Factors affecting the causality assessment of adverse events following immunisation in paediatric clinical trials: An online survey.

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ABSTRACT:

BACKGROUND:

Serious adverse events (SAEs) in clinical trials require reporting within 24 hours, including a judgment of whether the SAE was related to the investigational product(s). Such assessments are an important component of pharmacovigilance, however classification systems for assigning relatedness vary across study protocols. This on-line survey evaluated the consistency of SAE causality assessment among professionals with vaccine clinical trial experience.

METHODS:

Members of the clinical advisory forum of experts (CAFÉ), a Brighton Collaboration online-forum, were emailed a survey containing SAEs from hypothetical vaccine trials which they were asked to classify. Participants were randomized to either two classification options (related/not related to study immunisation) or three options (possibly/probably/unrelated). The clinical scenarios, were i) leukaemia diagnosed 5 months post-immunisation with a live RSV vaccine, ii) juvenile idiopathic arthritis (JIA) 3 months post-immunisation with a group A streptococcal vaccine, iii) developmental delay diagnosed at age 10 months after infant capsular group B meningococcal vaccine, iv) developmental delay diagnosed at age 10 months after maternal immunisation with a group B streptococcal vaccine.

RESULTS:

There were 140 respondents (72 two options, 68 three options). Across all respondents, SAEs were considered related to study immunisation by 28% (leukaemia), 74% (JIA), 29% (developmental delay after infant immunisation) and 42% (developmental delay after

maternal immunisation). Having only two options made respondents significantly less likely to classify the SAE as immunisation-related for two scenarios (JIA p=0.0075; and maternal immunisation p=0.045). Amongst study investigators (n=43) this phenomenon was observed for three of the four scenarios: (JIA p=0.0236; developmental delay following infant immunisation p=0.0266; and developmental delay after maternal immunisation p=0.0495).

CONCLUSIONS:

SAE causality assessment is inconsistent amongst study investigators and can be influenced by the classification systems available to them. There is a pressing need for SAE classification systems to be standardized across study protocols.

Introduction

Clinical trials of new and existing vaccines are an essential component of the prevention of infectious diseases by immunisation. A cornerstone of safety monitoring in any vaccine clinical trial (pre or post licensure) is the system of serious adverse event (SAE) reporting. As per ICH-GCP [1] the study Principal Investigator must report all adverse events (AEs) that meet the criteria of 'Serious Adverse Events' (see panel 1) to the study sponsor within 24 hours. Crucially, at the time of this initial reporting the investigator must report whether or not the SAE is related to the vaccine(s) received in the trial.

Panel 1

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

This classification, often made with limited information, can have a significant impact on trial conduct and the perceived safety of vaccines. SAEs that are considered related to the vaccine are described as serious adverse reactions (SARs). SAR's that are not 'expected' based on the vaccine's previous safety record, are considered SUSARs (suspected unexpected serious adverse reactions). These in turn attract additional reporting requirements to ethics committees and regulatory authorities, and require circulation of this information to other investigators in the form of 'Council for International Organizations of Medical Sciences' (CIOMS) reports. SUSAR reporting can also potentially activate clinical trial pausing rules, and are frequently reported in clinical trial publications, summaries of product characteristics, product monographs, and regulatory body assessment reports [2].

Despite the considerable impact that the initial, rapid assessment of serious adverse event causality may have, there are no data on the consistency with which clinical trial investigators will classify SAEs as being related or unrelated to vaccination, nor on which factors might influence these assessments.

