alternating ibuprofen and acetaminophen in the treatment of febrile children: a pilot study. BMC Med 2006;**4**:4.

52. Kramer LC, Richards PA, Thompson AM, Harper DP, Fairchok MP. Alternating antipyretics: antipyretic efficacy of acetaminophen versus acetaminophen alternated with ibuprofen in children. Clin Pediatr 2008;**47**:907–11.

53. Tenison M, Eberhardt M, Pellett N, Heller M. Is the combination of ibuprofen and acetominophen a better pediatric antipyretic than ibuprofen alone? Ann Emerg Med 2005;**46**:S54.

54. El-Radhi AS. Lower degree of fever at the initial febrile convulsion is associated with increased risk of subsequent convulsions. Eur J Paediatr Neurol 1998;**2**:91–6.

55. Uhari M, Rantala H, Vainionpaa L, Kurttila R. Effect of acetaminophen and of low intermittent doses of diazepam on prevention of recurrences of febrile seizures. J Pediatr 1995;**126**:991–5.

56. Schnaiderman D, Lahat E, Sheefer T, Aladjem M. Antipyretic effectiveness of acetaminophen in febrile seizures: ongoing prophylaxis versus sporadic usage. Eur J Pediatr 1993;**152**:747–9.

57. 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**:E51.

58. Van Esch A, Steensel-Moll HA, Steyerberg EW, Offringa M, Habbema JD, Derksen-Lubsen G. Antipyretic efficacy of ibuprofen and acetaminophen in children with febrile seizures. Arch Pediatr Adolesc Med 1995;**149**:632–7.

59. 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**:367–71.

60. McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. Arch Dis Child 1996;**74**:164.

61. European Parliament. European Clinical Trial Directive 2001/20/EC 2001.

62. Walson PD, Galletta G, Chomilo F, Braden NJ, Sawyer LA, Scheinbaum ML. Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. Am J Dis Child 1992;**146**:626–32.

63. Vauzelle-Kervroedan F, d'Athis P, Pariente-Khayat A, Debregeas S, Olive G, Pons G. Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children. J Pediatr 1997;**131**:683–7.

64. Richardson J, Sills J. Hypothermia following fever. Arch Dis Child 2004;**89**:1177.

65. Mathews John C, Shukla R, Jones CA. Using NSAID in volume depleted children can precipitate acute renal failure. Arch Dis Child 2007;**92**:524–6.

66. Ulinski T, Guigonis V, Dunan O, Bensman A. Acute renal failure after treatment with non-steroidal anti-inflammatory drugs. Eur J Pediatr 2004;**163**:148–50.

67. Del Vecchio MT, Eric R, Jonathan B, Mayoral CE, Rosenfeld W, Marino RV, et al. Alternating antipyretics: is this an alternative? Pediatrics 2001; **108**:1236–37.

68. Moghal NE, Hegde S, Eastham KM. Ibuprofen and acute renal failure in a toddler. Arch Dis Child 2004;**89**:276–7.

69. McIntire SC, Rubenstein RC, Gartner JC, Gilboa N, Ellis D. Acute flank pain and reversible renal dysfunction associated with nonsteroidal anti-inflammatory drug use. Pediatrics 1993;**92**:459–60.

70. Kauffman RE, Sawyer LA, Scheinbaum ML. Antipyretic efficacy of ibuprofen vs acetaminophen. Am J Dis Child 1992;**146**:622–5.

71. Lesko SM, Mitchell AA. Renal function after short-term ibuprofen use in infants and children. Pediatrics 1997;**100**:954–7.

72. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner- based randomized clinical trial. JAMA 1995; **273**:929–33.

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

74. Zerr DM, Alexander ER, Duchin JS, Koutsky LA, Rubens CE. A case-control study of necrotizing fasciitis during primary varicella. Pediatrics 1999;**103**:783–90.

75. Lesko SM, O'Brien KL, Schwartz B, Vezina R, Mitchell AA. Invasive group A streptococcal infection and nonsteroidal antiinflammatory drug use among children with primary varicella. Pediatrics 2001;**107**:1108–15.

76. Mikaeloff Y, Kezouh A, Suissa S. Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease. Br J Clin Pharmacol 2008;**65**:203–9.

77. NHS Direct. Management of fever in childhood (2004). URL: www.nhsdirect.nhs.uk/help/bodykey/questions/index.aspx?nodes=Zo2C8T%2fM90twO3uYRCkWehq5UEPMzWBQdMFZ4TSEtIlZ6pgm%2fWGm8uqDswB0uaeThxd0iu5rwsyjF5VL1LpAv6DXA3K1aDnURoAe123RCes%3d#pos1766 (accessed 31 March 2009).

78. Prodigy. Paracetamol and ibuprofen in the treatment of fever and acute pain in children under 16 years. Prodigy Quick Reference Guide 2006. URL: http://www.cks.library.nhs.uk/clinical_knowledge.

79. Department of Health. National Service Framework for children, young people and maternity services. London: HMSO; 2004

80. Li SF, Lacher B, Crain EF. Acetaminophen and ibuprofen dosing by parents. Pediatr Emerg Care 2000;**16**:394–7.

81. Wong A, Sibbald A, Ferrero F, Plager M, Santolaya ME, Escobar AM et al. Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in children: results of a multinational, randomized, modified double-blind study. Clin Pediatr 2001;**40**:313–24.

82. Kinmonth AL, Fulton Y, Campbell MJ. Management of feverish children at home. BMJ 1992;**305**:1134–6.

83. Hay AD, Redmond N, Fletcher M. Antipyretic drugs for children. BMJ 2006;**333**:4–5.

84. Redmond N, Hay AD. Treatments for fever in children. GP Magazine, 2 March 2007.

85. British Parliament. Medicines For Human Use (Clinical Trials) Regulations; 2004, 2007.

86. Department of Health. Research governance framework for health and social care; 2001.

87. 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**:971–3.

88. Zar J. Biostatistical Analysis, 2nd edn. Englewood Cliffs, NJ: Prentice-Hall; 1994.

89. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;**134**:663–94.

90. Curtis L, Netten A. Unit costs of health and social care 2005. PSSRU, University of Kent; 2005.

91. National tariff 2006/07. London: Department of Health; 2006.

92. Department of Health. Reference cost index. URL: http://www dh gov uk/assetRoot/04/10/55/53/04105553 xls; 2004.

93. Salisbury C, Chalder M, Manku-Scott T, Nicholas R, Deave T, Noble S, et al. The national evaluation of NHS walk-in centres. Final report. 2006.

94. Munro J, Nicholl J, O'Cathain A, Knowles E, Morgan A. Evaluation of NHS Direct first wave sites: Final report of the phase 1 research. Medical Care Research Unit UoS, editor. 2001. Ref Type: Report

95. British Medical Association and Royal Pharmaceutical Society of Great Britain. British national formulary (BNF). No. 53, March 2007. London: BMA and RPS; 2007.

96. The Automobile Association. The AA schedule of motoring costs. URL: www.theaa com/motoring-advice/motoring-costs html; 2005.

97. Office for National Statistics. Population estimates for England and Wales. URL: www.statistics.gov.uk; 2006.

98. Beale N, Hollinghurst S, Taylor G, Gwynne M, Peart C, Straker-Cook D. The costs of care in general practice: patients compared by the council tax valuation band of their home address. Fam Pract 2005;**22**:317–22.

99. Department of Health. National Tariff. URL: http:// www dh gov uk/assetRoot/04/09/15/32/04091532 xls; 2005 .

100. Medical Research Council. Primary health care research review. 1997. London, Medical Research Council; 1997.

101. Stocks N, Fahey T. Labelling of acute respiratory illness: evidence of between- practitioner variation in the UK. Fam Pract 2002;**19**:375–7.

102. Brewer EJ, Jr. A comparative evaluation of indomethacin, acetaminophen and placebo as antipyretic agents in children. Arthritis Rheum 1968;**11**:645–51.

103. Craig JV, Lancaster GA, Williamson PR, Smyth RL. Temperature measured at the axilla compared with rectum in children and young people: systematic review. BMJ 2000;**320**:1174–8.

104. Hollinghurst S, Gorst C, Fahey T, Hay A. Measuring the financial burden of acute cough in pre-school children: a cost of illness study. BMC Fam Pract 2008;**9**:10.

105. 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 2004;**291**:1203–12.

106. Van den Bruel A, Aertgeerts B, Bruyninckx R, Aerts M, Buntinx F. Signs and symptoms for diagnosis of serious infections in children: a prospective study in primary ca. Br J Gen Pract 2007;**57**:538–46.

107. Hay AD, Fahey T, Peters TJ, Wilson AD. Predicting complications from acute cough in pre-school children in primary care: a prospective cohort study. Br J Gen Pract 2004;**54**:9–14.

108. Hay AD, Wilson A, Fahey T, Peters TJ. The duration of acute cough in pre-school children presenting to primary care: a prospective cohort study. Fam Pract 2003;**20**:696–705.

109. Campbell H, Surry SA, Royle EM. A review of randomised controlled trials published in Archives of Disease in Childhood from 1982–96. Arch Dis Child 1998;**79**:192–7.

110. Vale C, Stewart L, Tierney J. Trends in UK cancer trials: results from the UK Coordinating Committee for Cancer Research National Register of Cancer Trials. Br J Cancer 2005;**92**:811–14.

111. Foy R, Parry J, Duggan A, Delaney B, Wilson S, Lewin-Van Den Broek NT, et al. How evidence based are recruitment strategies to randomized controlled trials in primary care? Experience from seven studies. Fam Pract 2003;**20**:83–92.

112. McKinstry B, Hammersley V, Daly F, Sullivan F. Recruitment and retention in a multicentre randomised controlled trial in Bell's palsy: a case study. BMC Med Res Methodol 2007;**7**:15.

113. Hay AD, Costelloe C, Redmond NM, Montgomery AA, Fletcher M, Hollinghurst S et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. BMJ 2008;**337**:a1302.

114. Hollinghurst S, Redmond N, Costelloe C, Montgomery AA, Fletcher M, Peters TJ, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): economic evaluation of the randomised controlled trial. BMJ 2008;**337**:a1490.

Appendix 1

CONSORT statement 2001 checklist

Table 22: CONSORT statement 2001 checklist

Paper section and topic	Item	Descriptor	Reported on page no.
Title and abstract	1	How participants were allocated to interventions (e.g. 'random allocation', 'randomised', or 'randomly assigned')	1, 7–9
Introduction			
Background	2	Scientific background and explanation of rationale	11–26
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected	27–32, 34, 35
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered	35–38
Objectives	5	Specific objectives and hypotheses	26
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measutsremen (e.g. multiple observations, training of assessors)	39–42
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	42, 43
Randomization – sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (e.g. blocking, stratification)	43
Randomization –allocation concealment	9	Method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	43, 44
Randomization – implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups	43, 44
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated	44, 82
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses	45, 46
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protoco, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons	53 –58, 86
Recruitment	14	Dates defining the periods of recruitment and follow-up	53
Baseline data	15	Baseline demographic and clinical characteristics of each group	59, 61
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by 'intention-to-treat'. State the results in absolute numbers when feasible (e.g. 10/20, not 50%)	59
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g. 95% confidence interval)	61–70

Table 22: CONSORT statement 2001 checklist (continued)

Paper section and topic	Item	Descriptor	Reported on page no.
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory	67–70
Averse events	19	All important adverse events or side effects in each intervention group	71–72
Discussion			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes	87 –98
Generalizability	21	Generalisability (external validity) of the trial findings	89
Overall evidence	2	General interpretation of the results in the context of current evidence	87

Appendix 2

Papers published in peer review journals

At the time of writing, three papers have been published in the British Medical Journal. The first, in January 2005, summarised the evidence for the use of both antipyretic medicines.[83] The second and third appeared as a paired publication reporting the clinical[113] and economic[114] findings with an accompanying editorial in September 2008. Further papers are planned detailing the recruitment lessons learned, the impact of protocol deviations and a comparison of nurse- and parent-measured child weights.

Appendix 3

PITCH poster (specific to GP surgeries)

PITCH

University of BRISTOL

Paracetamol and Ibuprofen for the Treatment of fever in CHildhood

Dear Parent or Guardian

Fever is a common problem in children. Medicines such as paracetamol (other names include Disprol® or Calpol®) and ibuprofen (Nurofen® or Calprofen®) are often used to treat fever. We are all concerned when children become feverish, but no one knows how best to treat the symptoms. Together, we would like to find out which medicine or combination of medicines work best. The PITCH study aims to answer this question.

We are inviting parents or guardians of children aged more than 6 months and less than five years old, who have come to the doctor or nurse today because of a fever (high temperature), to help with PITCH.

If you are interested in helping us, please ask your GP/ Nurse or Study Nurse (if present) for more information.

Thank you

[Site name]

Appendix 4

Invitation letter and summary parent information sheet

PITCH

University of BRISTOL

Paracetamol and ibuprofen for the Treatment of fever in Childhood

PITCH invitation letter v1.8

Dear Parent or Guardian

We are inviting parents or guardians of children aged between 6 months and less than five years old, who have come to the doctor/nurse today because of a fever (high temperature), to help with a research study called PITCH. This study is being run by Bristol University and will look at the best ways of treating fever. We would be grateful if you would answer the following questions by ticking the boxes that apply to you and your child. Please complete one form for each child seeing the doctor/nurse today.

	YES	NO
1. Is the child you have brought to the GP today aged more than 6 months and less than five years old?	☐	☐

If you have answered NO to question 1, please return this form to the research nurse in the waiting room. You don't need to do anything else.

	YES	NO
2. Does your child have a fever/high temperature OR have they recently had a fever/high temperature (in the last 24 hours)?	☐	☐

If you have answered NO to question 2, please could you indicate the reason for your visit below and then return the form to the research nurse in the waiting room.

Reason: _____

If you have answered YES to both questions, then please read the rest of this letter.

You are being invited to take part in the PITCH study. It will see which medicines (paracetamol and/or ibuprofen) work best for fever and will last for five days. Before you make a decision it is important for you to understand why the research is being done and what it will involve. There will be a number of chances to ask questions about the study: first, with the doctor or nurse you are about to see and second, with a research nurse, based at the [Site Name] or available by telephone. Please ask if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Thank you for reading this,
[Site Name]

1. What is the PITCH research study?

This study aims to see whether using paracetamol **and** ibuprofen together is any better than using either medicine alone when young children have a fever. We are all concerned when children become feverish, but no one knows how best to treat them. Together, we would like to find out which medicine or combination of medicines works best.

2. Why have I been invited to take part?

You are being invited because you have come to the doctor or nurse today with a young child with a fever. We hope that around 800 children in the Bristol area will take part in the PITCH study over its two-year course.

3. Do I have to decide now?

No. We understand that at the moment you are probably more concerned about your child and what the doctor/nurse will say. All you need to do for now is decide if you want to know more about the study. The doctor/nurse will see your child as usual and then ask you if you would like to talk to a PITCH study research nurse. She will be able to give you more information about the study so you can decide if you want to take part.

4. What do I do now?

If you have answered **yes to both questions on page 1**, and want to know more about the study please speak to the research nurse or mention it to the doctor/nurse you are about to see.

If you do not wish to know more about the study, it would help us if you felt you could tell us the reason, as this may help us with managing this study and in planning studies in the future. If you feel you can, please write these down below (together with your child's date of birth and your postcode) and then return this form to the research nurse in the waiting room.

REASONS _____

_____

_____

YOUR POSTCODE _____

CHILD'S DATE OF BIRTH / /

TODAY'S DATE / /

Thank you for considering taking part in this research.

Wendy Patterson

PITCH Study Co-ordinator.

Appendix 5

Fan-folded patient information sheet (PIS)

What will happen if my child takes part?

