Development of an Observer-Reported Outcome Measure to Capture the Signs and Impact of Fever Distress Symptoms in Infants and Young Children

Adam B. Smith (✉ adam.smith@rb.com)

Reckitt Benckiser <https://orcid.org/0000-0002-2461-458X>

Evi Tselenti

Reckitt Benckiser Plc

Dipak Kanabar

Guy's and Saint Thomas' Hospitals NHS Trust: Guy's and St Thomas' NHS Foundation Trust

Lisa Miles

Reckitt Benckiser Plc

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Abstract

Purpose

This qualitative study aimed to construct an observer-reported outcome measure (ObsRO) that evaluates fever distress in young children.

Methods

A literature review was conducted to identify fever-related concepts. Clinical experts were interviewed for feedback on these concepts. Parents of young children were interviewed to identify behaviours the child exhibited during a recent fever episode. Fever sign and behaviour concepts endorsed by $\geq 20\%$ parents were used to create items for the draft ObsRO. Parents of young children who recently had fever completed the ObsRO and gave feedback during two successive rounds of cognitive interviews.

Results

Twenty-five parents participated in the concept elicitation. Mean child age was 2.7 years (range: 0.6-5.8). Fever sign and behaviour concepts endorsed by $\geq 20\%$ participants were high temperature (80%), skin hot to touch (32%), skin redness/flushing (32%), reduced appetite/drink (48-96%), needy/clingy/irritable (48-92%), less active/interactive (68-84%) and lethargic (64-88%). Eighteen items, four in the Fever Signs Module and 14 in the Fever Behaviours Module, were developed for the draft ObsRO. Chosen recall period was 24 hours. Thirty participants (Round 1: $n=17$; Round 2: $n=13$), participated in cognitive interviews. Mean child age was 2.4 years (range: 0.3-5.8). Round 1 feedback resulted in two Fever Signs items being combined. Three Fever Behaviour items were deleted, six revised and four unchanged. No changes were made following Round 2 feedback. Most participants understood all aspects of the ObsRO and found it user-friendly.

Conclusion

The ObsRO will undergo further development in validation studies testing measurement properties of each item.

Plain English Summary

Parents and caregivers of young children who have a mild to moderate fever currently lack access to objective tools to determine whether or not fever is causing their child distress. This is important because the type of home-based treatment a child receives can depend on whether or not they are distressed. The aim of this study was to design a web-based questionnaire to help parents assess their child's distress. The questions were based on feedback received from parents who described behaviours, language or other cues that their child showed during a recent feverish episode. We also got feedback from clinicians. We asked 30 parents to complete a questionnaire and give feedback on whether they understood the questions and if the questions were relevant to their child's feverish illness. Most parents understood the

questions and thought most were relevant. The questions were modified based on parental suggestions. The anticipation is that this questionnaire will form the basis of a standard tool for parents to use to assess their child's distress and consider treatment options based on the level of that distress.

Introduction

Low-grade fever is common in young children. Although such fever is usually a symptom of underlying infection, some parents may believe that the fever itself is a disease or a harmful symptom in its own right [1, 2]. This common, albeit understandable, misconception (sometimes referred to as 'fever phobia') may lead to parental uncertainty and anxiety in managing fever symptoms in their child [1, 35]. As a result, fever in a child commonly leads to unscheduled physician visits, telephone calls by parents to healthcare professionals for advice on fever management. Estimates suggest that between 10% and 19% of out-of-hour family practitioner visits and 14% of emergency room visits in the United Kingdom (UK) for infants and children aged > 3 months are for fever [68]. Nevertheless, healthcare bodies recognise the importance of parental concerns as part of management of paediatric fever. The UK National Institute for Health and Care Excellence (NICE) states that 'reported parental perception of a fever should be considered valid and taken seriously by healthcare professionals', as even mild symptoms may indicate a life-threatening infection [9].

Country-specific guidelines exist for the management of fever in infants [10]. For instance, NICE guidelines for management of fever in children aged < 5 years recommend using acetaminophen/paracetamol or ibuprofen in children with fever only if the child appears distressed [9] with the aim of alleviating distress rather than reducing body temperature. The concept of 'distress' is difficult to define holistically as paediatric verbal articulation of distress and associated behaviours vary across different age groups and also depend on the caregiver's perception. Similar guidance in making reference to distress or discomfort is seen across many other countries [11].