Of relevance to this is that different classification systems are used in different clinical trial protocols, with the options available varying from 2 (related/unrelated) to 3 (probably related, possibly related, unrelated) to 5 (definitely related, probably related, possibly related, probably unrelated and definitely unrelated). ICH-GCP guidelines acknowledge there is no standard nomenclature for classification, but state that the criteria of 'reasonable suspected causal relationship' is meant to convey that 'there are facts (evidence) or arguments to suggest a causal relationship' [1]. It is important to note that even if multiple options are offered, reporting will still occur in a binary yes/no manner, i.e. if the investigator considers an SAE only possibly related to the vaccine, it is still reported as

a serious adverse reaction (SAR). Study protocols with only 2 classifications (related/unrelated) therefore have 50% of classification options which will result in an SAR, whereas study protocols with 3 or 5 options have 67% and 60% of options (respectively) which would result in an SAR being reported. It is not known what impact this difference in the proportion of options for classifying SAEs as related, or the psychological impact of having to present an SAE as being 'related' rather than 'possibly related' can have on the rate of SAR reporting. Studies of the assessment of causality of events in other settings such as for adverse drug reactions post-licensure, show that different classification systems can result in different levels of reactions being classified as 'related', and there is limited to poor agreement between assessments made using different methods [3-5].

Accordingly, this survey was conducted to study the consistency of classification of SAEs in paediatric clinical trials amongst investigators and other professionals with vaccine clinical trial experience, and to determine whether factors such as investigator experience and classification systems can affect the frequency of SAR reporting.

2. Methods

An online survey based on an in-house designed questionnaire was emailed to members of the Brighton Collaboration clinical advisory forum of experts (CAFÉ) [6] in May 2014 and was open to responses for 1 month. The online questionnaire asked respondents to classify 6 hypothetical clinical scenarios (outlined in Table 1) as either being related or unrelated to an immunisation received in a paediatric clinical trial. One scenario was intended as a positive control that would commonly be considered as related to immunisation (a febrile convulsion in a 12 month old child 6 hours following a pneumococcal conjugate vaccine) while one was a negative control (a child fracturing an arm following a cycling accident 4

90 weeks after immunisation). A further four ‘test’ scenarios were selected as examples of
91 clinical presentations that may occur in previously healthy children whose causal
92 relationship with the investigational vaccines would not be obvious, and if classified as
93 related would constitute SUSARs. The focus was particularly on chronic conditions of multi-
94 factorial aetiology, where the onset or diagnosis of illness might be delayed from the causal
95 event. The questionnaire and clinical scenarios were developed following a pilot survey of
96 14 members of the UK Paediatric Vaccine Group (UKPVG) [7].

97 Respondents were randomly allocated to surveys with either two options (‘related’ or ‘not
98 related’ to study immunisation) or three options (‘probably related’, ‘possibly related’ or
99 ‘unrelated’ to study immunisation).

100 Respondents to the survey provided information on their geographic region and
101 professional role (investigator on clinical trials, clinician (hospital based), clinician (primary
102 care), public health, or pharmaceutical industry). Investigators were further classified
103 according to their previous experience of clinical trials.

104 The percentage of respondents who considered each SAE to be related to immunisation was
105 calculated for the two and three option groups separately. For the three option group the
106 adverse event was classified as related to the vaccine if the respondent indicated the event
107 was either ‘probably’ or ‘possibly’ related to study immunisation, reflecting the process of
108 SAE reporting in clinical trials. For each scenario, the impact of the number of classification
109 options was assessed by comparing the percentage of SAEs considered related to
110 immunisation between groups using chi-squared tests or Fisher’s Exact tests where
111 appropriate. Logistic regression models which included an interaction term (investigator by
112 number of options) were used to assess whether the effect of having three options was

more pronounced in those who were investigators in clinical trials than in those who had other roles in vaccine research (non-investigators). The total number of SAEs classified as related was summed for each respondent (minimum=0, maximum possible=4) and compared between investigators and non-investigators, and between experienced investigators (>10 trials) and less-experienced investigators (≤ 10 trials), using Wilcoxon Rank Sum tests. In addition we calculated the expected number of SAEs for each investigator, assuming a binomial distribution of independent events, with probability equal to the overall proportion of SAEs classified as related by investigators. For those allocated to the 3 option group we inflated this expected proportion by (0.66/0.5) to allow for the increased number of options which result in a SUSAR classification available in this group.