Taking part in the study lasts for 2 days with a phone call on the 5th day. The nurse will visit you at the start and on the next 2 days. These visits will be somewhere to suit you, usually your own home. On the 5th day, the nurse will telephone you. The very first visit will be to talk through the study with you and will be in time for your child to be given the study medicines if still feverish. Until this meeting, you should carry on and treat your child's fever as you normally would or as advised by your GP. **You should not delay treatment unnecessarily**.

Once you have had the study explained and if you are happy to take part, your child will join one of three groups who will all be given a medicine to treat their fever. The treatment is different between the groups to allow us to see whether either medicine (paracetamol or ibuprofen) on its own or the two together work best.

The medicines

One group will all be given paracetamol and syrup that looks and tastes like ibuprofen but doesn't have the medicine in it (called a placebo).

A second group will all be given ibuprofen and syrup that looks and tastes like paracetamol but doesn't have the medicine in it (a placebo).

The third group will all be given paracetamol and ibuprofen (no placebos).

All medicines are sugar and gluten free and every child will be given at least one medicine to treat fever. A computer program will randomly decide the treatment given to your child.

The amount of medicine given will be based on your child's weight. For paracetamol, this will be 15mg per kg body weight given up to 4 times daily and for ibuprofen, this will be 10mg/kg up to 3 times daily. These may be slightly different to the doses you normally give but are the recommended licensed doses.

Looking at how your child recovers

To compare how well the children in the three groups get on, we will measure their temperatures using a little box (temperature data logger) they wear in a vest for 24 hours (1 day). We will also ask you to keep a careful note for the first 48 hours of how well they have been (on a special card) and also to measure their temperature for us occasionally so that we can check the box is working properly and can see how they do when it has been taken off.

The PITCH nurse will explain everything again and answer any questions you have during your time in the study. We will not need to do any other tests.

What will I have to do?

You will be asked to give the study medicines for the first 2 days. During these 2 days, we will ask that you do not use any other medicines that you may have at home for fever or pain. Other medicines your child normally receives should be continued as usual, **so long as they do not contain paracetamol or ibuprofen**. We will ask you to meet the nurse at arranged times after the 1st and 2nd days in the study and keep the record of how well your child recovers. On the 5th day, we will telephone you and ask about the cost to you and the Health Service of looking after your child through their illness.

What are the alternative treatments?

There are no other medicines licensed in the UK for the treatment of fever in children, but there are other non-medicine treatments. We will give you an advice sheet of the other things you can do to help control your child's temperature like giving extra drinks and loosening his or her clothing.

What are the side effects of the study medicines?

The study medicines are not new and are available to buy at the chemists. When taken at the right dose, they are safe. The doctor or nurse you see will check it is safe for your child to use them. As with any medicine, the study medicines can have side effects.

For paracetamol, side effects are rare and mild. Rarely, the following can happen: skin rashes or other sorts of allergy, bruising or bleeding.

For ibuprofen, side effects are uncommon. The most common are a mild laxative effect and stomach discomfort. Rare side effects are nausea (feeling sick), stomach pains, a rash, itching or worsening of asthma, unexplained wheezing or shortness of breath. Very rarely, facial swelling (get medical help immediately), black, tarry stools, bleeding from the stomach or bowels, skin peeling or easy bruising may happen.

If your child experiences these or any other symptoms, you should contact your GP in the usual way, telling him/her that your child is in the PITCH study. Where necessary, your GP will be able to find out which medicine/s your child has received.

What are the possible disadvantages and risks of taking part?

Taking part in this study is **very unlikely** to put you or your child at greater risk than if you chose not to take part because:

- Your child will be given treatments already widely used by parents
- Your doctor or nurse will have checked that the study medicines are safe for your child
- You will not be asked for any sensitive information.
- All the children will be given at least one medicine which treats fever.

The first visit may last for up to 1 hour, and the next two visits between 30 and 45 minutes (less than an hour). The telephone call on day 5 will last for up to 15 minutes. We wish to keep any demands on your family to a minimum and will be happy to arrange for the visits to be in your own home.

What are the possible advantages of taking part?

The study treatment is the same or similar to what you would normally be prescribed. We hope that the results from the study will help inform us of the best way to treat children with fever in the future.

What if something goes wrong?

It is unlikely that taking part in the study will harm your child, but if harm does result from this research, there are no special compensation arrangements.

If for any reason you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you should contact the Study Coordinator Ceire Costelloe, or the normal National Health Service complaints system can be used. If you are harmed due to someone's negligence, you may have grounds for a legal action but you may have to pay for it yourself.

Will my taking part in this study be kept confidential?

If you agree to take part in the study, your child's medical records may be inspected by authorised staff from the Department of Health or from the research team at Bristol University or from other regulatory authorities. This may be done to check the study is being carried out properly.
The research team will only use any personal information for the purposes of the study. (All information will be protected according to the UK Data Protection Act 1998).
We will let your GP know you are taking part but any information to do with the study will be kept strictly confidential. Any reports resulting from the study will have your name and address removed so that you or your child cannot be identified.

What will happen to the results of the research study?

We plan to publish the results of this study by the end of 2007. We will ask the GP practices and medical centres involved to display a summary of our findings and, if you are interested to know more, you will be able to ask your GP practice/medical centre for more information. You can also contact the PITCH study team directly.

Who is organising and funding this research?

The study is being organised by a team of researchers from the University of Bristol, led by Dr Alastair Hay. The study is supported by a grant from the National Coordinating Centre for Health Technology Assessment (part of the NHS) and is regulated and monitored by the Department of Health.

Who has reviewed this study?

This study has been approved by the Bath Local Research Ethics Committee.

Who do I contact for further information?

In most cases, the research nurse will be contacting you. If they don't, or you have any other questions or decide you would rather not take part, please contact:
Susan Doohan, or Ceire Costelloe.
Their telephone numbers and an email address are given on this leaflet.
You will be given copies of this information sheet and a signed consent form to keep.

What do I do now?

Please continue to treat your child as advised by your doctor/nurse until the PITCH study team contact you. If at any time you become concerned about your child's condition, **do not wait for the PITCH team to contact you**, but contact NHS Direct (0845 46 47) or your GP in the usual way.

Thank you for considering taking part in this research.

Ceire Costelloe
PITCH study coordinator on behalf of the PITCH study investigators.

Study Contact Details

Joy Farrimond,
Study Nurse Tel: 07768 557624
Becky Powell,
Study Nurse Tel: 07768 040125
Sheila Shatford,
Study nurse Tel: 07768 040117
Vicky Payne,
Study Nurse Tel: 07768 810679
Paula Richards,
Study Nurse Tel: 07881 836686
Susan Doohan
Study Secretary Tel: 0117 3313835 Fax: 0117 9546647
Dr. Ceire Costelloe
Study Co-ordinator Tel: 0117 331 3831
Dr Alastair Hay
Lead Investigator Tel: 0117 331 3853
PITCH **Office**:
Academic Unit of Primary Health Care, 25-27 Belgrave Road, Clifton, Bristol BS8 2AA
Email pitch-study@bristol.ac.uk
www.bris.ac.uk/primaryhealthcare/pitch

University of BRISTOL

With University of the West of England (UWE) and the University of Bath

PITCH

Paracetamol and Ibuprofen for the Treatment of fever in CHildhood

PARENT INFORMATION SHEET

What is the PITCH study about?

Fever is a common problem in children and medicines like paracetamol (in Disprol® and Calpol®) and ibuprofen (in Nurofen® or Calprofen®) are often used to treat the fever, though we don't know which works best. We are all concerned when children become feverish, but no one knows which medicines work best. Together we would like to try to find this out.

Why have we been invited to take part?

You are being invited because you contacted the doctor or nurse (or NHS Direct) today about a young child with a fever and agreed to let us contact you.

Do I have to take part?

It is for you to decide whether or not you and your child take part. If you do take part you will be asked to sign a consent form but you will still be free to change your mind and leave the study at any time and without giving a reason. The standard of care or treatment you and your child receive will not be affected in any way if you decide to leave the study or if you decide not to take part.

Fan fold PIS version 1.11 (ntc).doc Created on 18/01/07

DOI: 10.3310/hta13270

Appendix 6

Clinician paperwork

PITCH

Paracetamol and Ibuprofen for the Treatment of fever in Childhood

PITCH trial remote & local recruitment v1.11

1. CHILD CURRENTLY HOT OR RECEIVED ANTIPYRETICS FOR FEVER IN THE LAST 8 HOURS?

2. AGED BETWEEN 6 MONTHS AND LESS THAN 6 YEARS?

IF YOU CAN ANSWER YES TO THESE TWO QUESTIONS, THEN COMPLETE THE PITCH PAPERWORK AND

FAX TO (0117) 954 6647 ANYTIME

PLEASE ADVISE PARENTS THAT:

- THE **PITCH RESEARCH NURSE WILL CONTACT THEM BY TELEPHONE WITHIN 24 HOURS**.
- UNTIL THEN, **ANTIPYRETIC TREATMENT SHOULD CONTINUE AS PER YOUR ADVICE**.
- CONCERNS REGARDING THE CHILD'S MEDICAL CONDITION SHOULD BE DIRECTED TO NHS DIRECT OR THE CHILD'S GP.

THANK YOU

PITCH trial prescription

Trial number: ISRCTN 26362730

Child's Name: _____

Child's Date of Birth: _____/_____/20___

I confirm that **Please initial the box**

1. This child meets the eligibility criteria:

- Is aged between 6 months and less than 6 years ☐
- Has a fever now **OR** has been given ibuprofen or paracetamol for fever in the previous eight hours ☐
- Does not require hospital admission for diagnosis or treatment of the underlying cause for the fever at the present time ☐

2. The child:

- Has no known exclusion criteria

(exclusions are (i) dehydration, (ii) requires hospital admission or (iii) known to have epilepsy (or other chronic neurological disease), pulmonary disease (except for asthma, this is NOT an exclusion), liver, renal or cardiac disease, previous peptic ulceration or bleeding, an allergy or intolerance to paracetamol or ibuprofen). ☐

- Has no known contraindication to treatment with paracetamol and/or ibuprofen ☐
- Is not taking any regular medication that might adversely interact with paracetamol or ibuprofen (see Appendix 1, BNF for details). ☐

- If child is NOT eligible for the study please give reason_____

Please sign below to confirm that, if the parent consents to randomisation, you are happy for the following medicines to be given to the above patient by the PITCH study team

Medicine	Dose	Quantity to be given
Paracetamol 120mg/5ml SF suspension (or placebo)	**DAY 1:** Please give 15mg/kg every 4 to 6 hours REGULARLY maximum of 4 doses in 24 hours. **DAY 2:** Please give 15mg/kg every 4 to 6 hours AS NEEDED maximum of 4 doses in 24 hours.	140ml
AND		
Ibuprofen 100mg/5ml SF suspension (or placebo)	**DAY 1:** Please give 10mg/kg every 6 to 8 hours REGULARLY maximum of 3 doses in 24 hours. **DAY 2:** Please give 10mg/kg every 6 to 8 hours AS NEEDED maximum of 3 doses in 24 hours.	100ml

…… **……/……../20…..** **……..**

Name of Doctor (BLOCK CAPITALS or PRACTICE STAMP) | Date | Signature

PLEASE TURN OVER AND COMPLETE THE CLINICAL DETAILS

QUESTIONS ABOUT THE CHILD'S FEVER AND TREATMENT.

1. If measured (parent or clinician), please record the child's most recent temperature (°C) and time:
NB. A measured temperature is NOT a requirement for referral to the PITCH team

Temp (°C) ☐☐ : ☐☐ Time (24 hour clock)

2. Please explain how this was assessed (tick one box only)

By touch (e.g. hand on forehead) . ☐ 1
Electronic axillary thermometer . . ☐ 2
Tympanic thermometer . . ☐ 3
Other . . . ☐ 4

If other please explain:_____

3. How would you classify the cause of this child's fever?

Upper respiratory tract infection . . ☐ 1
Lower respiratory tract infection ☐ 2
Otitis media . . . . ☐ 3
Tonsillitis . . . ☐ 4
Infective exacerbation of asthma. . . ☐ 5
Pneumonia (clinical diagnosis) . ☐ 6
Gastroenteritis . . . ☐ 7
Non-specific viral illness . ☐ 8

Other ☐ 9 If other please specify:_____

4. How would you rate the severity of the underlying illness?

Minor . . . ☐ 1 (E.g. no follow up arrangements in place)
Intermediate . . ☐ 2 (E.g. asked to come back if not improving)
Moderate . . ☐ 3 (E.g. Does not require admission, but specific follow up arrangement in place)

5. Have you prescribed an antibiotic **Yes** ☐ **No** ☐

6. Please list the names (only) of all new medication (e.g. antibiotics, inhalers) you have advised or prescribed:

_____

_____

7. Is the child receiving regular medication? **Yes** ☐ **No** ☐

8. Please list the names (only) of all medication the child usually receives:

_____

_____

9. Please indicate which antipyretic medicines you would ordinarily have advised this child to use:
P = paracetamol, I = ibuprofen only, P+I = both

P ☐ **I** ☐ **P+I** ☐

Thank you. Please ask the parent to sign the form on the next page and then ask your secretary to fax the **WHOLE FORM** to the PITCH research team as soon as possible to **(0117) 954 6647**.

PITCH Permission for Release of Contact Details v 1.11

I agree that details of my child's current episode of illness, treatment and my contact details given below can be given (in person or by telephone or secure fax) to the researchers carrying out the PITCH trial. This will enable them to contact me and explain the trial in more detail so that I can then decide whether or not to take part.

(BLOCK CAPITALS PLEASE)

Child's name:

	…….	……...	……
Parent/Guardian's Name:	…….	……	……
	Mr/Mrs/Miss/Ms	Forename	Surname

Address: ……..

……..

……

Postcode: ……..

Main contact number: ……

Alternative contact number: ……

……. ……/……../20…..

Signature of parent/guardian Date

Appendix 7

Referral prompt sticker

Hot child OR received antipyretics for fever in the last 8 hours?

Aged between 6 mths-under 6 years?

Please remember…. fax to PITCH study team: 0117 954 6647

University of BRISTOL

Appendix 8

Community hotline telephone triage and management (first stage)

PITCH Community Recruitment Telephone Answering (Susan/Stephanie)

"Good morning/afternoon, PITCH fever study, you're through to Susan/Stephanie - can I help you?"
[Caller will explain reason for calling]
"Is your child currently unwell with a fever and you are interested in the study?"

NO

"Would you like information about the PITCH study?"
[You do not need to explain study]

YES

YES

= **STAGE 1** OF CONTACT DETAILS

- Take details of caller, age of child, time & date of call, location of advert
- Offer to send promotional leaflet (PL) & fridge magnet (FM)

"**Can I take your postcode please?"** *[To check family are in correct recruitment area]*
IN BS1 to BS16, BS20, BS30, BS32, BS34 OR BS48?

(If outside of these postcodes – please explain to parent that we can only take patients from the Bristol area)

YES

YES

"Can you please tell me how old your child is?

Between 6 months & under 6 yrs

Under 6 months?

Over 6 yrs?

= **STAGE 2** OF CONTACT DETAILS

"Child under 6 months?"

- Take details of caller, child's age, time & date of call, location of advert
- Offer to send PL/FM for future use.

"Child over 6 years? Have younger siblings?" If **YES**:

- Take details of caller, time & date of call, location of advert
- Offer to send PL/FM for future use.

If **NO**:

- Inform parent that child is unfortunately not in the correct age range & not eligible for study at moment.
- Offer to send PL for friends/relatives, thank for interest in study.