In its guidelines, NICE recognises there is a 'need to improve the recognition, assessment and immediate treatment of feverish illnesses in children' [9]. However, self-reported information from young children may not be reliable across all age groups and is virtually impossible to obtain from infants. Furthermore, there are currently no validated observer-reported outcome measures (ObsRO) available to evaluate fever distress in young children. We therefore describe a qualitative, cross-sectional study to develop an ObsRO measure that evaluates fever distress in children aged ≥ 3 months to < 6 years.

Materials And Methods

Study design

This study comprised four stages (Fig. 1). In Stages 1 and 2 (concept identification and elicitation, respectively), a conceptual framework for fever distress in children was developed based on scientific literature and feedback from both clinical experts and parents/caregivers of young children with fever.

The most common behaviours and signs of fever distress were used to develop concept items for the draft ObsRO instrument (Stage 3). Parents of young children with fever were recruited for participation in cognitive interviews whereby they completed an electronic version of the draft instrument and gave feedback on the usability of the instrument and relevance of the items (Stage 4).

All interviews were conducted on behalf of the sponsor (Reckitt Benckiser, RB) by a third-party agency (Evidera) in the UK by staff trained in qualitative interview techniques. The study protocol and informed consent forms (ICFs) were approved by the UK Health Research Authority. All documentation prepared as part of this work was carried out in accordance with the United States (US) Food and Drug Administration (FDA) patient-reported outcome (PRO) guidance recommendations and standards [12]. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Stage 1: concept identification

Targeted research studies, clinical articles and guidance documents were reviewed to identify fever-related concepts and create a definition of 'fever distress'. Signs of fever were conceptualised as those confirming the presence of fever (e.g., red cheeks). Fever distress was conceptualised as fever-related changes in behaviour (e.g., loss of appetite). The initial conceptual framework for fever distress included behaviours (restlessness/agitation, apathy/limpness and loss of appetite) and signs (red cheeks and glazed eyes). A conceptual disease model (CDM) was developed to understand fever distress. The authors interviewed three expert clinicians, two from the UK and one from the US, for feedback regarding the above concepts and the CDM.

Stage 2: concept elicitation

Recruitment

Participants were screened for eligibility using ethics committee-approved screening forms. Eligible participants were parents/caregivers of children aged ≥ 3 months to < 6 years who had recently resolved fever (within the previous 2 weeks). Participants had a good command of English, gave informed consent and were willing to be audiorecorded during the interview. Children of the participants were grouped according to age: 1) ≥ 3 months to 1 year; 2) 1 to < 2 years; 3) 2 to < 4 years; 4) 4 to < 6 years.

Telephone interviews were scheduled with eligible participants and an interview packet containing an introductory letter, two copies of the ICF and a sociodemographic form was delivered to the participant by courier.

Interview

All participants gave confirmation of written informed consent before the elicitation interview began. Each interview (including time for consent, interview and completion of case report forms) lasted approximately 60 minutes and was audio-recorded. The interviewer discussed parental understanding of

fever, recent experience with fever, fever-related signs and behaviour, caregiver fever management, caregiver actions and impact. Participants completed the sociodemographic questionnaire after the interview and returned this, along with the two signed copies of ICFs, to study personnel. A fully-signed ICF was returned to participants for their personal records.

Stage 3: instrument development

Item generation

Fever signs and behaviours endorsed by $\geq 20\%$ of participants elicited during interviews were selected for item development. These were further evaluated against item writing criteria adapted from the International Society for Pharmacoeconomic and Outcomes Research – Patient Reported Outcome (ISPOR PRO) Good Practice Task Force, Part II [13] (Supplementary Table 1).

Draft ObsRO instrument

Development of the ObsRO instrument, including creation of questions, recall period, and response choices, was guided by best practice guidance outlined in the ISPOR PRO Good Practice Task Force, Part I and Part II [13, 14]. The language of participants during elicitation interviews (i.e., their descriptions of fever signs and behaviours) guided the wording of the instructions for use, item stems and response options. Potential recall periods and response options were evaluated for best fit across sign and behaviour items. The recall period was determined by the time interval between the child exhibiting the sign/behaviour and it being described by parents and clinical experts (i.e., several days, hours, etc.) and the intended use of the measure in future trials where daily fever assessment was required.

Stage 4: cognitive interview

Cognitive interviews were conducted to test the content validity of the draft ObsRO. Parents of children with recently resolved fever were recruited using the same process as the elicitation interviews. Eligible participants were sent an ICF, sociodemographic form, the ObsRO and an importance questionnaire electronically at the time of the interview.