3. Results

535 members were approached through email invitation via the CAFÉ mailing list, 140 of whom responded and completed the survey (72 for the two option group, 68 for the three option group). There were 43 (31%) respondents who had previous experience as investigators on clinical trials. Non-investigators were mainly from pharmaceutical industries, public health and vaccine safety monitoring agencies.

The geographic region and professional role of respondents is shown in Table 2.

All but 8 of 140 (94.3%) respondents considered the febrile convulsion following immunisation (positive control) as related to the vaccine, while only 6 (4.3%) considered the fractured forearm as related to immunisation (negative control). Responses to the other scenarios were more variable (Table 3, Figure), with the percentage considering the SAE related to immunisation being 28.6% (leukaemia), 73.6% (juvenile inflammatory arthritis),

29.3% (global developmental delay (GDD) following infant immunisation) and 44.3% (global developmental delay following maternal immunisation).

Across all respondents, those given three options were statistically significantly more likely to classify an adverse event as related to immunisation for two of the four 'test' scenarios: juvenile inflammatory arthritis (84% vs 64%, p=0.0075) and developmental delay following maternal immunisation (53% vs 36%, p=0.045). In the remaining two scenarios, a 9% increase in SAEs reported as SUSARs was observed for GDD (34% vs 25% p=0.2515) and 2% increase observed for ALL (29% vs 27% p=0.8306). For investigators this difference was statistically significant for three scenarios: JIA (93% vs 54%), GDD following infant immunisation (47% vs 14%) and GDD following maternal immunisation (60% vs 29%) (Table 4). When comparing investigators to non-investigators, the influence of having three options rather than two was statistically significantly different for one scenario (GDD following infant immunisation p=0.0458, interaction p value).

When results from both groups were combined there was no difference in the total number of 'related' SAEs between investigators and non-investigators (p=0.1164, Table 5). Of note is that 34.9% of investigators considered none (23.3%), or all (11.6%) of the four test SAEs to be related to immunisation, proportions which would be 11.9% and 3.5% if the SAEs considered 'related' were equally distributed amongst investigators within each allocated group. The likelihood of reporting SAEs as SUSARs was not influenced by the experience of the investigators in working in clinical trials (p=0.4964) (table 6).

Amongst the respondents allocated to three options, SAEs were more likely to be classified as possibly related than probably related. Across all four test scenarios 122 SAEs were classified as possibly related compared to only 14 classified as probably related.

158 The SAE classification according to respondent's geographic origin is displayed in Table 7,
159 with no consistent trend towards different reporting patterns evident.

160 **4. Discussion**

161 Reporting a serious adverse event as being both unexpected and potentially related to the
162 study vaccine (i.e. a SUSAR) can have a significant impact on subsequent study conduct, the
163 information provided to future study participants, the investigational product's perceived
164 safety profile and, eventually, product monographs. Consideration therefore needs to be
165 given to the consistency of reporting and the factors which influence causality assessments.
166 In this survey we have shown that there is considerable variation in investigators'
167 assessment of the causal relationship between investigational vaccines and SAEs, and that
168 additionally, this assessment is influenced by the classification system for 'SAE relatedness'
169 provided in the study protocol. These novel findings provide an important insight into the
170 subjectivity of investigators' SAE assessments, and support the need for standardisation of
171 SAE classification systems across vaccine clinical trials to minimise this variation.

172 Many vaccines are designed primarily for use in a healthy paediatric population, therefore it
173 is essential that children (including infants in the first few months of life) are enrolled into
174 vaccine clinical trials. It is not uncommon for this population to subsequently develop or
175 manifest illnesses meeting the definition of a SAE during the course of a study, with our
176 local experience suggesting between 4 and 23 SAEs per 100 infant participants per year [8,
177 9]. Many of these are acute, self-limiting respiratory or gastrointestinal infections requiring
178 only brief hospitalisations, and unless these are closely temporally linked to immunisation
179 most investigators will tend to classify these as unrelated [10-12].