DOI: 10.3310/hta13270

"I'd just like to let you know that phoning the study team isn't a replacement to seeing your GP or calling NHS Direct if you are at all worried about your child. If you are concerned, please seek advice through your usual routes. Is that O.K?"
NB: This is a research team and not a medical assessment service

YES

"Are you happy for me to take some contact details from you to pass on to one of the study nurses? Your details will be kept strictly confidential."

YES

"Are you the parent or legal guardian of the child?"

NO →

"I'm really sorry but for legal reasons only a child's parent or guardian can give permission for them to take part in the study. Is it possible for them to phone us?"

YES

=STAGE 3 CONTACT DETAILS
Enter all details into computer.

NO

"If you are concerned about your child, please contact:
- **Your GP or GP out of hours service or**
- **NHS Direct, which is 0845 4647 or**
- **dial 999 if it is an emergency.**

Once you are happy, you are welcome to call PITCH back at a later date. Thank you for your interest in the study."

"Thank you, your details will now be passed to the PITCH study nurse who will contact you within the next 4 hours to discuss the study with you. Is that convenient?

In the meantime, please treat your child's illness as you normally would, and seek medical advice if you become concerned or worried. Thank you for your interest in the PITCH study and for calling the PITCH study team."

Appendix 9

PITCH promotional leaflet

The purpose of the study?

Temperatures (fevers) are a common problem in children. Medicines such as paracetamol (in Disprol or Calpol) and ibuprofen (Nurofen or Calprofen) are often used to treat a temperature, though we do not know which medicine works best. We are all concerned when children become feverish, but no one knows how best to treat them. Together, we would like to find out which medicines works best. We hope that around 300 children in the Bristol area will take part in the PITCH study over its two-year course.

What would happen if my child took part?

The study lasts for 2 days with a phone call on the 5th day. A PITCH nurse would visit you at the start and on the next two days. These visits would be somewhere convenient to you, usually your own home. On the 5th day the nurse would telephone you. The very first visit would be to talk through the study with you and would be in time for your child to be given the study medicines if s/he was still feverish. Until this meeting, you would continue to treat your child's fever as you normally would. **You would not be asked to delay treatment unnecessarily**.

Once you had the study explained and felt happy to take part, your child would join one of three groups who would all be given at least one medicine to treat their fever.

The medicines

All children receive at least one active medicine. One group would all be given paracetamol and syrup that looks and tastes like ibuprofen but doesn't have the medicine in it (called a placebo).

The second group would all be given ibuprofen and placebo paracetamol syrup.

The third group would all be given paracetamol and ibuprofen (no placebos). A computer will decide at random the group your child will be put in.

All medicines are sugar and gluten free and every child would be given at least one medicine to treat the fever and discomfort. The amount of medicine given would be calculated according to your child's weight. This may be slightly different to the dose you normally give.

Looking at how your child recovers

To compare how well the children in the three groups get on, we would measure their temperature using a special thermometer that they wear in a vest for 24 hours. We would also ask you to keep a note for 48 hours of how well they are recovering (on a diary card) and also to measure their temperature for us occasionally. This is to check the special thermometer is working properly and see how they do when it is taken off. The PITCH nurse would explain everything clearly at the time and be available to answer any questions you have during your time in the study.

What would I have to do?

You would be asked to give the study medicines for the first 2 days. During these 2 days, we would ask that you do not use any other medicines that you may have at home for fever or pain. Other medication your child normally takes would be continued as normal, **so long as they do not contain paracetamol or ibuprofen**. We would ask you to meet the study nurse at the arranged times on days 1 and 2, keep the special thermometer in place for up to the first 24 hours and to keep a diary of how well your child recovers.

What are the alternative treatments?

There are no other medicines licensed in the UK for the treatment of fever in children, but there are other non-medicinal treatments. We would give you an advice sheet of the other things you can do to help control your child's temperature, e.g. giving extra fluids and loosening his/her clothing.

I'm interested, but do I have to take part?

It is up to you to decide whether or not you and your child take part in the study. If you decided to take part, you would still be free to 'change your mind' and leave the study at any time and without giving a reason.

What are the side effects of the study medicines?

The study medicines are not new and are widely available to parents to buy at the chemist. When taken at the correct dose, they are safe. The PITCH nurse would check it is safe for your child to use them. As with any medicine, the study medicines can give side effects, but these are rare and mild.

If your child experienced any side effects or any new symptoms, you should contact your GP in the usual way, telling him/her that your child was in the PITCH study. If necessary, your GP would be able to find out which medicine/s your child had received.

What are the possible disadvantages and risks of taking part?

Taking part in this study is **very unlikely** to put you or your child at greater risk than if you chose not to take part because:

- Your child would be receiving treatments already widely used by parents
- The PITCH nurse would have checked that the study medicines are safe for your child
- You would not be asked for any sensitive information
- All children will be given at least one medicine which would help their fever.

The first visit will last for up to one hour and the next two visits between 30 and 40 minutes. We wish to keep any demands to your family to a minimum and would be happy to arrange for the visits to be in your own home.

What are the possible advantages of taking part?

The study treatment is the same or similar to what you would normally be prescribed. We hope that the results from the study will help inform us of the best treatment option for children with fever in the future.

What will happen to the results of the research study?

We plan to publish the results of this study in a medical journal by the end of 2007. We will ask your practice to display a summary of the results and, if you are interested to know more about the results, you will be able to ask your practice for further information. Alternatively, if you are interested to know more, you can contact the PITCH study team directly.

Who is organising and funding this research?

The study is being organised by a team of researchers from the University of Bristol, led by Dr Alastair Hay. The study is supported by a grant from the NHS and is monitored and regulated by the Department of Health.

Who has reviewed this study?

This study has been approved by the Bath Local Research Ethics Committee.

What do I do now?

At this stage we are asking only that you to consider whether or not you would participate if your child developed a fever in the next year. You do not need to do anything else at this stage. If you have any questions you can contact the study secretary on: 0117 331 0811.

How do I take part?

If your child develops a fever, there are 2 ways in which you and your child can be referred to the study team:

1. If you sought medical advice through either your GP/Nurse, the Walk-in Centre (Knowle West), NHS Direct, or the Children's Hospital Emergency Department, you may be invited to take part, or you can ask to be referred to the study.
2. Although not designed to be instead of seeing your doctor, if you feel that your child's fever or illness is not severe enough for you to seek medical advice, you can contact the study team directly on:

0117 331 0811

Thank you for considering taking part in this research.

Niamh Redmond
PITCH study coordinator on behalf of the PITCH study investigators
Academic Unit of Primary Health Care,
25-27 Belgrave Road,
Clifton,
Bristol BS8 2AA

Email: 💻: pitch-study@bristol.ac.uk
Fax: 0117 954 6647
Website: www.bris.ac.uk/primaryhealthcare/pitch

NHS
Bristol North Primary Care Trust
Bristol South and West Primary Care Trust
South Gloucestershire Primary Care Trust
United Bristol Healthcare NHS Trust

University of BRISTOL

With University of the West of England (UWE) and the University of Bath

FEVER?
?PITCH

Paracetamol and Ibuprofen for the Treatment of fever in CHildhood

Information about the study

This leaflet is to let you know that if your child is aged 6 months to less than 6 years of age and develops an illness with a high temperature, you may wish to consider taking part in the PITCH study. Deciding whether or not to take part might be difficult when your child is ill, so we wanted to give you the chance to consider the invitation now.

DOI: 10.3310/hta13270

Appendix 10

PITCH fridge magnet

Appendix 11

Nurse telephone triage form

Nurse telephone follow up to parent referral

Section 1- Demographic Details

Date: Time of call: Nurse:

Child's name .....

Date of Birth ..... **Checked Child's Name and DOB with parent** ☐

Parent/Guardian's Name: Mr/Mrs/Miss/Ms ..... Forename: ..... Surname: .....

Address: .....

.....

Post code .....

Main contact telephone number: .....

Alternative contact telephone number(s): .....

.....

Disclaimer

Before I tell you about the study, I'll be asking you some questions about your child's health so that I can make sure that this is the right time for your child to take part in the PITCH study if you decide you want to.
I just want to check that you have been told that the study is not in place of visiting your Dr or calling NHS Direct if you concerned about your child's medical condition. Is that ok? ☐

Where did parent hear about the study? .....
only ask if machine message

Section 2 – General assessment of child at this time

How is your child now? .....

.....

Why do you think your child has a temperature? .....

.....

Are you concerned about it?

.....

Have you taken him/her to your doctor/ practice nurse, or phoned anyone for advice about this illness ? (Including NHS Direct) .....

.....

Measured temperature? ☐ °C at ☐☐ : ☐☐

Last antipyretic: ..... at ☐☐ : ☐☐

Did antipyretic help? .....

Section 3. RED SECTION	Yes	No	Comments
If parent answers NO to ANY question, get further information, and may need to refer family to seek medical assessment.			
Is your child able to chat / gurgle/ cry?	☐	☐	.....
Is breathing normal?	☐	☐	.....
Colour of skin is normal?	☐	☐	.....
Absence of rash?	☐	☐	.....
If rash present, does it blanche with glass test?	☐	☐	.....
Absence of photophobia?	☐	☐	.....
Absence of headache/neck pain?	☐	☐	.....
Absence of limb pain?	☐	☐	.....
Hands & feet warm?	☐	☐	

	Yes	No	Comments
[note for nurses: cold extremities & pale/mottled limbs may be associated with raised temperature but also can be early pointers for meningococcal disease - see note below. Ask parent to check central capillary refill if possible. Any doubts – ask them to consult GP/OOH service for assessment			
(NB. Red Flag early symptoms for meningitis/septicemia include, cold hands & feet, pallor or mottling of the skin & pain in limbs– Meningitis Research Foundation. www.meningitis.org/news/newsitem.jsp. Accessed May 3, 2006)			
Is child interested in surroundings?	☐	☐	
Are they interacting/responding to parent as normal? [If you talk to him does he respond/turn to your voice?]	☐	☐	
Playing normally? (toddler)	☐	☐	
Smiled at you today? (infant)	☐	☐	

ADVICE GIVEN TO PARENT:

Dial 999 ☐

Phone GP/GP OOH ☐

Phone NHS Direct ☐

Other: .....

.....

Section 4. AMBER SECTION	Yes	No	Comments
Less than three days duration of fever?	☐	☐	
Do you feel your child has been more unwell with a temperature in past?	☐	☐	
Is child eating as usual? (toddler)	☐	☐	
drinking as usual?	☐	☐	

taking feeds as normal? (infant) ☐ ☐ .....

Usual number of wet nappies/ peeing as normal? ☐ ☐ .....

Urine smells normal/usual colour? ☐ ☐ .....

Absence of pain when peeing? ☐ ☐ .....

ADVICE GIVEN TO PARENT:

Dial 999 ☐

Phone GP/GP OOH ☐

Phone NHS Direct ☐

Other: .....

.....

Section 5. GREEN SECTION	Yes	No	Comments

Are there symptoms of minor illness present?

If parent answers YES to any question below, it gives possible reasons for fever which are usually minor

Runny Nose? ☐ ☐ .....

Cough? ☐ ☐ .....

Sticky eyes? ☐ ☐ .....

Ear pain/pulling at ears? ☐ ☐ .....

Sore throat? ☐ ☐ .....

Symptoms of tummy upset? [diarrhoea and/or vomiting?] ☐ ☐ .....

Section 6.Questions relating to eligibility criteria on concurrent/past health status

Is child taking any medicines at the moment? .....

Any past history of hospital admissions? .....

Child isn't Seeing/waiting to see hospital Consultant? .....

Any allergies? .....

Explain study aims and objectives at this point. If there are concerns about child [expressed by parent or from triage questions] this may be brief & it may be necessary to suggest parent consults their GP/NHS Direct for further assessment.
They may ring back later when they have done this. If child not eligible on health history grounds, explain reason to parent.

Child not eligible at the moment? ☐

Reason: .....

Parent advised to contact: .....

Parent declined study? ☐ Reason .....

.....

If parent interested and child eligible at this point:

	Yes	No	
Child hot/feels warm at the moment?	☐	☐	
Parent given paracetamol in last 24hrs?	☐	☐	Times given: .....
Parent given ibuprofen in last 24hrs?	☐	☐	Times given: .....
Time study medicines first possible.	Time ☐☐ : ☐☐		.....
Parent available? Does parent have legal responsibility?	☐	☐	.....
Visit planned?	☐	☐	Time ☐☐ : ☐☐

Phone back [to see if temperature raised] ☐ ☐ Time ☐☐ : ☐☐

Parent needs time to consider. ☐ ☐ .....

Phone back: ☐ ☐ Time ☐☐ : ☐☐

Parent will contact: ☐ ☐ .....

Nurse contact details given ☐ ☐ .....

Send leaflet: ☐ ☐ .....

Checked for content similarity at NHS Direct by Joy Farrimond, 5 May 2006

PITCH trial prescription

Trial number: ISRCTN 26362730

Child's Name: _____

Child's Date of Birth: _____/_____/20___

I confirm that **Please initial the box**

1. **This child meets the eligibility criteria:**
   - Is aged between 6 months and less than 6 years ☐
   - Has a fever now **OR** has been given ibuprofen or paracetamol for fever in the previous eight hours ☐
   - Does not require hospital admission for diagnosis or treatment of the underlying cause for the fever at the present time ☐
2. **The child:**
   - Has no known exclusion criteria (exclusions are (i) dehydration, (ii) requires hospital admission or (iii) known to have epilepsy (or other chronic neurological disease), pulmonary disease (except for asthma, this is NOT an exclusion), liver, renal or cardiac disease, previous peptic ulceration or bleeding, an allergy or intolerance to paracetamol or ibuprofen). ☐
   - Has no known contraindication to treatment with paracetamol and/or ibuprofen ☐
   - Is not taking any regular medication that might adversely interact with paracetamol or ibuprofen (see Appendix 1, BNF for details). ☐

- If child is NOT eligible for the study please give reason_____

Please sign below to confirm that, if the parent consents to randomisation, you are happy for the following medicines to be given to the above patient by the PITCH study team

Medicine	**Dose**	**Quantity to be given**
Paracetamol 120mg/5ml SF suspension (or placebo)	**DAY 1:** Please give 15mg/kg every 4 to 6 hours REGULARLY maximum of 4 doses in 24 hours. **DAY 2:** Please give 15mg/kg every 4 to 6 hours AS NEEDED maximum of 4 doses in 24 hours.	140ml
AND		
Ibuprofen 100mg/5ml SF suspension (or placebo)	**DAY 1:** Please give 10mg/kg every 6 to 8 hours REGULARLY maximum of 3 doses in 24 hours. **DAY 2:** Please give 10mg/kg every 6 to 8 hours AS NEEDED maximum of 3 doses in 24 hours.	100ml

…… **……/……../20…..** **……..**

Name of Doctor (BLOCK CAPITALS or PRACTICE STAMP) | Date | Signature

Appendix 12

Community recruitment posters

With University of the West of England (UWE)
and the University of Bath

The PITCH fever study

Paracetamol and Ibuprofen for the Treatment of fever in Childhood

The PITCH fever study is finding out which medicine or medicines **work best for fever** for babies and children (from 6 months and under 6 years old)

Can you help?

If your young child has a fever, you may be able to help our study. Children in the study all have at least one medicine for fever and we look at how well the medicine works in keeping the fever down and making them feel better.

Please phone the study hotline on:

0117 331 0811 for more information

Website: www.bris.ac.uk/primaryhealthcare/pitch

Taking part in this study is not instead of seeing your doctor if you are concerned about your child

Study ends Summer 2007

Appendix 13

Newspaper advert

University of BRISTOL

NHS
Bristol North Primary Care Trust
Bristol South and West Primary Care Trust
South Gloucestershire Primary Care Trust
United Bristol Healthcare NHS Trust

With University of the West of England and the University of Bath

The PITCH fever study

Paracetamol and Ibuprofen for the Treatment of fever in Childhood

Joy

The **PITCH** research nurses

Becky

Sheila

The **PITCH** fever study is finding out which medicine or medicines **work best for fever for babies and children** (from 6 months to under 5 years old)

Can you help?