Cognitive interviews were conducted in person, via webcam or by telephone; all sessions were audio-recorded. Interviews were performed in two rounds; in Round 1, participants completed Version 1 of the draft ObsRO instrument whereas in Round 2, participants completed Version 2. The interviewer sought feedback from participants on their understanding and comprehension of the items in the ObsRO, the timeframe and response options. Participants were also asked about usability.

Data analysis

Qualitative data analysis

Interview audio files were transcribed and transcripts were cleaned, de-identified and evaluated using ATLAS.ti qualitative software version 8.0 [15].

For elicitation data, a coding framework was developed to organize the text data for the major discussion topics and concepts that emerged during discussions. For cognitive interviews, feedback on instruction, response options and item meaning were coded, as well as emerging issues such as missing or confusing content. Team members were trained to use a codebook that coded words and phrases from interview participants. Two and three team members independently coded elicitation and cognitive interview transcripts, respectively, after which all codes were compared, discussed, and reconciled wherever differences occurred. A random sample of approximately 20% of coded transcripts was reviewed. If problems were identified, additional transcripts or codes were reviewed. Key concepts that emerged from coding of elicitation data were put into a concept frequency table that showed how many participants endorsed a particular concept. Concepts were also plotted on a saturation grid. Concept saturation was reached at a point when no new concepts continued to emerge.

An item tracking matrix was developed to capture participants' comprehension and relevance of each item on the ObsRO. The matrix also tracked changes made to each item during ObsRO development, providing supportive evidence and rationale for each change.

Quantitative data analysis

Tables summarizing quantitative data (means, standard deviations, and range) were presented for continuous variables and frequency and percentage for categorical variables. Quantitative information was used to characterize the study sample and document representation of the target population in accordance with regulatory guidance. In addition, descriptive statistics were calculated for the ObsRO scores.

Results

Stage 1: concept identification

Clinicians gave feedback on the initial concept framework of fever distress. They stated that symptoms of fever can be complex, as the underlying illness causes diverse symptoms, while the body raises its temperature to combat the illness. They also stated that some signs/symptoms would present differently in children of different ages. For example, infants might have trouble feeding, swallowing and breathing, whereas children aged 45 years might have a sore throat, be less active, and drink and eat less. Clinicians also noted that parents would be unlikely to report fever signs such as 'depressed fontanelle' (a sign of dehydration) as this would be identified by a clinician during a physical examination.

Clinicians noted that the CDM should focus more on fever instead of immune function and physiological health factors. The preliminary fever distress CDM is presented in Fig. 2.

Stage 2: concept elicitation

Demographic and clinical characteristics of participants

Twenty-five participants were recruited, all of whom were parents of a child who had fever (Table 1). Twenty (80%) parents were female, 16 (64%) were white, and 21 (84%) lived with their partner and child. Children were predominantly white (n = 14, 56%), with an almost equal proportion of male and female children (n = 13 female, 52%). Mean age of the children was 2.7 (1.9) years; five (20%) children were between 3 months and 1 year, five (20%) children were between 1 and 2 years, eight (32%) children were between 2 and 4 years and seven (28%) children were between 4 and 6 years. The majority (n = 23, 92%) of children had no other health conditions. All parents rated their child's overall health as 'very good' (n = 18, 72%) or 'good' (n = 7, 28%).

Table 1
Demographic and clinical characteristics of participants in concept elicitation

Characteristic	Total (N = 25) n (%)
Relationship to child	
Parent	25 (100.0)
Parent/caregiver gender	
Female	20 (80.0)
Parent/caregiver ethnicity	
White	16 (64.0)
Black or African	4 (16.0)
Mixed ethnicity ^a	4 (16.0)
Asian	1 (4.0)
Parent/caregiver current living/domestic situation	
With partner and children	21 (84.0)
Alone with children	2 (8.0)
With friends or other relatives	1 (4.0)
With partner	1 (4.0)
Parent/caregiver education	
University degree	14 (56.0)
Post graduate degree	4 (16.0)
GCSE/O levels or equivalent	3 (12.0)
A levels and/or diplomas or equivalent	3 (12.0)
Vocational/work-based qualifications	1 (4.0)
Parent/caregiver employment	
Full-time	17 (68.0)
Part-time	3 (12.0)
Homemaker	3 (12.0)
Unemployed	1 (4.0)