However, the classification of causal relationships is more challenging for previously healthy study participants who develop medically significant illnesses of a sub-acute or chronic nature where the underlying cause may not be apparent, such as we have assessed here. One additional challenge for vaccine studies is that, unlike most therapeutic investigational products, it is not possible to evaluate a dose-dependent effect nor 'withdraw' the study intervention to assess for resolution and recurrence of the SAE in question in a 'challenge, de-challenge and re-challenge' model[13].

This difficulty is well recognised for adverse events following immunisation (AEFI) for licensed vaccines used in the general population. Many resources exist to assist decision-making at either an individual or population level in these circumstances, including an algorithm and aide-mémoire developed by the World Health Organisation (WHO)[13, 14]. Such guidelines take into account factors including the existing safety data, the evidence for an alternative cause for the AEFI, the temporal association and biological plausibility of an association. Although similar factors will be taken into account by investigators classifying SAEs in clinical trials, there are also important differences. Most obviously, investigators assessing SAEs will usually have a smaller safety database on which to draw, and will have only 24 hours to make their initial assessment (and may therefore have limited clinical information about the case). Also, the AEFI guidelines described above indicate that for many AEFIs it will be necessary to describe the AEFI as 'unclassifiable' (i.e. not possible to describe as related or unrelated). Importantly, this is not an option for SAE classification in clinical trials.

Our data suggest that, given such constraints, in some scenarios the investigator's assessment of casual association can become almost arbitrary. Perhaps the most striking

example from our study was the assessment of developmental delay following maternal immunisation, where overall 44% of respondents considered the SAE related and 56% considered it to be unrelated to immunisation (39%/61% of investigators), however in none of the test scenarios did the level of agreement exceed 25% (22% for investigators). Alongside this variability in reporting, a degree of consistency in responses for individual investigators was also apparent, such that over a third of investigators reported either all or none of the SAE scenarios as causally related to immunisation, a proportion that would be 15.4% if, for an individual investigator, each causality assessment for each SAE was independent of the other. This suggests a tendency towards different investigators being inherently more or less conservative in reporting SAEs, and in this regard it is interesting that there was no relationship between investigators experience and their SAR reporting rates. Beyond geographic origin, we did not further explore what other elements in an investigator's profile might influence this tendency (e.g. gender or clinical experience), and this is an area that warrants further research. Similarly, it would be worth exploring whether having a panel of investigators within an institution to make this causal assessment could lead to more consistent results.

The impact that varying the SAE causality classification system used had in our study is also notable. Limiting the available options to only related/unrelated, reduced the likelihood that the SAE of developmental delay following infant immunisation would be reported as an SAR from approximately 1 in 2 investigators to 1 in 7. This increase was driven by a preference for investigators to describe an SAE as 'possibly' related, rather than a definitive 'related' or 'unrelated', and this is perhaps understandable give the inherent uncertainty in the

scenarios described. This tendency could lead study sponsors to preferentially favour the 'two option' approach in order to minimise SUSAR reporting, and potentially creates a more favourable safety profile for vaccines evaluated in studies using only two reporting options. In this context, it is relevant that the SAE classification system used is rarely described in publications reporting vaccine clinical trials, and is not required in CONSORT guidelines on clinical trial reporting [15, 16].

In this survey the amount of information provided to respondents about the investigational vaccine and the clinical scenarios was deliberately limited. This was in part to optimise survey completion rates, but also to reflect the limited information that is frequently available to reporting investigators. Further information will often become available after the time of initial reporting, and investigators are encouraged to complete 'follow-up' SAE reports in this instance. It is possible for investigators to change the causality assessment provided in the initial report (either downgrading from a SUSAR or upgrading to a SUSAR), but this may well come after initial reports (potentially including CIOMS reports) have been circulated and/or decisions about study conduct have been made.

