Paediatric Clinical Research Infrastructure Network

Procedures for the management of paediatric trials

Causality assessment of adverse events in paediatric clinical trials

Description	A visual algorithm based on the Naranjo scale and specifically adapted for the paediatric population to help researchers in their assessment of causality of adverse events occurring during a clinical study
Key words	Children, adolescents, paediatrics, adverse event, adverse drug reaction, causality assessment, clinical trials

Disclaimer: Sponsors and researchers unfamiliar with paediatric clinical trials are advised to seek expert advice due to the novel complexities of the paediatric clinical research

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Abbreviations

ADR	Adverse Drug Reaction
ADRIC	Adverse Drug Reactions in Children
AE	Adverse Event
EMA	European Medicines Agency
GCP	Good Clinical Practice
LCAT	Liverpool ADR Causality Assessment Tool
NIHR	National Institute of Health Research
PedCRIN	Paediatric Clinical Research Infrastructure Network
SOP	Standard Operating Procedure
WHO-UMC	World Health Organization - Uppsala Monitoring Centre

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1. Introduction

Until recently, it was assumed that children reacted to medications as 'small adults' and clinical practice focused on adjusting dosage to account for smaller body mass, with the postulation that clinical effects would be equivalent to those observed in adults [1]. However, today we are well aware that the paediatric population presents a variety of different features compared to adults. As it was well-illustrated in the European Medicines Agency's (EMA) "Guideline on conduct of pharmacovigilance for medicines used by the paediatric population" [2] before and in the EMA "Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations IV: Paediatric population" [3] now, progressive and irregular changes in body size and composition, which accompany growth and maturation, explain the pharmacological differences between the paediatric and the adult populations.

Consequently, safety data in the paediatric population cannot necessarily be extrapolated from data in adults because certain adverse drug reactions (ADRs) may only be seen in the paediatric population depending on the maturation of organ systems (e.g., skin, airways, kidney, liver, and blood-brain-barrier), metabolism, growth and development. In addition, childhood diseases and disorders may be qualitatively and quantitatively different from their adult equivalents and these differences may affect either the benefit or the risk of therapies (or both), with a resulting impact on the risk/benefit balance. Moreover, children may be more susceptible to ADRs due to excipients, different ADRs may be relevant for different paediatric age groups, and children may be susceptible to permanent effects that may result from a drug exposure at a sensitive point in the development (critical window). Moreover, children are not always able to communicate adverse reactions clearly to their carers/health care professionals or may not be aware of the adverse reactions as such. In the specific context of paediatric clinical trials, safety assessments become particularly difficult because: (i) the sample sizes are usually very low and the size calculations are nearly always based on efficacy assumptions; and (ii) for many conditions the target paediatric population is relatively small and there may be a number of distinct age ranges to be considered.

All of the above means that the ability to assess the safety profile in children of a drug during a clinical trial is particularly limited and that the detection and evaluation of adverse drug reactions in this population require specific expertise in order to minimise bias and maximise the information obtained from the occurrence of an adverse effect during the drug development programme in paediatrics. Different methods are available to assess the causality of an adverse event observed in the adult population and they are used both in the clinical practice and in clinical trials.

1.1. Causality assessment

The assessment of causality comprises the evaluation of the probability that the detected untoward event is caused by a specific medication [4]. A large number of causality tools have been developed ranging from the simple to the complex [5], but to date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases. Usually, the causal relationship between an AE and a medicinal product is assessed applying the Naranjo scale [6] or the Bradford Hill criteria [7]. These methods can be used for the evaluation of individual case reports as well as on a population scale. For describing the degree of certainty of the assessment of causality the World Health Organization - Uppsala Monitoring Centre (WHO–UMC) scale is also often used [8]. Specific paediatric causality tools are not available.

2. Methodology

A literature search was performed between September and October 2017 to identify the already available tools for ADR assessments. Starting from the search question i.e. "to identify the already

available tools for assessing AEs/ADRs in paediatric clinical trials" the search strategy has been defined as reported in Table 1. In order to correctly address the literature search, the PICO Model has been applied [9]. For the systematic review it was decided to use the most widely used database in the biomedical community, MEDLINE (PubMed), and we focused on all publications describing or potentially describing a study that evaluated or measured AEs/ADRs.

The terms used were *(((children) AND (((("paediatric") OR "adolescent") OR "new born") OR "infant")) AND ((((adverse drug reaction [MeSH Terms]) OR "adverse effect") OR "adverse drug effects") OR "side effect")) AND (((("assessment tool") OR "causality assessment") OR "severity assessment") OR "adverse reactions").*

No language restrictions were applied and the timeframe used was from 2012 to 2017, considering that a previous systematic review was carried out with similar parameters [10]. The retrieved references were assessed by one reviewer for possible inclusion on the basis of the evaluation of the title and the abstract, or in full if no abstract was available. A second reviewer independently confirmed the final selection. Disagreements were resolved by consensus. Finally, the bibliographies of the retrieved studies were reviewed manually to identify any potential additional references.