Characteristic	Total (N = 25) n (%)
On disability	1 (4.0)
Child's age, years	
Mean (standard deviation)	2.7 (1.9)
Median [range]	2.2 [0.6–5.8]
Child's gender	
Female	13 (52.0)
Child's racial background	
White	14 (56.0)
Mixed ethnicity ^b	6 (24.0)
Black or African	4 (16.0)
Asian	1 (4.0)
Child's current living/domestic situation	
With both of his/her parents	23 (92.0)
With his/her mother only	2 (8.0)
Child's health conditions	
No other health conditions	23 (92.0)
Other health conditions ^c	1 (4.0)
Missing	1 (4.0)
Child's health rating	
Very good	18 (72.0)
Good	7 (28.0)
^a Parent/caregiver mixed ethnicity: Black African and Asian; Black Caribbean and White; White and Chinese; White and Black African ^b Child mixed ethnicity: Black African, Asian and English; Mixed White/Chinese/Middle eastern; White and Black African/Caribbean; White and Black Caribbean ^c Child's other health conditions: autism, attention deficit hyperactivity disorder	

Interview results

Participants were asked if they understood the term 'fever'. All participants (n = 25, 100%) stated that a fever is a high temperature (higher than considered medically normal). Participants were also asked what they believe causes fever. The most common response (n = 11, 44%) was that fever is caused by an infection, whether viral or bacterial. Ten (40%) participants considered fever to be the result of an immune response against disease; body temperature rises because the body is "fighting off infection."

The most common signs of fever identified by participants were objective assessment of body/skin temperature using a thermometer (n = 20, 80%), subjective assessment of body/skin temperature by touching (n = 8, 32%) and redness/flushing (n = 8, 32%; Table 2). Saturation of fever signs in the overall sample was reached by the third participant. Overall, the most common fever-associated behaviours identified by participants were reduced appetite (n = 24, 96%), needy/clingy behaviour (n = 23, 92%) and crying (n = 22, 88%; Table 2). The duration of fever ranged from 0.5–5 days (median 4 days). Fever signs and behaviour concepts endorsed by $\geq 20\%$ participants are shown in Fig. 3.

Table 2
Concept frequency of fever signs and fever distress behaviours

	< 1 year (N = 5) n (%)	1–2 years (N = 5) n (%)	2–4 years (N = 8) n (%)	4–6 years (N = 7) n (%)	Total (N = 25) n (%)
Fever signs					
Temperature measurement	4 (80.0)	3 (60.0)	7 (87.5)	6 (85.7)	20 (80.0)
Redness/flushing	1 (20.0)	0	5 (62.5)	2 (28.6)	8 (32.0)
Hot to the touch	2 (40.0)	2 (40.0)	1 (12.5)	3 (42.9)	8 (32.0)
Warmer than normal	0	0	3 (37.5)	2 (28.6)	5 (20.0)
Fever distress behaviours					
Less appetite	5 (100.0)	5 (100.0)	8 (100.0)	6 (85.7)	24 (96.0)
Needy/clingy	5 (100.0)	5 (100.0)	8 (100.0)	5 (71.4)	23 (92.0)
Less playful	2 (40.0)	5 (100.0)	6 (75.0)	6 (85.7)	19 (76.0)
Less active	4 (80.0)	4 (80.0)	7 (87.5)	6 (85.7)	21 (84.0)
Less talkative/quiet	5 (100.0)	2 (40.0)	7 (87.5)	6 (85.7)	20 (80.0)
Not smiling/unhappy	4 (80.0)	5 (100.0)	7 (87.5)	5 (71.4)	21 (84.0)
Less social interaction	2 (40.0)	4 (80.0)	7 (87.5)	4 (57.1)	17 (68.0)
Irritable	4 (80.0)	3 (60.0)	8 (100.0)	5 (71.4)	20 (80.0)
Crying	5 (100.0)	5 (100.0)	8 (100.0)	4 (57.1)	22 (88.0)
Less energy/lethargic	5 (100.0)	3 (60.0)	7 (87.5)	4 (57.1)	19 (76.0)
Sleepy/tired	3 (60.0)	2 (40.0)	6 (75.0)	5 (71.4)	16 (64.0)
Fussy	4 (80.0)	4 (80.0)	4 (50.0)	1 (14.3)	13 (52.0)
Less fluid intake	5 (100.0)	2 (40.0)	2 (25.0)	3 (42.9)	12 (48.0)
Difficult to console	4 (80.0)	5 (100.0)	2 (25.0)	1 (14.3)	12 (48.0)

The most common actions participants took on realisation their child was unwell was to give medication (n = 24, 96%), offer fluids (n = 23, 92%) and food (n = 17, 68%). The most common medications participants gave their children were Calpol® (n = 19, 76%) and Nurofen® (n = 7, 28%). The majority of participants (n = 14, 56%) did not take their children to a healthcare provider because the fever symptoms were not severe. Those participants that did take their children to a healthcare provider (n = 11, 44%) were

not prescribed any additional medication, but were advised to continue to treat with Calpol® or Nurofen for Children® and to monitor the child.