The finding related to maternal immunisation is especially important as the number of vaccines used in pregnancy is increasing. In addition to recommendations for use of pertussis, influenza and tetanus in pregnancy [17], all of which had an extensive safety database for non-pregnant recipients, investigational vaccines against group B strep and RSV are currently being developed primarily for use in pregnant women[18]. The data presented here highlight the difficulties in interpretation of SAEs occurring in children of women vaccinated in pregnancy, and this uncertainty needs to be considered when defining safety reporting criteria for clinical trial data safety monitoring committees.

Our survey had a number of limitations. The response rate of 26%, although not unexpected for an online survey, does raise the possibility that respondents were not a representative sample. The relatively high proportion of respondents from North America (27%), Asia (23.5%) and Europe (32%) does however reflect that these regions accounted for the majority of paediatric vaccine clinical trials registered on clinicaltrials.gov (33%, 26% and 20% respectively) [19]. Additionally, a minority of respondents were clinical trial investigators, and it was not determined if any of these had received specific training in causality assessment. Nevertheless, despite the small sample size and relatively small numbers of investigators, statistically significant differences in SAE relatedness outcomes between the two randomized groups were observed for three of the four test scenarios. An additional limitation is that this survey assessed the evaluation of individual investigators, whereas in some institutions SAE causality may be determined by a committee.

It is not realistic, and perhaps not desirable, for all clinicians to reach the same conclusion about a possible causal relationship between an investigational product and an SAE. It is also highly unlikely that defining a single SAE as being related or unrelated to a vaccine will ultimately affect the chances of a vaccine becoming licensed, nor the reported safety profile of a vaccine. Nevertheless, in this study we have highlighted the subjective nature of this key aspect of clinical trial pharmacovigilance, and identified that different protocol-defined SAE classifications could influence the reporting of an SAE following immunisation as a SUSAR. Further research on whether inter-rater variability can be reduced by additional training or use of institution-based SAE evaluation committees is warranted, and there is now a pressing need to agree a standardised approach to SAE causality classification.

Conflict of Interest:

MDS has participated in advisory boards for vaccine manufacturers, has presented at industry-sponsored symposia and has had assistance from vaccine manufacturers to attend conferences and has acted as an Investigator for clinical trials funded by vaccine manufacturers. Payments for these activities are made to the University of Oxford and MDS has not received any personal financial benefit. MV, RT, YF and MDS are employees of the University of Oxford, which conducts clinical trials funded by vaccine manufacturers. PTH has conducted studies on behalf of St Georges, University of London funded by vaccine manufacturers but does not receive any personal payments or travel support. JB has no conflict of interest to declare.