3. Results

A total of 718 paediatric studies have been reviewed and only 151 (21%) reported that a tool for causality assessment of adverse events was used. Sixty-eight of these studies (45%) did not specify the method used to assess causality, while among those studies that did report the algorithm employed for the evaluation of causality, the most used tool was the Naranjo Algorithm (25%), followed by the WHO-UMC system (6%).

An interesting new causality assessment tool was identified: the Liverpool ADR Causality Assessment Tool (LCAT) [5]. A visual algorithm developed by the University of Liverpool in the framework of the ADRIC (Adverse Drug Reactions in Children) research programme, a project funded by the National Institute of Health Research (NIHR), the LCAT is a flowchart specifically adapted to the paediatric population based on the Naranjo scale. It consists of dichotomous questions that determine the path to the next question in an ordered sequence, eventually leading to a causality assessment of: unlikely, possible, probable, or definite.

The LCAT can be utilised by both the sponsor and the investigator as a support in the relatedness evaluation of the adverse events occurring during the conduct of a clinical trial. A user guide was specifically prepared to help users in employing the tool as effectively as possible. It includes explanations of every step, together with some examples to help with evaluation of the correct responses.

4. The Liverpool ADR Causality Assessment Tool
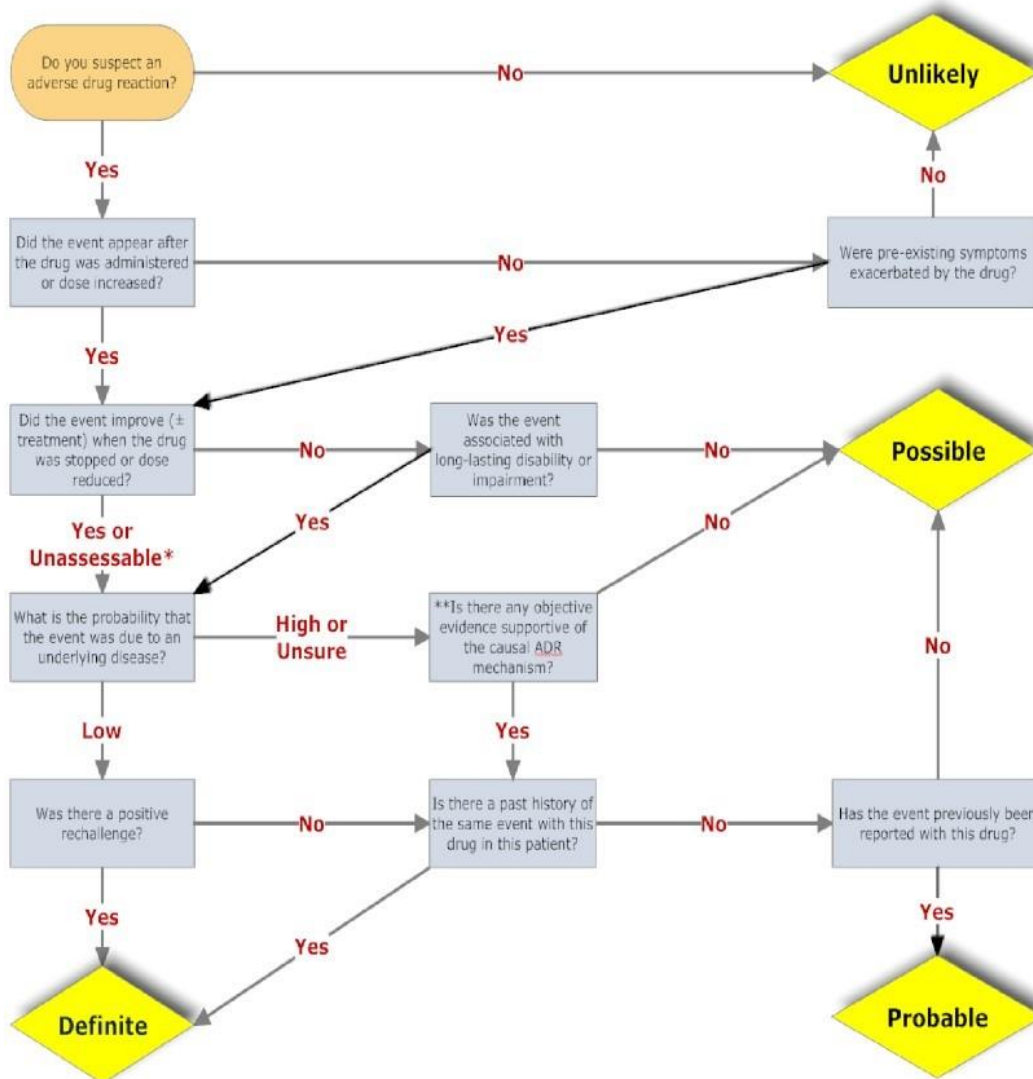
*Unassessable refers to situations where the medicine is administered on one occasion (e.g. Vaccine), the patient receives intermittent therapy (e.g. Chemotherapy), or is on medication which cannot be stopped (e.g. Immunosuppressants)