The most commonly-reported impacts of fever on the participants' lives were disruption to daily activities (n = 17, 68%), reduced sleep (n = 15, 60%), disruption to social life and strained family relationships (n = 12, 48% each).

Stage 3: instrument development

Fever signs and behaviours endorsed by ≥ 20 participants during the elicitation interviews were further mapped to item writing criteria. The following instructions were provided to parents when completing the draft instrument:

The following questions assess how fever has affected your child in the past 24 hours. Please answer all questions by selecting the one option that best describes your observations of your child.

A 24-hour recall period was selected for both signs and behaviours items. A modular approach was developed for the draft questionnaire; participants would first answer questions about fever signs (Fever Signs Module) to ascertain whether or not the child had fever before answering questions about the child's behaviour (Fever Behaviour Module). The Fever Signs Module contained four items which were simple yes/no questions to indicate presence/absence of a sign in the previous 24 hours. The Fever Behaviours Module contained 14 items which allowed participants to compare their child's behaviour in the past 24 hours to how they behaved normally. Four responses were possible for each item: more than usual; the usual; less than usual; not at all.

The draft ObsRO instrument was adapted to a web-based platform for participants to complete on any electronic device.

Stage 4: cognitive interviews

Demographic and clinical characteristics of participants

Thirty participants were recruited, 17 to Round 1 and 13 to Round 2, all of whom were parents (Table 3). Participants were predominantly female in both rounds (Round 1: n = 16, 94%; Round 2: n = 8, 62%). Eighteen (60%) of 30 participants were white (predominantly British), five (17%) were Asian and four (13%) were African/Caribbean. The majority of participants (n = 24, 80%) lived with their partner and child. In Round 1, 10 (59%) children were female compared with six (46%) in Round 2. Twelve (40%) of 30 children were white (predominantly British), 11 (37%) had mixed ethnicity and five (17%) were Asian; there were more children of mixed ethnicity in Round 1 than Round 2 (Table 3). Mean ages of the children were similar in both rounds (Round 1: 2.8 years; Round 2: 2.3 years), with similar numbers of children across age categories in both rounds.

Table 3
Demographic and clinical characteristics of participants in cognitive interview

Characteristic	Round 1 (N = 17) n (%)	Round 2 (N = 13) n (%)	Total (N = 30) n (%)
Relationship to child			
Parent	17 (100.0)	13 (100.0)	30 (100.0)
Parent/caregiver gender			
Female	16 (94.1)	8 (61.5)	24 (80.0)
Parent/caregiver ethnicity			
White English/Welsh/Scottish/Northern Irish/British	8 (47.1)	6 (46.2)	14 (46.7)
Irish	0	1 (7.7)	1 (3.3)
Any other White background	3 (17.6)	0	3 (10.0)
White and Black African	1 (5.9)	0	1 (3.3)
Any other Mixed/Multiple Ethnic Background	0	1 (7.7)	1 (3.3)
Indian	0	1 (7.7)	1 (3.3)
Pakistani	1 (5.9)	0	1 (3.3)
Bangladeshi	1 (5.9)	2 (15.4)	3 (10.0)
Caribbean	0	1 (7.7)	1 (3.3)
Any other Black/African/Caribbean background	2 (11.8)	1 (7.7)	3 (10.0)
Any other ethnic group (not specified)	1 (5.9)	0	1 (3.3)
Parent/caregiver current living/domestic situation			
With partner and children	14 (82.4)	10 (76.9)	24 (80.0)
Alone with children	3 (17.6)	2 (15.4)	5 (16.7)
With friends or other relatives and children	0	1 (7.7)	1 (3.3)
Parent/caregiver education			
University Degree	5 (29.4)	7 (53.8)	12 (40.0)
Post Graduate degree	4 (23.5)	1 (7.7)	5 (16.7)
GCSE/O levels or equivalent	4 (23.5)	1 (7.7)	5 (16.7)
A Levels and/or diplomas or equivalent	3 (17.6)	2 (15.4)	5 (16.7)