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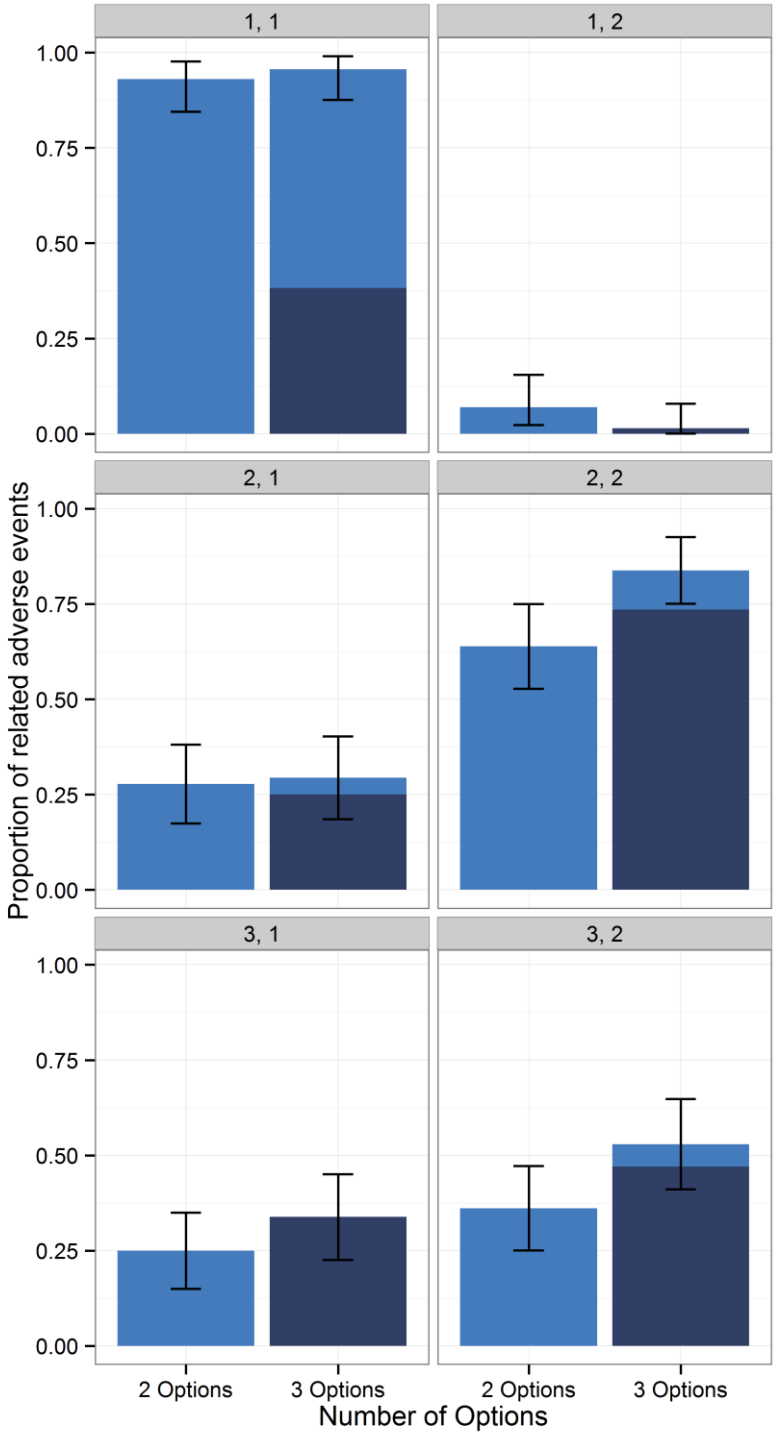

Figure Legend

Figure: Proportion of adverse events assessed as related to the investigational product

GDD: global developmental delay. P value from chi-square test. Error bars: 95% confidence intervals for proportions. Light blue: related or probably related, dark blue: possibly related.

ALL: acute lymphocytic leukaemia, JIA: juvenile idiopathic arthritis, GDD: global developmental delay. P value from chi-square test. Error bars: binomial exact confidence intervals for proportions. Light blue: related or probably related, dark blue: possibly related.

Table 1: Clinical Scenarios

- **Febrile convulsion:** A 12 months old baby developed a febrile convulsion 6 hours after PCV 13. (Positive control).

- **Fall:** A 3 year old girl was admitted to the hospital for a fall from her bike 4 weeks after immunisation with dTaP/IPV vaccine (Negative control).

- **ALL:** A one and a half year old girl developed acute lymphocytic leukemia (ALL) 5 months after immunisation with an investigational live vaccine against RSV. She had no symptoms prior to immunisation. Symptoms of lethargy and pallor were apparent 2 weeks prior to diagnosis. She had no symptoms prior to immunisation and had no significant past medical or family history

- **JIA**: A three year old girl developed juvenile idiopathic arthritis (JIA) diagnosed 3 months after immunisation with an inactivated investigational vaccine against group A streptococcus. The vaccine was in phase II trials and given to approximately 300 children (and 200 adults) with no safety concerns. The child developed a low grade fever one day after vaccination; otherwise well. Approximately 6 weeks after immunisation she developed persistent intermittent fever, with associated symptoms of rash and synovitis. She had no significant past medical history. There was no FH of autoimmune disease.