When your child has a fever please call the study hotline on:

0117 331 0811 for more information

Website: www.bris.ac.uk/primaryhealthcare/pitch

Taking part in this study is not instead of seeing your doctor if you are concerned about your child

Study ends Summer 2007

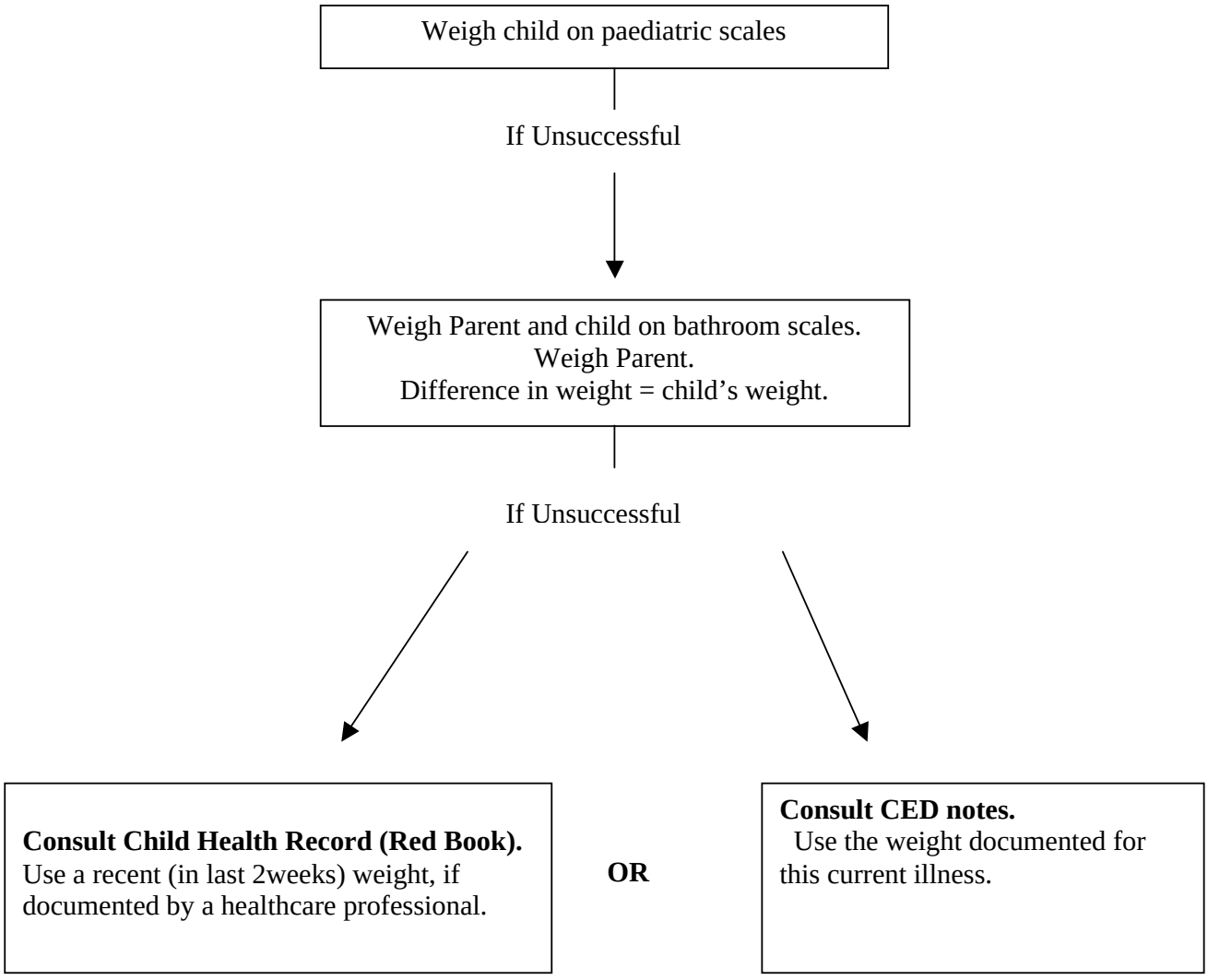
CI.info poster v1.3 Created on 21/03/06

Appendix 14

Weighing the child standard operating procedure

PITCH trial:
Standard Operating Procedure for weighing children at baseline visit

Rationale: On occasions, due to child feeling unwell, it has proved difficult to encourage a child to be weighed on the scales. An accurate weight is essential in order to establish the correct dosage of trial medicines for the child (via the Aberdeen randomisation service).



Notes: (Written by NR 11.12.06 in light of comments by Nurses):

- Gold standard in obtaining weights in order to randomise patients should be an accurate weight for the child, by any of the 4 methods:
    - Weight on scales
    - Weight with Parent (and subtracted parent weight)
    - CED weight for this illness
    - Red book weight during the last 2 weeks.

- Medicine dosages should be based on an accurate weight and not an estimated one. However, the randomisation should not necessarily be abandoned if this SOP is not followed, but if a weight is obtained by any other means, then this should be classed as a "Deviation from protocol" and documented as such.

Appendix 15

Study medicine dose calculation chart (used by Aberdeen to randomise)

Paracetamol (120 mg/5 ml) dose to be given up to four times daily (at 15 mg/kg)

Table 23 Paracetamol (120 mg/5 ml) dose to be given up to four times daily (at 15 mg/kg)

Child's weight (kg)	Usual age for weight	Dose (mg) to be given up to four times daily	Dose (ml) to be given up to four times daily	Dose (ml) to be given up to four times daily, to nearest 0.5 ml
7	6 months	105	4.4	4.0
8		120	5.0	5.0
9		135	5.6	5.5
10	1 year	150	6.3	6.0
11		165	6.9	6.5
12		180	7.5	7.5
13		195	8.1	8.0
14	3 years	210	8.8	8.5
15		225	9.4	9.0
16		240	10.0	10.0
17		255	10.6	10.5
18		270	11.3	11.0
19		285	11.9	11.5
20		300	12.5	12.5
21		315	13.1	13.0
22	7 years	330	13.8	13.5
23		345	14.4	14.0
24		360	15.0	15.0
25		375	15.6	15.5
26	8 years	390	16.3	16.0
27		405	16.9	16.5
28		420	17.5	17.5

Ibuprofen (100 mg/5 ml) dose to be given up to three times daily (at 10 mg/kg)

Table 24 Ibuprofen (100 mg/5 ml) dose to be given up to three times daily (at 10 mg/kg)

Child's weight (kg)	Usual age for weight	Dose (mg) to be given up to four times daily	Dose (ml) to be given up to four times daily	Dose (ml) to be given up to four times daily, to nearest 0.5 ml
7	6 months	70	3.5	3.5
8		80	4	4
9		90	4.5	4.5
10	1 year	100	5	5
11		110	5.5	5.5
12		120	6	6
13		130	6.5	6.5
14	3 years	140	7	7
15		150	7.5	7.5
16		160	8	8
17		170	8.5	8.5
8		180	9	9
19		190	9.5	9.5
20		200	10	10
21		210	10.5	10.5
22	7 years	220	11	11
23		230	11.5	11.5
24		240	12	12
25		250	12.5	12.5
26	8 years	260	13	13
7		270	13.5	13.5
8*		280	14	14

Appendix 16

Patient participation card

IMPORTANT MEDICAL INFORMATION

CONTACTS

For queries regarding the study please contact:

Study Nurse Tel:……..

Other Study Contacts:
Niamh Redmond (Study Co-ordinator)
Tel: 0117 331 3831 or 0117 331 3835

Alastair Hay (Lead Investigator)
Tel: 0117 331 3853

In a Medical Emergency please contact your GP immediately

For Doctors use only:

For **emergency unblinding** in a situation where the management of a child requires immediate knowledge of the exact treatment allocated, please call:

BRI pharmacy on 0117 928 2053 between 9am-5.30pm Monday to Friday.
Or BRI switchboard 0117 923 0000 and ask for the on-call pharmacist (if out of hours).

STUDY APPOINTMENTS

(enter date and time of appointment)

Visit at 24 hours:

Date: ……..Time:……..

Visit at 48 hours:

Date: ……..…Time:……..

Telephone contact at day 5:

Date: ……..…Time:……..

IMPORTANT MEDICAL INFORMATION

PITCH research study

Paracetamol & **I**buprofen for the **T**reatment of fever in **CH**ildhood

Patient Name:…….……

Enrolment Number:……

Randomisation Number:……

This patient is participating in a clinical study and has been randomised to either paracetamol only, ibuprofen only or a combination of both.

For dose instructions please see inside. Note that patients receive study medications for up to 48 hours only. Over the counter medications may be taken after this time.

Date commenced study:……../……./……...
(i.e. Visit 1 date)

Time of first dose: ……

DOSE INSTRUCTIONS

Paracetamol 120mg/5ml SF suspension/placebo

DAY 1: Please give …… ml every 4 to 6 hours REGULARLY maximum of 4 doses in 24 hours.

DAY 2: Please give ……ml every 4 to 6 hours AS NEEDED maximum of 4 doses in 24 hours.

Ibuprofen 100mg/5ml SF suspension/placebo

DAY 1: Please give ……ml every 6 to 8 hours REGULARLY maximum of 3 doses in 24 hours.

DAY 2: Please give ……ml every 6 to 8 hours AS NEEDED maximum of 3 doses in 24 hours.

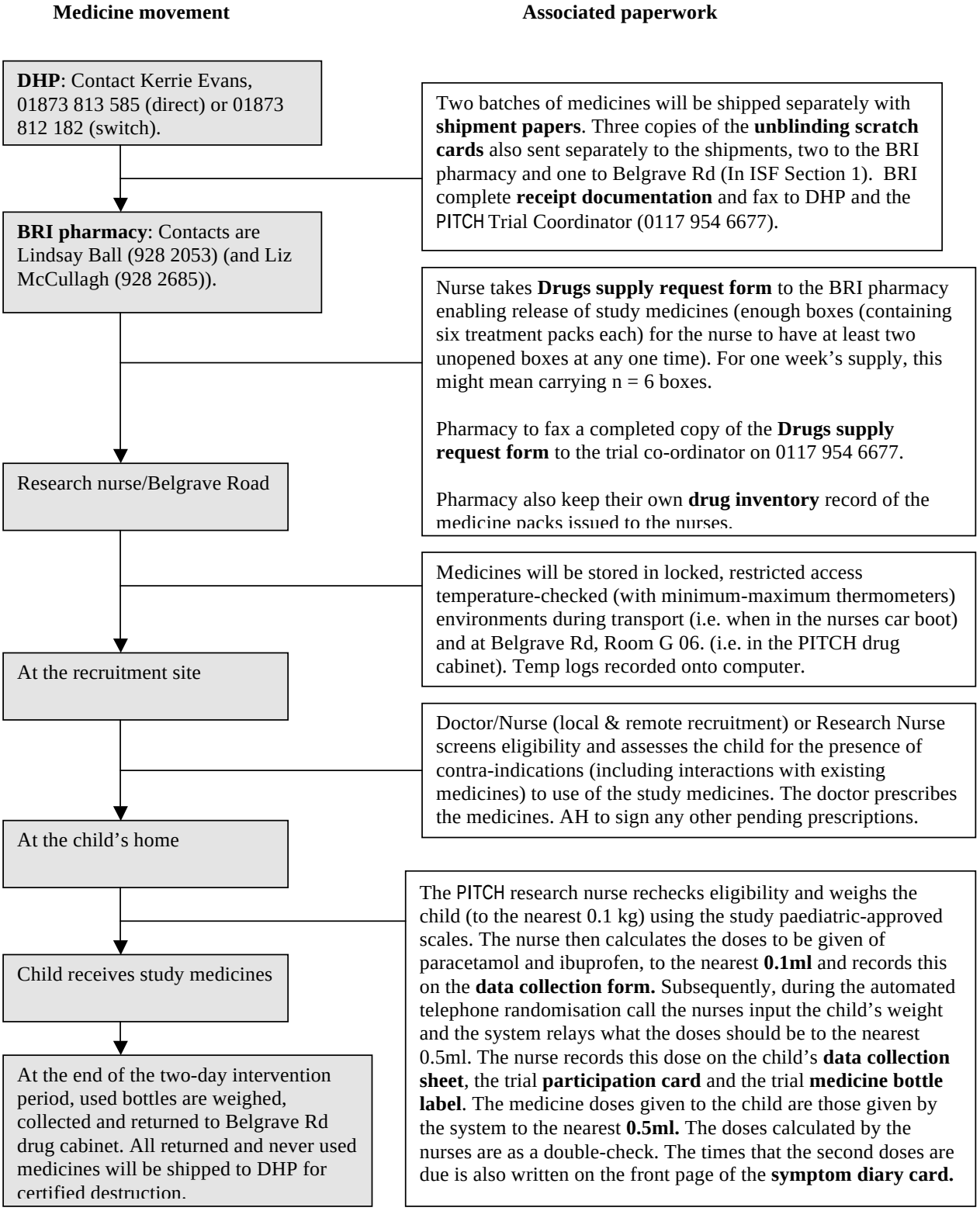
Please keep this card with you at all times during the study. Please take with you to any doctor or hospital appointments

Appendix 17

Handling, dispensing and administration of the study medicines standard operating procedure

Version 1.1

The PITCH trial – Handling, dispensing and administration of the study medicines



Version 1.1

Further Notes

Paediatric scales:

- The study paediatric scales read to 2 decimal places (i.e. 0.01kg). However the nurses round down to 1 decimal place (0.1kg). If it reads to 0.04 kg the weight is rounded down, if it reads to 0.05kg or above, the weight is rounded up.

Calculation of doses by nurses:

- Paracetamol dose = **15mg/kg**
- Study medicine bottle contains **120mg/5ml**

Therefore paracetamol dose calculation = (15mg x child's weight) / (5ml/120mg)

- Ibuprofen dose = **10mg/kg**
- Study medicine bottle contains **100mg/5ml**

Therefore ibuprofen dose calculation = (10mg x child's weight) / (5ml/100mg)

The doses calculated are rounded down to the nearest 0.1ml

Administration of first dose of medicines:

- Medicine bottle is shaken
- First dose of study medicines is administered using 5 ml and 10ml oral syringes (whose precision is to 0.5ml). This dose is administered by the parent, in the nurse presence at the baseline visit, with nurse assistance if necessary.

Explanation of subsequent administration of medicines to parents (proactive in first 24 hours and reactive between 24 & 48 hours):

- The time the second dose is due for both medicines is written on the front page of the patient symptom diary card and is highlighted to the parent
- The research nurse explains to the parent that the study medicines need to be given regularly for the first 24 hours i.e. every 4 to 6 hours for the paracetamol (up to a maximum of 4 doses in 24 hours) and every 6 to 8 hours for the ibuprofen (up to a maximum of 3 doses in 24 hours), regardless of whether child is hot or symptomatic.
- The research nurse explains that for the second 24 hours the parent needs to give the doses as they think the child needs the medicine but again not exceeding the maximum dose in the 24 hour period.
- For parents who do not understand the above explanation, the nurse writes down the time of the first dose of paracetamol and Ibuprofen and explains that the child will need 4 doses of paracetamol at least 4 hours apart before the next nurse visit. Similarly that the ibuprofen needs to be given 3 times before the next nurse visit. At the next visit (at 24 hours) the nurse explains that the study medicines need to be given when the child is feeling ill or showing some of the unwell symptoms.
- Parents are advised to keep study medicines out of reach and sight of children

Calculation of doses by the telephone randomization system:

The system uses an algorithm to generate the doses:

- For paracetamol this = child's weight x 0.625
- For ibuprofen this = child's weight x 0.5

The doses calculated are rounded down to the nearest 0.5ml

Appendix 18

Advice sheet to parents regarding reducing fever

PITCH

Paracetamol and Ibuprofen for the Treatment of fever in Childhood

High Temperature (Fever) in Children

If your child has a high temperature (fever) then in addition to medicines such as paracetamol and ibuprofen, you can: take off their clothes and give them lots to drink. See a doctor if they do not improve.