Characteristic	Round 1 (N = 17) n (%)	Round 2 (N = 13) n (%)	Total (N = 30) n (%)
Vocational/work-based qualifications	1 (5.9)	2 (15.4)	3 (10.0)
Parent/caregiver employment			
Full-time	11 (64.7)	11 (84.6)	22 (73.3)
Part-Time	3 (17.6)	2 (15.4)	5 (16.7)
Homemaker	2 (11.8)	0	2 (6.7)
Unemployed	1 (5.9)	0	1 (3.3)
Child's age (years)			
Mean (standard deviation)	2.8 (1.84)	2.3 (1.75)	2.6 (3.59)
Median [range]	2.8 [0.3–5.7]	2.0 [0.3–5.8]	2.4 [0.3–5.8]
Child's gender, n (%)			
Female	10 (58.9)	6 (46.2)	16 (53.3)
Child's racial background			
White English/Welsh/Scottish/Northern Irish/British	5 (29.4)	6 (46.2)	11 (36.7)
Irish	0	1 (7.7)	1 (3.3)
Any other White background	1 (5.9)	0	1 (3.3)
White and Black Caribbean	3 (17.6)	1 (7.7)	4 (13.3)
White and Black African	1 (5.9)	0	1 (3.3)
White and Asian	1 (5.9)	0	1 (3.3)
Any other mixed/multiple ethnic background	3 (17.6)	1 (7.7)	4 (13.3)
Indian	0	1 (7.7)	1 (3.3)
Bangladeshi	1 (5.9)	2 (15.4)	3 (10.0)
Any other Asian background	1 (5.9)	0	1 (3.3)
Any other Black/African/Caribbean background	0	1 (7.7)	1 (3.3)
Other	1 (5.9)	0	1 (3.3)
Child's current living/domestic situation			
With both of his/her parents	14 (82.4)	10 (76.9)	24 (80.0)

Characteristic	Round 1 (N = 17) n (%)	Round 2 (N = 13) n (%)	Total (N = 30) n (%)
With his/her mother only	3 (17.6)	2 (15.4)	5 (16.7)
Child's health conditions			
No other health conditions	16 (94.1)	12 (92.3)	28 (93.3)
Allergies	1 (5.9)	0	1 (3.3)
Asthma	0	1 (7.7)	1 (3.3)
Child's health rating			
Very good	13 (76.5)	12 (92.3)	25 (83.3)
Good	4 (23.5)	1 (7.7)	5 (16.7)

The majority (n = 28, 93%) of children had no other health conditions. All parents rated their child's overall health as 'very good' (n = 25, 83%) or 'good' (n = 5, 17%).

Interview results

Round 1 feedback

All participants understood the instructions and thought they were clear; none gave any suggestions for improvement. Eight (47%) participants felt that the 24-hour recall period was appropriate. However, when taking into account the duration of fever and administration of medicine, participants felt the recall period could be lengthened. No modifications were made to the recall period or response options after Round 1 of the cognitive interviews. Two (12%) participants felt that response options were inappropriate for some of the items (e.g., it is unlikely that a child with fever will play 'more than usual') and one suggested changing responses to yes/no for some items.

Most participants understood all four Fever Signs items and felt they were important. However, nine (53%) participants commented on redundancy between Items 1 ('my child felt warmer than usual') and 2 ('my child felt hot') and suggested combining these. Two (12%) participants suggested that Item 4 ('my child had a temperature') needed to specify 'high' temperature. The above suggestions were included in Version 2 of the ObsRO after consultation with clinical experts (Table 4).

Table 4
Summary of changes of fever sign and fever behaviour module

Round 1 Version		Module	Decision	Revisions
1	In the past 24 hours, my child felt warmer than usual	Fever Signs	Combine with #2	In the past 24 hours, my child felt warmer/hotter than usual
2	In the past 24 hours, my child felt hot	Fever Signs	Combine with #1	See above
3	In the past 24 hours, my child looked red or flushed	Fever Signs	Retain	No change
4	In the past 24 hours, my child had a temperature	Fever Signs	Add 'high'	In the past 24 hours, my child had a high temperature
5	In the past 24 hours, my child ate...	Fever Behaviours	Retain	No change
6	In the past 24 hours, my child drank water or juice...	Fever Behaviours	Remove 'water or juice'	In the past 24 hours, my child drank...
7	In the past 24 hours, my child was active or moving around ...	Fever Behaviours	Remove "moving around" revise to add "activity level"	In the past 24 hours, my child's activity level was...
8	In the past 24 hours, my child played...	Fever Behaviours	Redundant with items #7 and #11 Delete #8	–
9	In the past 24 hours, my child interacted with family and friends...	Fever Behaviours	Remove 'family and friends'	In the past 24 hours, my child interacted...
10	In the past 24 hours, my child talked to me and others...	Fever Behaviours	Redundant with items #9 Talking not relevant for younger children Delete #10	–
11	In the past 24 hours, my child had energy...	Fever Behaviours	Retain	No change
12	In the past 24 hours, my child was sleepy...	Fever Behaviours	Retain	No change
13	In the past 24 hours, my child was quiet...	Fever Behaviours	Retain	No change