- **GDD**: A 10 month old boy was diagnosed with global developmental delay (GDD). He had his routine immunisations at 2, 3 and 4 months along with an investigational serogroup B meningococcal vaccine previously administered to 1000 adolescents and 50 children with no safety concerns. There were no risk factors for developmental delay during pregnancy/ neonatal period. There were no concerns until 6 months of age when the child was noted be falling behind gross motor milestones. No significant past medical or family history was present. His two older siblings were healthy.

- **GDD following maternal immunisation:** A 10 month old girl was diagnosed with global developmental delay. Her mother was immunised with a group B streptococcus conjugate vaccine at 28 weeks gestation as part of a phase II study. The vaccine was previously administered to 50 pregnant women with no safety concerns. There were no risk factors for developmental delay during pregnancy/ neonatal period. There were no concerns until 6/12 when the child was noted to be falling behind her gross motor milestones. No significant past medical or family history was present. Her two older siblings were healthy.

Table 2: Characteristics of survey respondents

Participants	*Two options: (related/unrelated) N=72*	*Three Options: (probably/possibly/ or not related) N=68*	*Total N=140*
Investigator on clinical trials	28	15	43
1-5 trial experience	*6*	*4*	
6-10 trial experience	*6*	*1*	
11-20 trials experience	*7*	*6*	
21-50 trials experience	*6*	*2*	
>50 trials experience	*3*	*2*	
Clinicians	10	11	21
Public Health	16	20	36
Pharmaceutical	13	10	23
Other	5	12	17
USA + Canada	21	17	38
Europe	22	23	45
Asia	15	18	33
Africa	9	4	13
Australia	1	4	5
South America	4	2	6

Table 3 Adverse event classification according number of available options

	Related	*Two Options (N=72)*	*Three Options (N=68)*	*Total (N=140)*	*p value*
Febrile convulsion (positive control)	Yes	67 (93%)	65 (96%)	132 (94%)	0.7194*
	possibly		26		
	probably		39		
	No	5 (7%)	3 (4%)	8 (6%)	
Fall (negative control)	Yes	5 (7%)	1 (1%)	6 (4%)	0.2097*
	possibly		1		
	probably		0		
	No	67 (93%)	67 (99%)	134 (96%)	
ALL	Yes	20 (27%)	20 (29%)	40 (29%)	0.8306
	possibly		17		
	probably		3		
	No	52 (73%)	48 (71%)	100 (71%)	
JIA	Yes	46 (64%)	57 (84%)	103 (74%)	0.0075
	possibly		50		
	probably		7		
	No	26 (36%)	11 (16%)	37 (26%)	
GDD	Yes	18 (25%)	23 (34%)	41 (29%)	0.2515
	possibly		23		
	probably		0		
	No	54 (75%)	45 (66%)	99 (71%)	
GDD , pregnancy trial	Yes	26 (36%)	36 (53%)	62 (44%)	0.0451
	possibly		32		
	probably		4		
	No	46 (64%)	32 (47%)	78 (56%)	

* p value from Fisher's Exact test. All other p values from chi-square tests.