** Examples of objective evidence: positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient

5. LCAT user guide

Liverpool Adverse Drug Reaction Causality Assessment Tool

User Guide

Dear Doctor,

As you know, causality assessment of adverse drug reactions (ADRs) is used for estimating the strength of the relationship between drug(s) exposure and occurrence of an adverse reaction(s).

Many algorithms have been developed over the years to help evaluate the likelihood that taking a medicinal product is the cause of an adverse event. These instruments, known as causality assessment tools (CATs), aim to formalise causality assessment and to limit disagreement between assessors of ADR cases as to the likelihood that a reaction is related to a particular medication taken by the patient. To date, however, there are no internationally agreed upon standards or criteria for evaluating relatedness in individual cases.

The Liverpool ADR CAT (LCAT) [Gallagher RM et al, 2011] is one of these tools.
A visual algorithm developed by the University of Liverpool in the framework of the ADRIC (Adverse Drug Reactions in Children) research programme, a project funded by the National Institute of Health Research (NIHR), the Liverpool ADR CAT is a flowchart specifically adapted to the paediatric population based on the Naranjo scale. It consists of dichotomous questions that determine the path to the next question in an ordered sequence, eventually leading to a causality outcome of: unlikely, possible, probable, or definite.
The algorithm uses a series of decision boxes, each containing a question, and arrows, representing the possible answers. Every decision box is linked to one or more other boxes through the arrows that lead the user to the next appropriate box, depending on the answer chosen. The user starts with the question in the first decision box and continues the process by choosing the most suitable/appropriate of the available answers. The answer, which is represented by an arrow starting from the decision box, leads the user to a new decision box with a new question. This process is repeated until the user is eventually led to a final causality assessment.

We would like to propose the use of the Liverpool ADR CAT for the relatedness evaluation of the serious adverse events occurring during the conduct of the _____ clinical trial. The aim of this exercise is to compare the grade of relationship attributed to ADRs between Investigators using the LCAT and assessors not using the algorithm.

This user guide has been specifically prepared to help you utilise the tool as effectively as possible. It includes explanations of every step, together with some examples to help you with your evaluation of the correct responses.

The Liverpool ADR Causality Assessment Tool is a flow diagram designed by a multidisciplinary team to be quick and easy to use
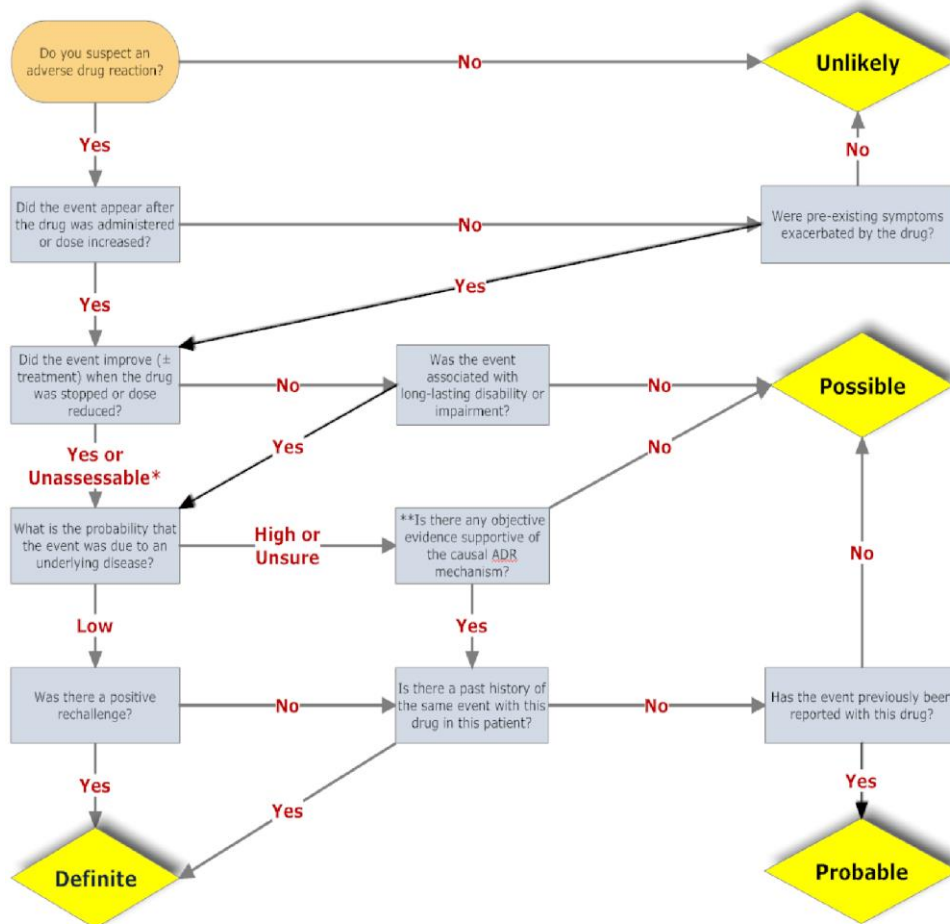
*Unassessable refers to situations where the medicine is administered on one occasion (e.g. Vaccine), the patient receives intermittent therapy (e.g. Chemotherapy), or is on medication which cannot be stopped (e.g. Immunosuppressants)