Round 1 Version		Module	Decision	Revisions
14	In the past 24 hours, my child sat/lay still...	Fever Behaviours	Redundant with #11 and #15. Delete #14	–
15	In the past 24 hours, my child was irritated...	Fever Behaviours	Redundant with #16. 'Irritated' suggests symptom known only to patient. Reword to "irritable" which is observable.	In the past 24 hours, my child was irritable...
16	In the past 24 hours, my child was fussy...	Fever Behaviours	Redundant with #15 Delete	–
17	In the past 24 hours, my child was difficult to quiet down...	Fever Behaviours	Revise to use 'soothe'	In the past 24 hours, my child was difficult to soothe...
18	In the past 24 hours, my child was clingy or needed me....	Fever Behaviours	Use 'needed my attention'	In the past 24 hours, my child needed my attention....

Most participants understood all 14 Fever Behaviour items and thought all questions were important. However, participants commented on redundancy in a few items (e.g., was the child active [Item 7] did the child play [Item 8]). A couple of items were found not to be relevant to infants (e.g., 'my child ate' [Item 5] and 'my child talked to me and others' [Item 10]). Some participants did not feel that all items were relevant to fever (e.g., 'my child sat/lay still' [Item 14]). Participants suggested rewording a few items for clarity (e.g., 'my child interacted with family and friends' [Item 9]; participants explained that the important part is whether the child *interacted*, not with whom). Items were modified or deleted based on Round 1 feedback and consultation with clinical experts (Table 4).

Round 2 feedback

Thirteen participants completed, and gave feedback on, Version 2 of the ObsRO. All participants understood the instructions, although nine (69%) felt the wording could be simplified. All participants understood the 24-hour recall period and eight (62%) felt 24 hours was appropriate. However, one (8%) participant felt that 24 hours was too short given the duration of fever. Two (15%) felt that the 'not at all' response option was not suitable for two items ('activity level was' and 'child was quieter'). One (8%) participant would have liked to give a more detailed account of his/her child's fever.

Most participants understood all three Fever Signs items and felt they were important signs of fever. However, three (23%) participants would have liked a definition for 'high' temperature. There were no comments regarding redundancy between items. No further revisions were made to any Fever Signs items.

Most participants understood all 10 Fever Behaviour items and felt they were important. The majority of comments were concerning clarity of the wording in some items, for instance, three (23%) participants

were confused by the word 'interacted' (Item 7). Three (23%) participants felt that asking whether the child was more/less irritable in the past 24 hours (Item 15) was not very important as a child could be irritable for reasons other than fever. No further revisions were made to any Fever Behaviours items.

Feedback on the usability of the ObsRO instrument

Most participants (n = 26, 87%) considered their overall experience of completing the ObsRO to be good. Twenty-two (73%) participants felt the ObsRO was easy to complete using their electronic device and 28 (93%) gave positive feedback about the layout of the ObsRO on their electronic device; one participant liked that all the text was on one page. Twenty-three (77%) participants found it 'easy' to navigate between questions. One participant experienced some difficulty navigating between screens as the ObsRO did not load correctly on his/her device. All participants reported they would be willing to complete this questionnaire on a daily basis during a fever episode. Participants' suggestions include adding graphics, reformatting questions so that each question stands out clearly and simplifying the date field.

Fever signs and behaviours conceptual framework

A preliminary fever signs and behaviours conceptual framework was drafted based on concept elicitation interviews. Additional modifications were made based on feedback from the cognitive interviews. The revised hypothesized conceptual framework for fever distress is shown in Fig. 4.

Discussion

The Fever Signs and Fever Behaviour ObsRO measures were developed based on a review of the NICE guidance on fever signs, input from clinical experts and based on concept elicitation and cognitive interviews with caregiver of young children < 6 years of age.