What causes high temperatures?

- **Viral infections** are the common cause. Virus infections cause many common illnesses such as colds, coughs, 'flu, diarrhoea, etc. Sometimes virus infections cause more serious illnesses.
- **Bacterial infections** are less common than viral infections, but also cause high temperatures. Bacteria are more likely to cause serious illness such as pneumonia and meningitis.
- **Other types of infection** are uncommon causes of a high temperature in the UK.

What should I do?

- **Use the study medications as instructed.**
- **Keep the child lightly dressed** if the room is normal 'room temperature'. IT IS WRONG TO WRAP UP A FEVERISH CHILD.
- **Give cool drinks.** This helps to lower the temperature and prevents dehydration.

Do not 'cold-sponge' a child who has a high temperature. This used to be popular, but it is now not advised. This is because the blood vessels under the skin may become narrower (constrict) if the water is too cold. This reduces the heat lost from the body, and can trap heat in deeper parts of the body. The child may then get worse. Many children also find cold-sponging uncomfortable.

Some people use a fan to cool a child. Again, this may not be a good idea if the fanned air is too cold. However, a gentle flow of air in a room which is 'room temperature' may be helpful. Perhaps just open the window, or use a fan on the other side of the room to keep the air circulating.

What should I look out for?

A child with a high temperature may look quite unwell. He or she may be flushed and irritable. However, most bouts of high temperature are not caused by serious illness, and the temperature often comes down quickly. It is quite common to see a child happily playing an hour or so later when their temperature has come down. They will not be entirely back to normal, but it is reassuring if a child improves with the drop in temperature.

As a rule, a child with a serious infection will usually become worse, and more ill, despite efforts to bring their temperature down. In addition, they may have other worrying symptoms. For example, breathing problems, drowsiness, convulsions, pains, or headaches, which become worse despite paracetamol and/or ibuprofen.

See a doctor if a child does not improve soon, or has any worrying symptom.

Appendix 19

Letter to general practitioner re adverse event occurrence

PITCH

Paracetamol and Ibuprofen for the Treatment of fever in Childhood

Ceire Costelloe, *Trial Co-Ordinator*
Tel: 0117 331 3831
Email: Niamh.Redmond@bristol.ac.uk

Dr Alastair Hay, *Lead Investigator*
Tel: 0117331 3853
Email: Alastair.Hay@bristol.ac.uk

PITCH Study Office:-
Academic Unit of Primary Health Care,
25-27 Belgrave Road, Clifton, Bristol BS8 2AA

Ms Susan Doohan,
Trial Secretary
Tel: 0117 3313835. Fax: 0117 954 6647
Email: pitch-study@bristol.ac.uk

GP notification of adverse event version 1.2

26 January 2009

Re: [Click **here** and enter Child's name**], Date of Birth:**
[Click **here** and enter Child's DOB**]**
[Click **here** and enter Address**]**

Dear [Click **here** and enter Child's GP],

This letter is further to our previous letter dated [Click **here** and enter date GP notification letter sent] notifying you of [Click **here** and enter Child's first name]'s recruitment to the PITCH trial and to inform you that, unfortunately, [Click **here** and enter Child's first name] has experienced an adverse event whilst taking the PITCH trial medicines, namely paracetamol and/or ibuprofen. This consists of **< insert one of following: new onset of rash, angio-oedema, bronchospasm (or wheeze), bloody diarrhoea, haematuria >.**

We are notifying you of this in case this problem requires further investigation or is a possible herald marker of future, more serious potential reaction to paracetamol or ibuprofen.

If you require more information, please do not hesitate to contact our study team.

Yours sincerely

Alastair Hay
Lead Investigator
On behalf of the PITCH study team

Appendix 20

Adverse event and serious adverse event standard operating procedure

SAE reporting flowchart version 3.doc Created on 23/02/07

SERIOUS ADVERSE EVENT REPORTING:

Serious adverse events are defined as follows:
- **Requires in-patient hospitalisation or prolongation of hospitalisation**
- **Is immediately life threatening**
- **Results in persistent or significant disability or incapacity**
- **Results in death**

All Serious Adverse Events (SAEs) need to be reported to the study team whether they are suspected to be related to study medication and/or trial process or not.

THE PROCESS:

PITCH Research Nurse (RN) becomes aware that a randomised child has become a SAE.

↓

- RN reports SAE to Trial Coordinator (TC) (Ceire Costelloe Tel: 07810264771) as soon as possible.
- Research Nurse gives child's CRF to TC as soon as possible.
- If TC unavailable, then report to Principal Investigator (PI) (Alastair Hay Tel: 07817495050) as soon as possible.
- All SAE's should be reported to both TC and PI within 24 hours of onset.
- SAE reported to child's GP if not already aware.

↓

- RN to establish and note down in as much detail as possible, the course of events leading to SAE from (a) their own point of view and (b) that of parent. The following information is specifically needed:
  - Names, doses, times of administration of study medicines and any other medication
  - Information on clinicians or NHS contacts made since randomisation up until the point TC informed of SAE
  - The opinion of parent as to whether being in the trial helped or hindered their ability and willingness to contact the NHS.
- TC to establish NHS contacts† since randomisation.
- Call them to inform of SAE and request current notes of their consultation with child ASAP. Follow up with a fax to the contact, **with a copy of the completed trial consent form**. Templates for faxes and cover sheet are located here:

L:\Studies\PITCH\Trial management\SAEs and AEs\SAEs\SAE reporting templates

- RN to keep in regular contact with parent to establish how SAE is progressing. TC to keep in regular contact with RN.

↓

- Once the following information has been obtained the 'SAE initial report form' can be completed:
  - All consultation notes from sites where SAE child has had contact with NHS since randomisation
  - Notes of events from randomisation to SAE event from (a) RN's point of view and (b) parents point of view. Template can be found here:

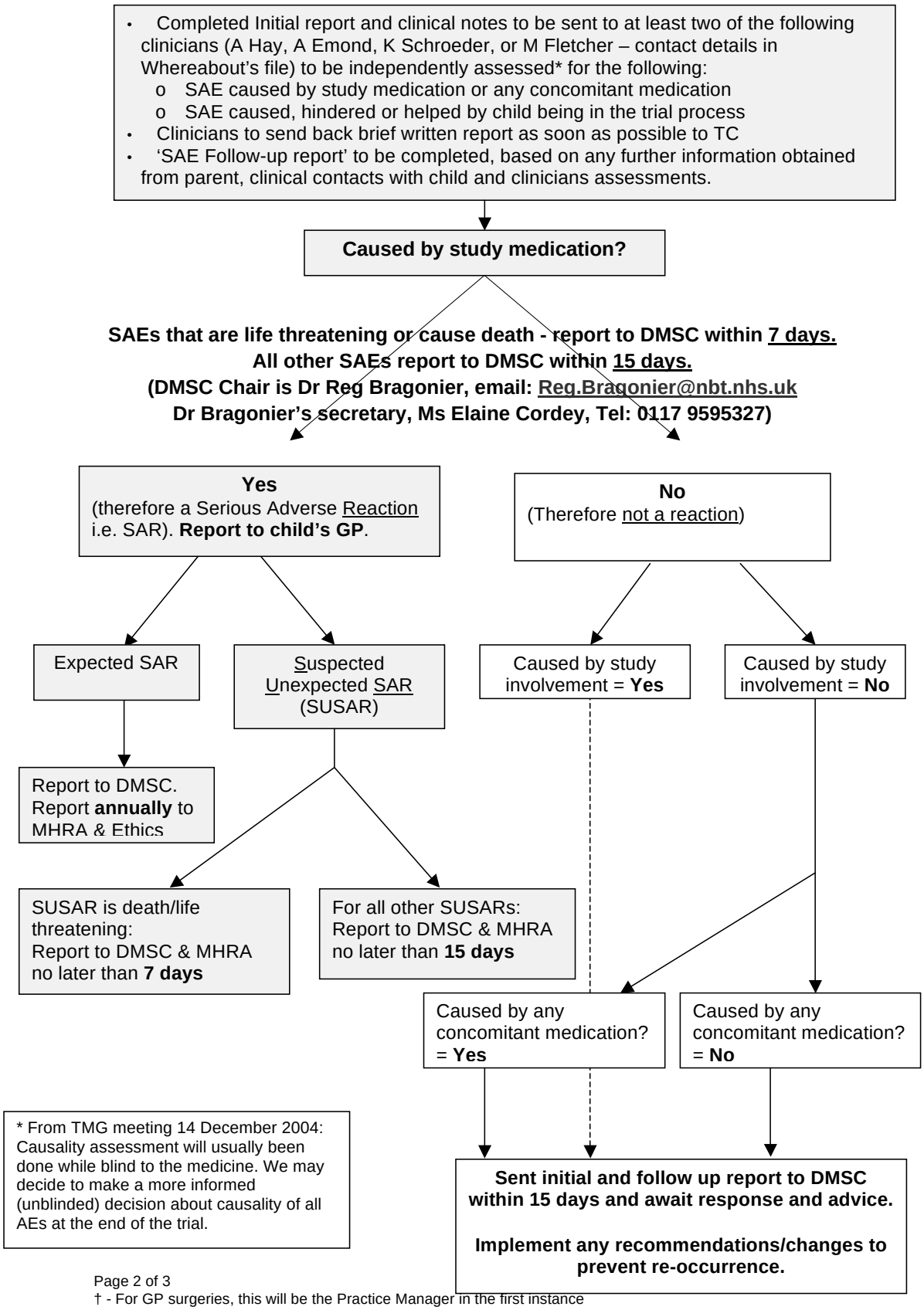
L:\Studies\PITCH\Trial management\SAEs and AEs\SAEs\SAE reporting templates

NB: AH is happy to interpret any medical notes and summarise for the initial report.

↓

† - For GP surgeries, this will be the Practice Manager in the first instance

SAE reporting flowchart version 3.doc Created on 23/02/07



Page 2 of 3
† - For GP surgeries, this will be the Practice Manager in the first instance

DEFINITIONS:

Adverse event: any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse reaction: any untoward and unintended response in a subject to an investigational medicinal product, which is related to any dose administered to that subject.

Serious adverse event,
Serious adverse reaction,
Or Unexpected serious adverse reaction:
These are any adverse event, adverse reaction or unexpected adverse reaction respectively that results in any of the following:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect (not applicable for Pitch trial)

PHARMACOVIGILANCE

(and our legal obligations – see 'the medicines for human use in clinical trials regulations 2004')

SUSARs - Suspected Unexpected Serious Adverse Reactions
A sponsor must ensure that all relevant information about a Suspected Unexpected Serious Adverse Reaction, which occurs during the course of a clinical trial in the UK that is fatal or life-threatening is:

a) recorded
b) reported asap to the licensing authority and the ethics committee but no later than 7 days after the sponsor was first aware of the reaction

For all other SUSARs (i.e those that are not fatal or life-threatening, so for the PITCH trial this would be those requiring hospitalisation or prolongation of hospitalisation or resulting in persistent or significant disability or incapacity) a report to the licensing authority and ethics committee shall be made asap but no later than 15 days.

The licensing authority shall keep a record of all the SUSARs relating to an investigational product that is brought to it's attention. They will also ensure that the details of those reactions are entered into the European database (Eudract).

SSARs – annual list of Suspected Serious Adverse Reactions and safety report.

A list of all SSARs must be reported annually to the licensing authority and to the ethics committee. The report on the safety of the subjects in the trial must also be given.

† - For GP surgeries, this will be the Practice Manager in the first instance

Appendix 21

Photograph of datalogger attached to child

Figure 14 Photograph of datalogger attached to child

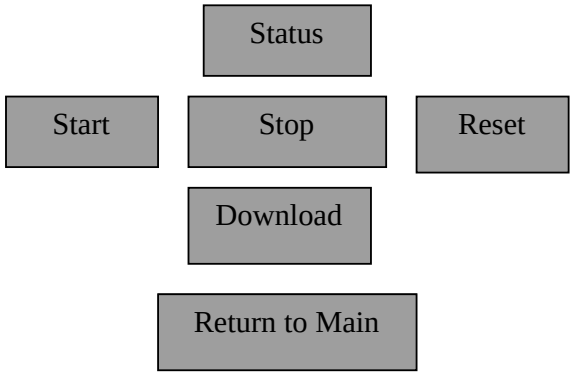
Appendix 22

Starting dataloggers with personal digital assistant standard operating procedure

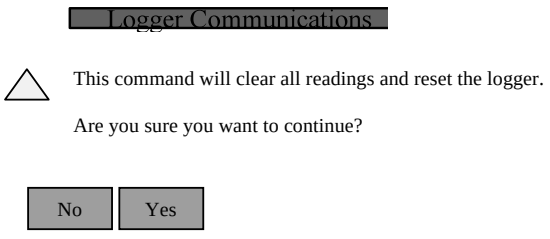
Up to date: 14/04/06

Standard Operating Practice for starting data loggers with palm pilot

- Check data logger looks intact – no loose connections
- Connect PDA interface cable to palm pilot and data logger
- Turn on palm pilot and select Omega Software. Information on viewing disclaimer comes on screen – press continue and then select **logger communications,** which brings up main device screen:



- Select **Status** if wishing to check this. This function will inform the user of device type and serial number; latest start date and time; reading interval that is set (should be 30 seconds) and whether the device is still running or stopped. If the reading interval is not set at 30 seconds this needs to be changed when the device is reset or started as explained below.
- Select **Start** and this will ask you if you want to continue which will result in all readings being cleared and device reset.



Select **Yes**

- Check all details on screen. Device can be started now or at a time selected. Usually select now. **Serial device** should match that on the data logger. **Reading time** should be set at **30seconds** with a **log time** of **7 days.**

Up to date: 14/04/06

- Select **Start device**. Logger communication screen will come up saying **Device communicating, please wait.** Then changes to **Device started.** It can take up to 30seconds for this to happen. (Sometimes a message of "invalid start date" will be shown – select **Start Device** again)

- Press **OK**. This returns user to device screen. Select **device status** to see that data logger is now running and note the time of activation.

- Disconnect PDA interface cable from data logger and Palm Pilot

- Place data logger into black pouch; probe connector side up, seal Velcro & close with tie cable. Use side cutters to cut off excess tie cable so that it is shear with closure point, and tuck the closure point under one of the loops of the pouch to prevent any scratching.

- All the above can be done prior to a home visit as long as the start-time of the device (use Palm pilot clock) is recorded. This can be done on the data collection sheet if a home visit is arranged. Alternatively it can be written on a label that is then attached to the data logger cable.

- Try and keep loggers in pouches when re-started, so possible damage to wires is limited. Only remove loggers from pouches when they need to be washed after a visit.

Appendix 23

Attaching datalogger to the child SOP

Standard operating Practice for applying data logger to child

- Put sealed data logger pouch into an appropriate sized vest for the child after discussing with parent whether front or back pocket is best for current activity.