Table 4 Adverse event classification for investigators and non-investigators

		Investigators				*Non-investigators*			
	Related †	*Two Options (N=28)*	*Three Options (N=15)*	*All (N=43)*	*P value (two vs three options)*	*Two Options (N=44)*	*Three Options (N=53)*	*All (N=97)*	*P value (two vs three options)*
Febrile convulsion	Yes	27 (96%)	14 (93%)	41 (95%)		40 (91%)	51 (96%)	91 (94%)	
(positive control)	No	1 (4 %)	1 (7%)	2 (5%)		4 (9%)	2 (4%)	6 (6%)	
Fall	Yes	1 (4 %)	0 (0%)	1 (2%)		4 (9%)	1 (2%)	5 (5%)	
(negative control)	No	27 (96%)	15 (100%)	42 (98%)		40 (91%)	52 (98%)	92 (95%)	
ALL	Yes	5 (18%)	3 (20%)	8 (19%)	0.8634	15 (34%)	17 (32%)	32 (33%)	0.8335
	No	23 (82%)	12 (80%)	35 (81%)		29 (66%)	36 (68%)	65 (67%)	
JIA	Yes	15 (54%)	14 (93%)	29 (67%)	0.0236	31 (70%)	43 (81%)	74 (76%)	0.2214
	No	13 (46%)	1 (7%)	14 (33%)		13 (30%)	10 (19%)	23 (24%)	
GDD	Yes	4 (14%)	7 (47%)	11 (26%)	0.0266	14 (32%)	16 (30%)	30 (31%)	0.8628*
	No	24 (86%)	8 (53%)	32 (74%)		30 (62%)	37 (70%)	67 (69%)	
GDD , pregnancy trial	Yes	8 (29%)	9 (60%)	17 (40%)	0.0495	18 (41%)	27 (51%)	45 (46%)	0.3247
	No	20 (71%)	6 (40%)	26 (60%)		26 (59%)	26 (49%)	52 (54%)	

Table 5: Number of SUSARs reported by respondents.

Total number of SUSARs	***Non-investigator N (%)***	***Investigator N (%)***	***Total N***
0	14 (14.4%)	10 (23.3%)	24
1	32 (33.0%)	17 (39.5%)	49
2	18 (18.6%)	5 (11.6%)	23
3	19 (19.6%)	6 (14%)	25
4	14 (14.4%)	5 (11.6%)	19
Total	97	43	140

P=0.1164 Wilcoxon Rank Sum test

Table 6: Number of SUSARs reported by investigators according to experience

Number of SUSARs	***>10 Trials N (%)***	***<=10 Trials N (%)***	***Total N***
0	6（23.1%）	4（23.5%）	10
1	12（46.2%）	5（29.4%）	17
2	3（11.5%）	2（11.8%）	5
3	2（7.7%）	4（23.5%）	6
4	3（11.5%）	2（11.8%）	5
Total	26	17	43

P=0.4964 Wilcoxon Rank Sum test

Table 7: Adverse event classification according to region

	Related	*North America N= 38 (Investigators: n=13)*	*South America N= 6 (Investigators: n=1)*	*Europe N= 45 (Investigators: n=13)*	*Asia N= 33 (Investigators: n=9)*	*Africa N=13 (Investigators: n=5)*	*Australia N=5 (Investigators: n=2)*
Febrile convulsion	Yes	37 (97%)	6 (100%)	40 (89%)	31 (94%)	13 (100%)	5 (100%)
(positive control)	No	1 (3%)	0	5 (11%)	2 (6%)	0	0
Fall	Yes	0	0	2 (4%)	0	4 (31%)	0
(negative control)	No	38 (100%)	6 (100%)	43 (96%)	33 (100%)	9 (69%)	5 (100%)
ALL	Yes	5 (13%)	3 (50%)	14 (31%)	8 (24%)	7 (54%)	3 (60%)
	No	33 (87%)	3 (50%)	31 (69%)	25 (76%)	6 (46%)	2 (40%)
JIA	Yes	26 (68%)	2 (33%)	34 (76%)	27 (82%)	10 (77%)	4 (80%)
	No	12 (32%)	4 (67%)	11 (24%)	6 (18%)	3 (23%)	1 (20%)
GDD	Yes	8 (21%)	1 (17%)	14 (31%)	9 (27%)	6 (46%)	3 (60%)
	No	30 (79%)	5 (83%)	31 (69%)	24 (73%)	7 (54%)	2 (40%)
GDD , pregnancy trial	Yes	13 (34%)	4 (67%)	21 (47%)	10 (30%)	10 (77%)	4 (80%)
	No	25 (66%)	2 (33%)	24 (53%)	23 (70%)	3 (23%)	1 (20%)