In Stage 1, key concepts of fever identified from the literature review were put to three clinical experts. They indicated that it was important to gauge the parent/caregiver's understanding of fever and which signs/symptoms they were likely to report, which could vary due to the age of the child. Clinicians felt that the CDM should make fever the primary focus. The preliminary CDM was refined based on the clinicians' feedback.

In Stage 2, 25 parents with children who recently had fever were interviewed to elicit responses on fever signs and behaviours. Fever-associated signs and behaviours endorsed by $\geq 20\%$ parents were used to develop items for the draft ObsRO. An *a priori* cut-off has been used to prioritise the most relevant concepts for item development in other clinical outcome assessment studies [1619].

In Stage 3, the draft ObsRO (Version 1) was developed containing a Fever Signs Module with four items and a Fever Behaviours Module with 14 items. The ObsRO was designed so that participants would complete the Fever Signs Module, which detected the presence of fever, first before going on to the Fever Behaviours Module, which assessed the extent of fever. For this reason, items in the Fever Signs Module were all deterministic (i.e., yes/no); this included one objective item, 'does the child have a (?an elevated)

temperature', which is determined using a thermometer. If the answer to this is 'no', the child does not have fever and the Fever Behaviours module would not need to be completed. All items in the Fever Behaviours Module were 4-point ordinal verbal response scales; the response options for these were derived by examining how participants described their child's behaviour in terms of duration, frequency or intensity of the behaviour. We maximised participant understanding of all items by using their own form of language.

In Stage 4, 17 participants completed Version 1 of the ObsRO in Round 1 of the cognitive interviews and 13 completed Version 2 of the ObsRO in Round 2. A qualitative content analysis approach was used to examine ObsRO feedback. This method classifies large amounts of text into an efficient number of categories that represent similar meanings [20]. Most participants understood the instructions, recall period and response options, and most of the items. However, many participants in both rounds regarded the 24-hour recall period to be too short. No change was made to the recall period based on participant feedback; the study team thought 24 hours was appropriate given the potential future use of the ObsRO as a daily diary in a clinical treatment trial. After Round 1 feedback, three of the four original Fever Signs items were retained: warmer/hotter than usual; red/flushed skin; high temperature. Three Fever Behaviour items (played, sat/lay still, fussy) were deleted because of redundancy with other items, six items were revised to improve the clarity of the item (drank water or juice, active or moving around, interacted with friends and family, irritable, difficult to quiet down, clingy/needed me) and four items were unchanged (ate, energy, sleepy, quiet). All participants found the ObsRO user-friendly and easy to complete.

One potential limitation of this study was that the participants were all based in the UK, so findings may not be applicable to other countries due to possible language barriers and differences in how fever is considered and treated. The sample population was reasonably well educated; 72.0% of participants in the elicitation interviews and 56.7% of participants in the cognitive interviews had a university degree. This may not be representative of the wider UK population.

Conclusion

Results from this qualitative study provide support for the content validity of the Fever ObsRO among caregivers with children ages 3 months to 6 years. Overall, participants provided positive feedback on the Fever ObsRO and found the measure to be relevant, straightforward, easy to understand, and comprehensive of their child's fever experience. As a next step, a validation study is required exploring measurement properties of the Fever ObsRO in a larger sample of parents/caregivers to ensure that the final Fever ObsRO is a clinically relevant and psychometrically sound measure of fever distress for use in young children with fever both for future clinical trials and for use by parents of young children with feverish illnesses.

Declarations

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Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical approval

This study was performed in line with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Approval was granted by the UK Health Research Authority.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Author Contributions And Acknowledgements

Adam Smith and Lisa Miles designed, and co-developed the idea for, the study. Evi Tselenti performed the analyses and Dipak Kanabar contributed to the design and provided expert opinion. All authors were involved in drafting the manuscript. The authors are grateful to KOLS, as well as to the parents/caregivers for their time and contributions to the development of the ObsRO. The authors also acknowledge Evidera/PPD, in particular, Anne Skalicky, Hayley Karn and Ella Brookes, for undertaking the parent and caregiver interviews and qualitative analysis, and Global Perspectives for participant recruitment. The authors also acknowledge Dr Desirée Douglas at Niche Science & Technology Ltd for medical writing services and editorial assistance with the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Study design flow chart

Figure 2

Preliminary fever distress conceptual disease model

Figure 3

Fever signs and behaviour concepts endorsed by $\geq 20\%$ of participants

Figure 4

Revised preliminary fever distress conceptual framework

Supplementary Files

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- [SupplementaryTable1.docx](#)