- Help parent to put vest on child and when in place attach the probe into the crease of the axilla, silver side to child's skin. Secure with **DuoDERM® Extra Thin** & a strip of **Microfoam** tape. *(An insulating tape was chosen to reduce the cooling effect of air contact, therefore optimising the response of the thermometer probe. See attached notes from MF 06/04/2004 – Data logger review)*

- Tuck any excess cable into the pouch and use zinc tape or micropore tape to secure cable to vest (Foam tape doesn't stick)

- Explain to parent what you are doing whilst attaching the probe so that they know how to re-attach if it should be taken off (for a bath, or by child!) or it becomes dislodged during play/sleep. Check the time probe attached using palm pilot clock (or mobile phone synchronised to PC at time of data logger activation) and record on data collection form.

- Explain to parents where to record on the diary card the times when probe off and re-applied. Stress the importance of recording the times as accurately as possible and also the importance to the study of keeping the data logger on for the 24hour period if possible.

- Leave a small supply of **Microfoam** tape & half of a **DuoDERM®** with the parents so that they can reapply the probe if it comes off. Do not leave a whole roll of Microfoam. (Too expensive and infection control means the tape would need to be disposed of after each participant.

Revised 26th June 2007 (JF)to include justification of tape used

Appendix 24

Symptom diary

Diary of your child's illness

	With nurse (0 hours)	Family (2 hours)	Family (4 hours)	Family (16 hours)	Family with nurse (24 hours)	Family (32 hours)	Family (40 hours)	With nurse (48 hours)	Nurse (phone call)
Date									
Planned time									
Actual time									
Temperature (now)									
Discomfort (now)					If asleep, score when last awake + Time			If asleep, score when last awake + Time	
Activity (now)									
Appetite (since last time)									
Sleeping (since last time)									

Fill in the chart at the times written in by the nurse, or as near then as possible. If time is different, please write the correct time in the box

Temperature	Fill in your child's temperature after taking it with the thermometer supplied				
Discomfort (due to the illness)	**1** = asleep	**2** = normal (laughing or quiet but happy)	**3** = not quite normal (quiet, not moving, not happy),	**4** = some pain/distress, moaning, trying to curl up/ stretch away from discomfort (attempting to withdraw)	**5** = crying, very distressed, hard to settle (agitated)
Activity	**1** = asleep	**2** = normal	**3** = playing sometimes, quiet for longer than usual	**4 =** not interested in playing, hardly moving about	**5** = not moving about willingly
Appetite	**A** = no meal or drink due	**B** = normal	**C** = eating less than normal	**D** = much less than normal	**E** = vomiting or refusing all food and drink
Sleeping	**A** = normal	**B =** more sleep than usual (day or night)	**C =** sleep a bit more disturbed than usual	**D =** sleep a lot more disturbed than usual	

Study Medicines given at:- please write in the date & time medicines were given. (NB: This may differ to the dates and times above)									
Paracetamol									
Ibuprofen									
How well swallowed? Choose from the following: **Easy** (all medicine swallowed), **OK** (most swallowed, less than a few drops lost), **Difficult** (probably more than a few drops lost)									
Paracetamol									
Ibuprofen									

Please describe anything else done to try and help bring temperature down

Please write date, time and what was done.								

Important – please remember to fill in any other problems (such as temperature probe coming off, being sick, having diarrhoea, headache) on the back page

Other changes or problems	Please write in any health or behaviour problems which are not already included. Please record any times temperature probe comes off and goes back on	
Day and time started or first noticed	Problem	What was done (if anything)

Contact with GP, hospital, NHS direct or others	Please write in any contact with GP, hospital, NHS Direct, out of hours service		
Day and time	Who was contacted	Why (what the problem was)	What happened or was suggested

Thank you for completing this diary!

The PITCH Study Team

Academic Unit of Primary Health Care
University of Bristol
25-27 Belgrave Road, Clifton, Bristol BS8 2AA

FEVER IN YOUNG CHILDREN

Child's name……..

Relationship to the child
of person completing diary……

Enrolment number ☐☐☐☐☐

Randomisation number ☐☐☐☐

Nurse to complete: *Doctor's or nurse's diagnosis* Symptoms of illness (tick box)				
Cough	Headache	Diarrhoea	Stomach ache	Earache
Cold	Vomiting	Rash	Other (please specify)	

Time second dose of paracetamol due:	Between ……. and ……
Time second dose of Ibuprofen due:	Between ……. and ……

Version 1.5 dated 16/10/2006 (main study)

DOI: 10.3310/hta13270

Appendix 25

Explaining the symptom diary SOP

Standard Operating Procedure (SOP) for: Explaining the completion of the diary card to parents

Baseline visit

1) Research Nurse fully completes the front of the diary card, entering the following details: Childs name, Relationship to the child of person completing diary, enrolment number, randomisation number, Doctor/Nurse's diagnosis, and symptoms of illness. The nurse also documents the times that the next doses of paracetamol and ibuprofen are due, and explains this to the parents. It is then reinforced that the times of the 3rd and 4th doses are dependant on the times of the 2nd dose and are 4-6 hours after (for paracetamol) and 6 to 8 hours after (for ibuprofen).

2) The nurse completes the date and planned time sections of the card up to and including the 24-hour visit. The time zero is the time at which the 1st dose of medicine is given. The nurse explains to the parent that these are the times we would like them to measure their child's temperature using the study thermometer and they are shown how to use it. It is explained that the box which says "actual time" gives the parent the opportunity to tell us what time they managed to take the temperature and record the 4 scores. Parents are asked to use their watch to complete the time or a reliable clock and are asked to use the same timepiece at each measure rather than guessing the time.

3) The nurse explains that as well as taking the child's temperature at these times, we would like them to record 4 scores in respect of the child's discomfort, activity, appetite and sleeping. Each score is talked through with the parent in order to complete the scores for time zero and it is explained that we want them to do the same at each of the times written in the diary card.

It is explained that there is a key at the bottom of the diary card, which explains each score. Parents are asked to choose a score that they think is most suitable for their child. If there is any doubt about which score a child should be given, (for example showing characteristics for 2 scores) then the higher score should be given, rather than the lower score. It is explained that the appetite score 'a' can be used when they haven't been due to have any food or drink.

4) It is explained that the discomfort and activity scores are to be taken **at the time** that the temperature is taken. The appetite and sleeping scores are based on how the child has been **since they were last assessed/scored.** In order to obtain an accurate discomfort score at the baseline visit, the nurse can gauge the child's discomfort from observations in the time that she has been in the home. If the child is sleeping, a discomfort score can be obtained after waking the child up to weigh them. If it is felt that by waking the child and weighing them, this has caused the child to be more distressed (and therefore an accurate discomfort score cannot be obtained) the nurse should discuss with the

parent how the child has been in the last hour or so prior to nurse visit in order to obtain a suitable score. Nurses to document in instances where the discomfort score was obtained by reporting from parents, rather than nurse/parent observation.

5) The research nurse records the date & time that the initial study medicines are given with an 'I' or a 'P' beside the relevant time and asks the parent to do the same every time a dose of medicine is given. At this point it is also explained that the box underneath asks how well the medicines were swallowed and the key at the bottom of the page identifies the answers. Again, the research nurse completes the boxes to demonstrate how it is done.

6) It is then explained that there is a box for the parent to write down anything else they did to reduce the child's temperature e.g. stripping off, opening windows etc. Parents are asked to record the date and time against any action recorded

7) The back of the diary card is then explained. It gives the parent the opportunity to record any new health related problems, and whether the data loggercame off.The research nurse reinforces the importance of recording accurate times for when the data logger came off and was replaced. . It is also explained that there is a space for recording telephone or face-to-face contact with any health professionals that the parent has regarding the child with over the study period.

24 hour visit

1) The research nurse discusses the diary card with parent to see if it has been fully completed. Any blanks are either completed or an explanation written about why it wasn't completed.
2) The times are put in for the checks needed at 32 hours and 40 hours and it is explained that the 48-hour scores will be completed when the nurse next visits.
3) The 24-hour temperature and scores are completed, if the parent hasn't already done so, with the parent encouraged to take the temperature and asked for the scores.
4) The parent is reminded to complete the sections on medicines and how well they were swallowed, as well as the description of anything else that was done to reduce the child's temperature.
5) If the child has been given any NON study paracetamol or ibuprofen, the nurse should clearly document time, dose, type of medicine, and make it explicitly clear on the diary card that these medicines are NOT study medicines. Also note at the top of the card that non-study paracetamol/ibuprofen were given as a prompt for trial secretary when inputting data.

48 hour visit

1) Again, the nurse completes the section with the parent regarding the temperature and the scores. The parent is asked whether they have

recorded any study medicines given and how easily they were swallowed.

2) The card is checked to ensure it has been fully completed and taken away for the 5-day telephone call.
3) If the child has been given any NON study paracetamol or ibuprofen, the nurse should clearly document time, dose, type of medicine, and make it explicitly clear on the diary card that these medicines are NOT study medicines. Also note at the top of the card that non-study paracetamol/ibuprofen were given as a prompt for trial secretary when inputting data.

Appendix 26

Handling of unblinding requests – pharmacy standard operating procedure

PITCH STUDY
Pharmacy procedure for handling unblinding requests
Written by Niamh Redmond

Requests for unblinding should only be accepted from a clinician taking responsibility for the care of the child. Other than in exceptional circumstances, requests to unblind should not usually be accepted from parents, but referred instead to the child's GP.

1. Collect the following information from the caller:
   - The child's **4-digit Randomisation Number** and **5-digit Enrolment number**
   - Child's initials
   - Name of the clinician
   - Clinicians position and/or title
   - Contact number of clinician/caller
   - Location or site where the clinician is from
   - **Reason for unblinding**
   - Date of call
   - Time of call

Write this information in the **Accountability Log for Unblinding**, log can be found behind this procedure.

2. Ask the caller to hold while you complete the unblinding.

3. Locate the Unblinding Codes, which are A4 cards with scratch-off sections to reveal the treatment allocated when scratched. There are 2 copies with Pharmacy and these can be found in:
   - The Clinical Pharmacy Office, level 3 in the grey filing cabinet at the far end of the office in the 3rd drawer down, marked Clinical Trials Active in the hanging file marked PITCH Study – **for use during office hours**

   - The On-call pharmacist's bag – **for use during out-of-normal hours**

4. Select the Unblinding Code with the appropriate **Randomisation Number**

5. Using a coin, scratch the card to reveal the **Treatment Allocation**

6. Inform the caller of the **Treatment Allocation**

7. Place the Unblinding Codes back in either the hanging file and back in the grey cabinet or back in the on-call bag.

8. Please **fax a copy** of the completed **Accountability Log for Unblinding** to:

PITCH trial co-ordinator/Dr Alastair Hay on 0117 954 6647

NB: Contact details for PITCH study team should you need them:

Name	Role	Office hours Tel No	Emergency No.	Email address
Dr. Alastair Hay	Principal Investigator	(0117) 331 3853	07817495050	Alastair.Hay@bristol.ac.uk
Ceire Costelloe	Trial co-ordinator	(0117) 331 3831/13845	07810264771	Ceire.Costelloe@bristol.ac.uk
Ms Susan Doohan	Project Administrator	0117 331 3835		Pitch-study@bristol.ac.uk

The PITCH trial team will try to warn Pharmacy staff of possible unblindings if they become aware of a request prior to Pharmacy staff.

Appendix 27

Handling of unblinding requests – trial team standard operating procedure

PITCH study (Paracetamol & Ibuprofen for the Treatment of Childhood fever):

Standard Operating Procedure (SOP) for handling unblinding requests

Written by Niamh Redmond

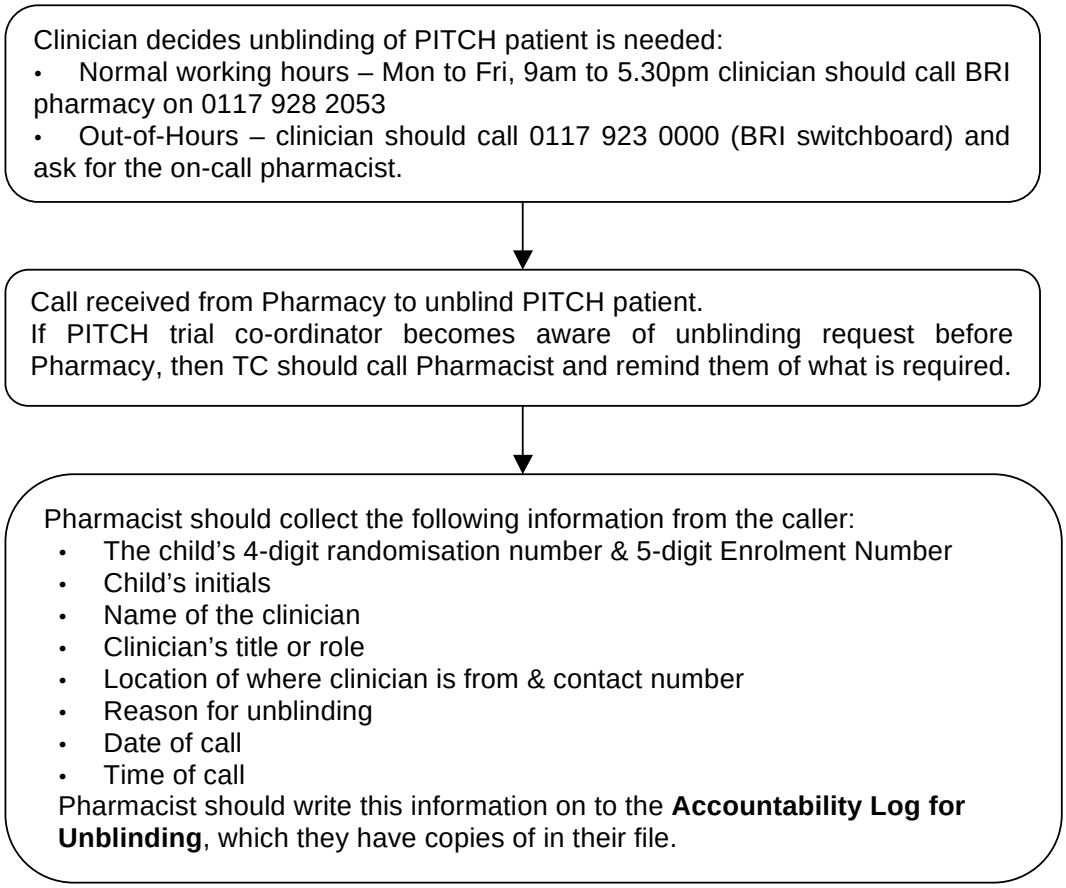
The PITCH trial unblinding requests are handled by Pharmacy staff at all times.
This SOP is for the use of the PITCH team so that they are aware of how requests to unblind a randomised participant from the PITCH trial (currently recruiting until May 2007) is managed. Pharmacy's procedure for unblinding can be found in the following document, which they have copies of.
Pharmacy's SOP for handling unblinding requests v 2.0 March 07.doc
Located here:
L:\Studies\PITCH\SOPs\Unblinding\current documents

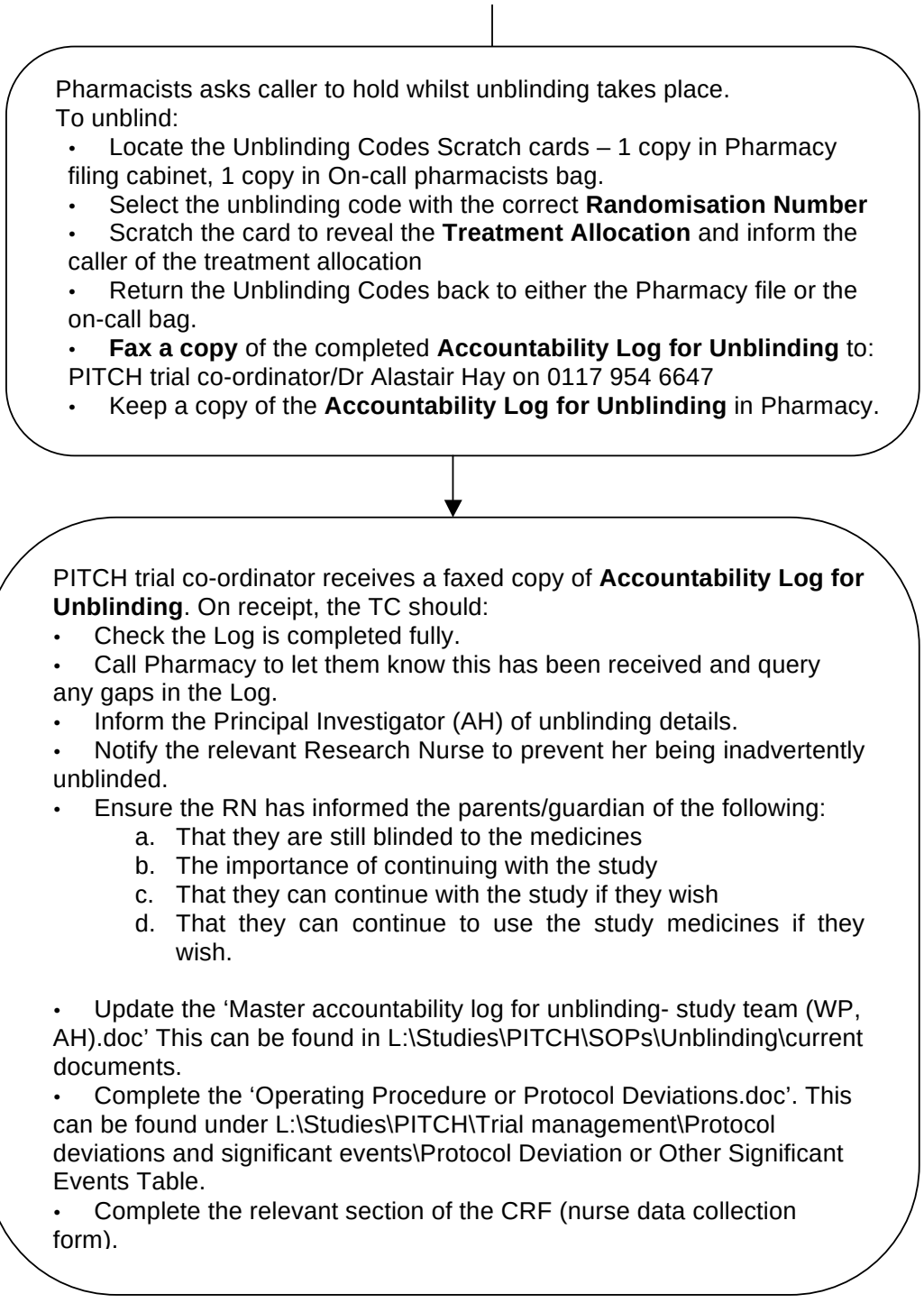
1. Requests to unblind:

Requests for unblinding **should only be accepted from a clinician taking clinical responsibility for the care of the child**. Other than in exceptional circumstances, requests to unblind should not be accepted from parents or relatives, but referred instead to the child's GP.

2. Process to unblind

The flowchart below should be followed:





Appendix 28

Data query checking standard operating procedure

Updated April 2007

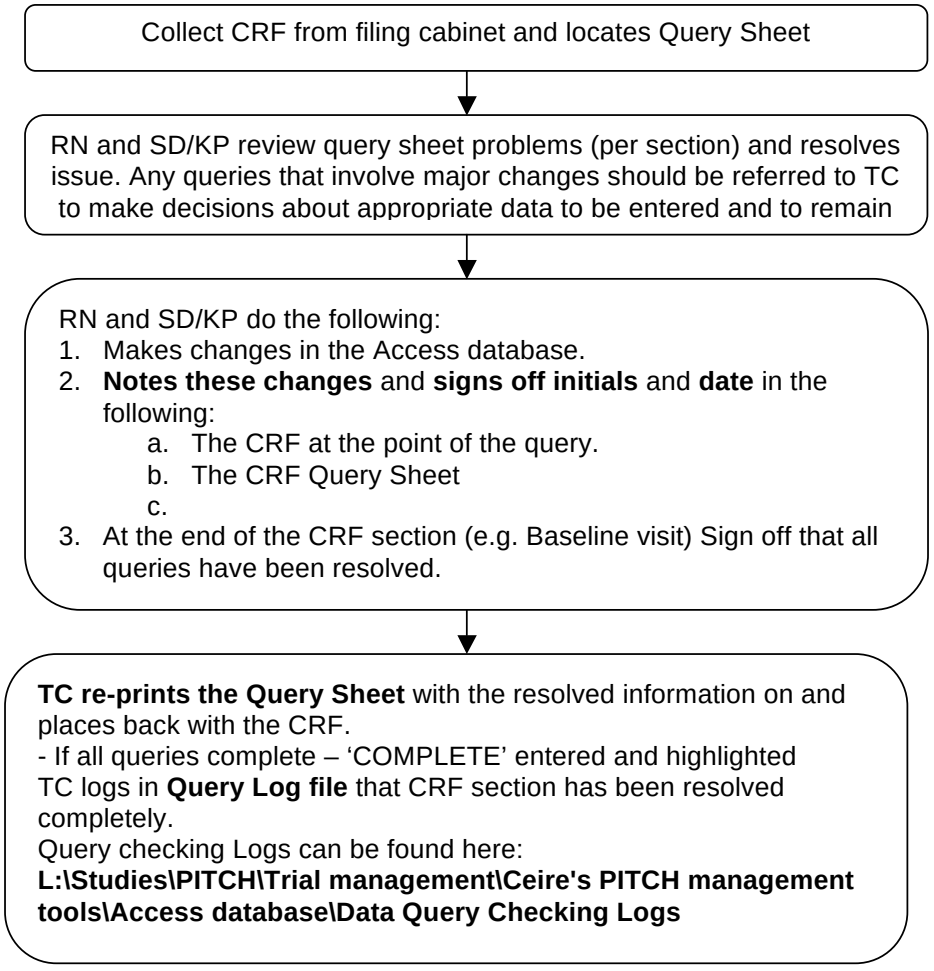
SOP (Standard Operating Procedure) for PITCH Data Entry Query Checking

Written by Niamh Redmond

Query sheet generation:
Persons responsible for entering the PITCH CRF data into to the Access database create Query sheets to inform the trial co-ordinator (TC) of whether data has been entered successfully or not.
These are located here:
L:\Studies\PITCH\Trial management\Ceire's PITCH management tools\Access database\Data Entry Query Sheets

Occasionally, data enterers come across problems that they cannot resolve alone. These have to be highlighted to the TC via the Query Sheet for that particular participant, identified by their PITCH Enrolment Number. Any uncertainties with regards to the data entered or data that appears missing or cannot be input are grouped via section of the CRF/Access database forms.
These sheets are printed out and placed inside the front cover of the CRF folder by the data enterer. For any new data entered, the Query Sheet must be updated and re-printed and returned to the CRF.

Query Sheet checking:
The following process needs to be followed in order to resolve queries highlight from the CRF Query Sheets.



Appendix 29

Data quality checking standard operating procedure

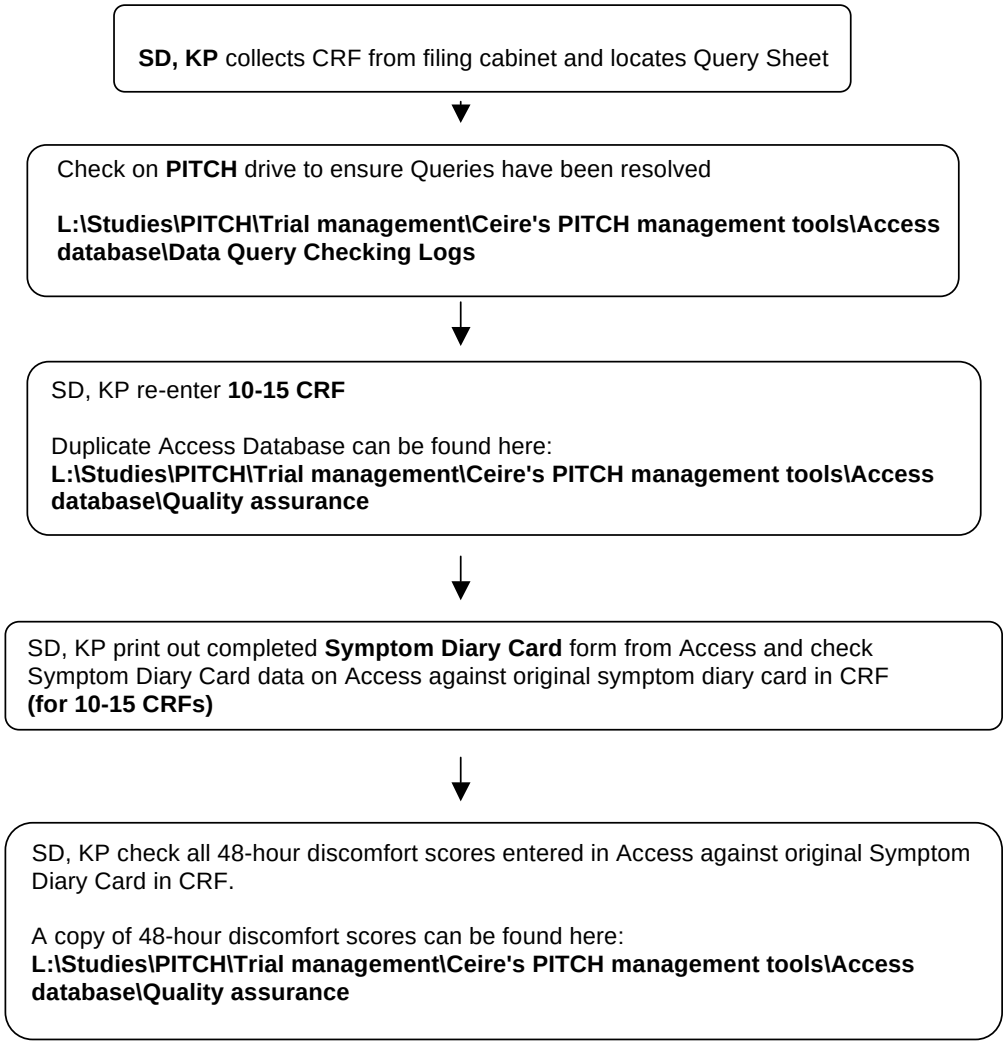
Created 9th April 2007

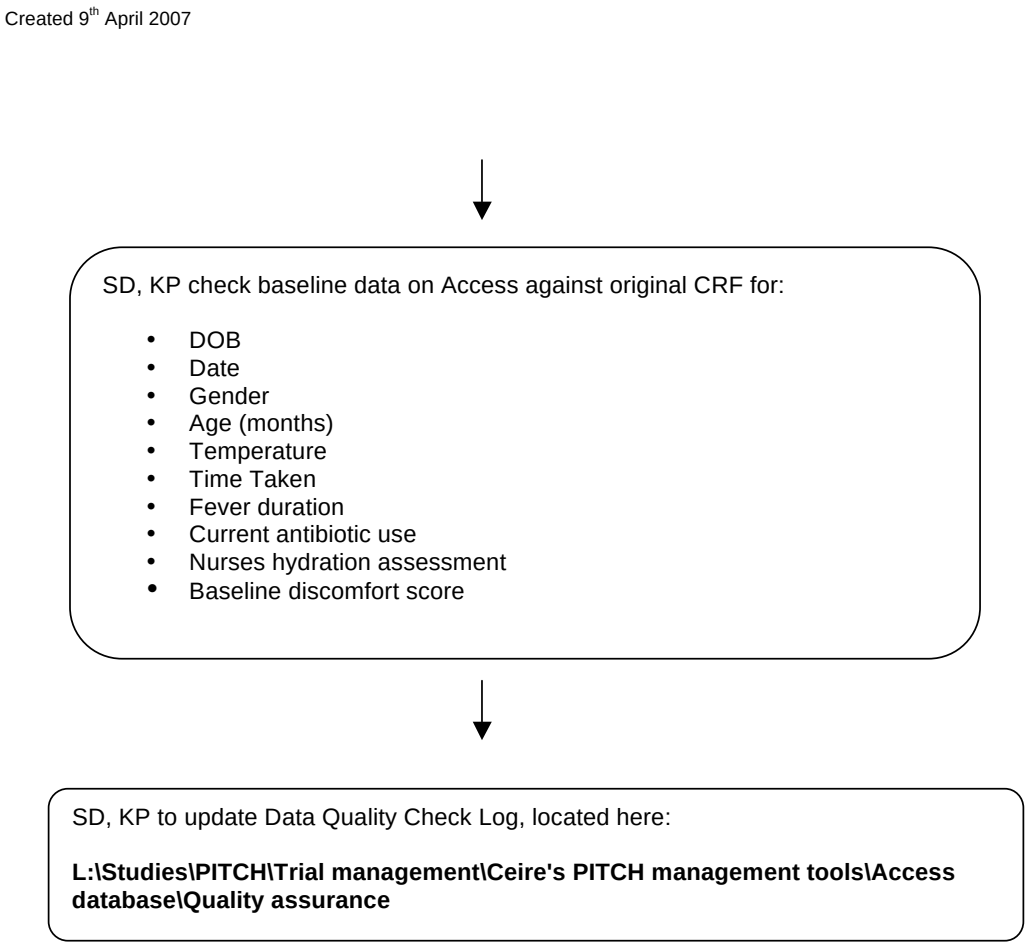
SOP (standard Operating procedure) for PITCH Data Quality Checking

Written by Céire Costelloe

Data Quality:
Persons responsible for entering the PITCH CRF data into the Access database must carry out checks to ensure correct data entry. The process of data entry is as follows: SD, SB or KP enters Data from CRF into the Access database. Any uncertainty regarding data is entered into a word document Query Sheet for that particular patient. CC, SD and RNs check through Query Sheets and resolve according to Data Query Resolution SOP. Once the query has been resolved the Data can then undergo a quality check. A process of double entry and checking is needed. Aiming for 100% agreement and any disagreements should be corrected for primary outcomes measured.

Data Quality Checking:
The following process needs to be followed in order to ensure data have been entered correctly:





Double entry ensures 900 points have been checked. TC aids Data Quality checking by generating Access Queries to extrapolate data for 48 hour discomfort scores and Baseline data if necessary.

Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, et al.

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, et al.

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, et al.

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, et al.

No. 4
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, et al.

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.
By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, et al.

No. 19
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.
A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, et al.

Volume 3, 1999

No. 1
Informed decision making: an annotated bibliography and systematic review.
By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, et al.

No. 2
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

No. 3
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4
A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.
By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, et al.

No. 5
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

No. 8
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10
Methods for the analysis of quality-of-life and survival data in health technology assessment.
A review by Billingham LJ, Abrams KR, Jones DR.

No. 11
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, et al.

No. 13
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

No. 14
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, et al.

No. 15
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

No. 17 (Pt 1)
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, et al.

No. 19
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, et al.

No. 20
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, et al.

No. 21
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

No. 22
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, et al.

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, et al.

No. 8
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, et al.

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, et al.

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, et al.

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

No. 21
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

No. 22
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

No. 23
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

No. 24
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, et al.

No. 25
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

No. 26
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

No. 27
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

No. 28
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, et al.

No. 29
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

No. 30
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

No. 31
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

No. 32
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

No. 33
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

No. 34
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

No. 35
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, et al.

No. 36
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

No. 37
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

No. 38
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

No. 39
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, et al.

No. 40
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

Volume 5, 2001

No. 1
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, et al.

No. 2
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, et al.

No. 3
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

No. 4
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

No. 5
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, et al.

No. 6
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

No. 7
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

No. 8
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, et al.

No. 9
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

No. 10
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, et al.

No. 11
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

No. 12
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

No. 13
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

No. 14
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

No. 15
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, et al.

No. 16
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

No. 18
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

No. 20
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, et al.

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, et al.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, et al.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, et al.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, et al.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, et al.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, et al.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, et al.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, et al.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, et al.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, et al.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, et al.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, et al.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, et al.

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, et al.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, et al.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, et al.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, et al.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, et al.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, et al.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, et al.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, et al.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, et al.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, et al.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, et al.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, et al.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, et al.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, et al.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, et al.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, et al.

No. 7
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, et al.

No. 8
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, et al.

No. 9
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, et al.

No. 11
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, et al.

No. 14
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, et al.

No. 15
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, et al.

No. 16
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

No. 21
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, et al.

No. 22
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

No. 25
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al.

No. 28
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, et al.

No. 29
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, et al.

No. 31
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

No. 32
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

No. 35
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

No. 36
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

No. 37
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, et al.

No. 38
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

No. 39
Systematic review of isolation policies in the hospital management of methicillin-resistant Staphylococcus aureus: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, et al.

No. 40
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

No. 41
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

No. 42
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, et al.

Volume 8, 2004

No. 1
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, et al.

No. 2
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, et al.

No. 3
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

No. 4
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, et al.

No. 5
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

No. 6
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, et al.

No. 7
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

No. 8
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

No. 9
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

No. 10
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, et al.

No. 11
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

No. 12
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

No. 13
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

No. 14
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, et al.

No. 15
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, et al.

No. 16
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, et al.

No. 17
Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, et al.

No. 18
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, et al.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, et al.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, et al.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, et al.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, et al.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, et al.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, et al.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, et al.

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, et al.

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, et al.

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, et al.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, et al.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, et al.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, et al.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, et al.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, et al.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, et al.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, et al.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, et al.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, et al.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, et al.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, et al.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, et al.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, et al.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, et al.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, et al.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, et al.

No. 24
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, et al.

No. 25
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, et al.

No. 26
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, et al.

No. 27
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, et al.

No. 28
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

No. 29
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, et al.

No. 30
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, et al.

No. 31
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, et al.

No. 33
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

No. 34
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, et al.

No. 36
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, et al.

No. 38
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, et al.

No. 39
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, et al.

No. 40
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, et al.

No. 41
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, et al.

No. 43
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, et al.

No. 46
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, et al.

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, et al.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, et al.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, et al.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, et al.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, et al.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, et al.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, et al.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, et al.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, et al.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, et al.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, et al.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, et al.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, et al.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, et al.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, et al.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, et al.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, et al.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, et al.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, et al.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, et al.

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, et al.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, et al.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, et al.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, et al.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, et al.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, et al.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, et al.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, et al.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, et al.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, et al.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, et al.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, et al.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, et al.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, et al.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, et al.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, et al.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, et al.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, et al.

No. 49
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, et al.

No. 50
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, et al.

Volume 11, 2007

No. 1
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, et al.

No. 2
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, et al.

No. 3
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, et al.

No. 4
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

No. 5
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, et al.

No. 6
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, et al.

No. 7
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

No. 8
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, et al.

No. 9
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, et al.

No. 10
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, et al.

No. 11
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

No. 12
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

No. 13
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, et al.

No. 14
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al.

No. 15
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, et al.

No. 16
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

No. 17
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, et al.

No. 18
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, et al.

No. 19
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

No. 20
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, et al.

No. 21
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

No. 22
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, et al.

No. 23
Systematic review of the effectiveness of preventing and treating Staphylococcus aureus carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, et al.

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, et al.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, et al.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, et al.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, et al.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, et al.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, et al.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, et al.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, et al.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, et al.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, et al.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, et al.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, et al.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, et al.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, et al.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, et al.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, et al.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, et al.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, et al.

No. 49
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, et al.

No. 50
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

No. 51
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, et al.

No. 52
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, et al.

No. 53
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

Volume 12, 2008

No. 1
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, et al.

No. 2
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

No. 3
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, et al.

No. 4
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

No. 5
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, et al.

No. 6
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, et al.

No. 7
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

No. 8
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, et al.

No. 9
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

No. 10
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

No. 11
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, et al.

No. 12
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.
By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, et al.

No. 13
Stepped treatment of older adults on laxatives. The STOOL trial.
By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, et al.

No. 14
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.
By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, et al.

No. 15
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

No. 16
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.
By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

No. 17
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.
By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, et al.

No. 18
Structural neuroimaging in psychosis: a systematic review and economic evaluation.
By Albon E, Tsourapas A, Frew E, Davenport C, Oyebode F, Bayliss S, et al.

No. 19
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, et al.

No. 20
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.
By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, et al.

No. 21
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.
By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, et al.

No. 22
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.
By Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, et al.

No. 23
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.
By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, et al.

No. 24
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.
By Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, et al.

No. 25
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.
By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, et al.

No. 27
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.
By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, et al.

No. 28
Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.
By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

No. 29
Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.
By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, et al.

No. 30
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.
By French B, Leathley M, Sutton C, McAdam J, Thomas L, Forster A, et al.

No. 31
The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.
By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, et al.

No. 32
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

No. 34
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.
By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, et al.

No. 35
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.
By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, et al.

No. 36
Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

Volume 13, 2009

No. 1
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.
By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, et al.

No. 2
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.
By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

No. 3
Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.
By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

No. 4
Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.
By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, et al.

No. 5
Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.
By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, et al.

No. 6
The harmful health effects of recreational ecstasy: a systematic review of observational evidence.
By Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, et al.

No. 7
Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.
By Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, et al.

No. 8
The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.
By Taylor RS, Elston J.

No. 9
Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.
By Potter J, Mistri A, Brodie F, Chernova J, Wilson E, Jagger C, et al.

No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.
By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11
Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.
By Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, et al.

No. 12
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.
By Hobart J, Cano S.

No. 13
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, et al., on behalf of the CAST trial group.

No. 14
Non-occupational postexposure prophylaxis for HIV: a systematic review.
By Bryant J, Baxter L, Hird S.

No. 15
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.
By Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, et al.

No. 16
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.
By Feder G, Ramsay J, Dunne D, Rose M, Arsene C, Norman R, et al.

No. 17
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

No. 18
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.
By Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, et al.

No. 19
Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study.
By Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA, et al.

No. 20
Systematic review of respite care in the frail elderly.
By Shaw C, McNamara R, Abrams K, Cannings-John R, Hood K, Longo M, et al.

No. 21
Neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities: a randomised controlled trial (NACHBID).
By Tyrer P, Oliver-Africano P, Romeo R, Knapp M, Dickens S, Bouras N, et al.

No. 22
Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREshold for AntiDepressant response) study.
By Kendrick T, Chatwin J, Dowrick C, Tylee A, Morriss R, Peveler R, et al.

No. 23
Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation.
By Bryant J, Cooper K, Picot J, Clegg A, Roderick P, Rosenberg W, et al.

No. 24
Enhanced external counterpulsation for the treatment of stable angina and heart failure: a systematic review and economic analysis.
By McKenna C, McDaid C, Suekarran S, Hawkins N, Claxton K, Light K, et al.

No. 25
Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).
By Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, et al.

No. 26
A systematic review of presumed consent systems for deceased organ donation.
By Rithalia A, McDaid C, Suekarran S, Norman G, Myers L, Sowden A.

Health Technology Assessment programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

Observers

Diagnostic Technologies & Screening Panel

Members

Chair,
Professor Paul Glasziou,
Professor of Evidence-Based Medicine, University of Oxford

Deputy Chair,
Dr David Elliman,
Consultant Paediatrician and Honorary Senior Lecturer, Great Ormond Street Hospital, London

Professor Judith E Adams, Consultant Radiologist, Manchester Royal Infirmary, Central Manchester & Manchester Children's University Hospitals NHS Trust, and Professor of Diagnostic Radiology, Imaging Science and Biomedical Engineering, Cancer & Imaging Sciences, University of Manchester

Ms Jane Bates, Consultant Ultrasound Practitioner, Ultrasound Department, Leeds Teaching Hospital NHS Trust

Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales

Dr Ron Gray, Consultant Clinical Epidemiologist, Department of Public Health, University of Oxford

Professor Paul D Griffiths, Professor of Radiology, University of Sheffield

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Dr Anne Mackie, Director of Programmes, UK National Screening Committee

Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Barts and The London NHS Trust, Royal London Hospital

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr W Stuart A Smellie, Consultant in Chemical Pathology, Bishop Auckland General Hospital

Dr Nicholas Summerton, Consultant Clinical and Public Health Advisor, NICE

Ms Dawn Talbot, Service User Representative

Dr Graham Taylor, Scientific Advisor, Regional DNA Laboratory, St James's University Hospital, Leeds

Professor Lindsay Wilson Turnbull, Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary

Observers

Dr Tim Elliott, Team Leader, Cancer Screening, Department of Health

Dr Catherine Moody, Programme Manager, Neuroscience and Mental Health Board

Dr Ursula Wells, Principal Research Officer, Department of Health

Pharmaceuticals Panel

Members

Chair,
Professor Robin Ferner,
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Deputy Chair,
Professor Imti Choonara,
Professor in Child Health, University of Nottingham

Mrs Nicola Carey, Senior Research Fellow, School of Health and Social Care, The University of Reading

Mr John Chapman, Service User Representative

Dr Peter Elton, Director of Public Health, Bury Primary Care Trust

Dr Ben Goldacre, Research Fellow, Division of Psychological Medicine and Psychiatry, King's College London

Mrs Barbara Greggains, Service User Representative

Dr Bill Gutteridge, Medical Adviser, London Strategic Health Authority

Dr Dyfrig Hughes, Reader in Pharmacoeconomics and Deputy Director, Centre for Economics and Policy in Health, IMSCaR, Bangor University

Professor Jonathan Ledermann, Professor of Medical Oncology and Director of the Cancer Research UK and University College London Cancer Trials Centre

Dr Yoon K Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Professor Femi Oyebode, Consultant Psychiatrist and Head of Department, University of Birmingham

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge

Dr Martin Shelly, General Practitioner, Leeds, and Associate Director, NHS Clinical Governance Support Team, Leicester

Dr Gillian Shepherd, Director, Health and Clinical Excellence, Merck Serono Ltd

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Mr David Symes, Service User Representative

Dr Lesley Wise, Unit Manager, Pharmacoepidemiology Research Unit, VRMM, Medicines & Healthcare Products Regulatory Agency

Observers

Ms Kay Pattison, Section Head, NHS R&D Programme, Department of Health

Mr Simon Reeve, Head of Clinical and Cost-Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health

Dr Heike Weber, Programme Manager, Medical Research Council

Dr Ursula Wells, Principal Research Officer, Department of Health

Current and past membership details of all HTA programme 'committees' are available from the HTA website (www.hta.ac.uk)

Therapeutic Procedures Panel

Members

Chair,
Dr John C Pounsford,
Consultant Physician, North Bristol NHS Trust

Deputy Chair,
Professor Scott Weich,
Professor of Psychiatry, Division of Health in the Community, University of Warwick, Coventry

Professor Jane Barlow,
Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School, Coventry

Ms Maree Barnett,
Acting Branch Head of Vascular Programme, Department of Health

Mrs Val Carlill,
Service User Representative

Mrs Anthea De Barton-Watson,
Service User Representative

Mr Mark Emberton,
Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital, London

Professor Steve Goodacre,
Professor of Emergency Medicine, University of Sheffield

Professor Christopher Griffiths,
Professor of Primary Care, Barts and The London School of Medicine and Dentistry

Mr Paul Hilton,
Consultant Gynaecologist and Urogynaecologist, Royal Victoria Infirmary, Newcastle upon Tyne

Professor Nicholas James,
Professor of Clinical Oncology, University of Birmingham, and Consultant in Clinical Oncology, Queen Elizabeth Hospital

Dr Peter Martin,
Consultant Neurologist, Addenbrooke's Hospital, Cambridge

Dr Kate Radford,
Senior Lecturer (Research), Clinical Practice Research Unit, University of Central Lancashire, Preston

Mr Jim Reece
Service User Representative

Dr Karen Roberts,
Nurse Consultant, Dunston Hill Hospital Cottages

Observers

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council

Professor Tom Walley,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Department of Health

Disease Prevention Panel

Members

Chair,
Dr Edmund Jessop,
Medical Adviser, National Specialist, National Commissioning Group (NCG), London

Deputy Chair,
Dr David Pencheon,
Director, NHS Sustainable Development Unit, Cambridge

Dr Elizabeth Fellow-Smith,
Medical Director, West London Mental Health Trust, Middlesex

Dr John Jackson,
General Practitioner, Parkway Medical Centre, Newcastle upon Tyne

Professor Mike Kelly,
Director, Centre for Public Health Excellence, NICE, London

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Corfe Mullen, Dorset

Ms Jeanett Martin,
Director of Nursing, BarnDoc Limited, Lewisham Primary Care Trust

Dr Julie Mytton,
Locum Consultant in Public Health Medicine, Bristol Primary Care Trust

Miss Nicky Mullany,
Service User Representative

Professor Ian Roberts,
Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine

Professor Ken Stein,
Senior Clinical Lecturer in Public Health, University of Exeter

Dr Kieran Sweeney,
Honorary Clinical Senior Lecturer, Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth

Professor Carol Tannahill,
Glasgow Centre for Population Health

Professor Margaret Thorogood,
Professor of Epidemiology, University of Warwick Medical School, Coventry

Observers

Ms Christine McGuire,
Research & Development, Department of Health

Dr Caroline Stone,
Programme Manager, Medical Research Council

Expert Advisory Network

Members

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford

Professor John Bond, Professor of Social Gerontology & Health Services Research, University of Newcastle upon Tyne

Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer and Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing and Head of Research, The Medical School, University of Birmingham

Professor Barry Cookson, Director, Laboratory of Hospital Infection, Public Health Laboratory Service, London

Dr Carl Counsell, Clinical Senior Lecturer in Neurology, University of Aberdeen

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, Institute of Child Health, London

Mr John Dunning, Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Dean of Faculty of Medicine, Institute of General Practice and Primary Care, University of Sheffield

Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts and The London School of Medicine and Dentistry

Mr Leonard R Fenwick, Chief Executive, Freeman Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher, Antenatal Teacher and Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, University of Birmingham

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Professor Fiona Gilbert, Consultant Radiologist and NCRN Member, University of Aberdeen

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, South Tees Hospital NHS Trust

Bec Hanley, Co-director, TwoCan Associates, West Sussex

Dr Maryann L Hardy, Senior Lecturer, University of Bradford

Mrs Sharon Hart, Healthcare Management Consultant, Reading

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Richard Hobbs, Head of Department of Primary Care & General Practice, University of Birmingham

Professor Alan Horwich, Dean and Section Chairman, The Institute of Cancer Research, London

Professor Allen Hutchinson, Director of Public Health and Deputy Dean of ScHARR, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Royal Marsden Hospital and Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director and Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester

Professor Julian Little, Professor of Human Genome Epidemiology, University of Ottawa

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Professor Rajan Madhok, Medical Director and Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Miranda Mugford, Professor of Health Economics and Group Co-ordinator, University of East Anglia

Professor Jim Neilson, Head of School of Reproductive & Developmental Medicine and Professor of Obstetrics and Gynaecology, University of Liverpool

Mrs Julietta Patnick, National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Director of Clinical Research, Bayer Diagnostics Europe, Stoke Poges

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon Primary Care Trust, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, St James's University Hospital, Leeds

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Professor Sarah Stewart-Brown, Professor of Public Health, Division of Health in the Community, University of Warwick, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick, Coventry

Mrs Joan Webster, Consumer Member, Southern Derbyshire Community Health Council

Professor Martin Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Children's Health, Lymington

Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278