** Examples of objective evidence: positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction), supra-therapeutic drug levels, good evidence of dose-dependent relationship with toxicity in the patient

> **Do you suspect an adverse drug reaction?**

1. Do you suspect an adverse drug reaction?

To answer the question, please consider the definition of adverse reaction provided in article 2 of the Directive 2001/20/EC, reported below:

> *All untoward and unintended responses to an investigational medicinal product related to any dose administered*

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

If your answer is **YES**, please proceed to question no. 2.

If you don't suspect an adverse reaction and your answer is therefore **NO**, it is ***unlikely*** that the event is causally related to the IMP.

> **Unlikely**

- **Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)**
- **Disease or other drugs provide plausible explanations**

EXAMPLE:

Suspected ADR: Vomiting

Past Medical History: osteosarcoma of right proximal tibia diagnosed July 2009; previous amputation of affected limb.

Suspected Medicines:

Medicine	Route	Dose	Frequency	Start date	Stop date
Ceftazidime	IV	2g	1-2 times daily	28/10/2009	30/10/2009
Amikacin sulphate	IV	800mg	Once daily	28/10/2009	01/11/2009
Amoxicillin	IV	1g	1-3 times daily	30/10/2009	02/11/2009
Ciprofloxacin	Oral	750mg	Twice daily	30/10/2009	05/11/2009

Case Summary:
- 13 years old female, attended day care ward 27/10 and noted to have lost 2.7kg in 2/52. Reduced dietary intake since last chemotherapy and complained of nausea and occasional vomiting.
- 28/10 admitted with febrile neutropenia. Also noted to have infected gastrostomy site (red and tender).
- Nausea and occasional vomiting continued during this stay but improved towards the end. 3 episodes of vomiting were associated with bolus feeds.
- On most days with vomiting she was reported to tolerate oral diet well otherwise. There was also a suggestion that some vomits were possibly triggered by coughing.

The causality outcome here is **UNLIKELY** because there were pre-existing symptoms which were not exacerbated by the suspected medicines

Did the event appear after the drug was administered or dose increased?

2. Did the event appear after the drug was administered or dose increased?

Please consider the following:

Is there a plausible temporal relationship between the onset of the reaction and the administration of the IMP?

The time between administration of the IMP and onset of the reaction must be plausible for the specific reaction.
When making the assessment, you should also take into account:
- the pharmacokinetic (PK) proprieties of the IMP, i.e., the bodily absorption, distribution, metabolism, and excretion of the drug, and
- the half-life of the IMP, i.e., the time it takes for the drug to lose its pharmacologic, physiologic, or radiologic activity.

If you think that there is no plausible temporal correlation between the IMP and the onset of reaction and your answer is therefore **NO**, please proceed to question no. 3.

If you think that there is a plausible temporal correlation between the IMP and the onset of reaction and your answer is therefore **YES,** please proceed to question no. 4.

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**Were pre-existing symptoms
exacerbated by the drug?**

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3. Were pre-existing symptoms exacerbated by the drug?

Please consider the following:

Were the symptoms already present before the IMP was administered? Did they worsen after the IMP was taken by the patient?

If your answer is **YES**, please proceed to question no. 4.

If your answer is **NO**, it is unlikely that the event is causally related to the IMP.

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Unlikely

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- **Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)**
- **Disease or other drugs provide plausible explanations**

Did the event improve (±
treatment) when the drug was
stopped or dose reduced?

4. Did the event improve (± treatment) when the drug was stopped or dose reduced?

The question evaluates the information related to the dechallenge of the IMP and should be translated as follows:

Did the event improve after the IMP was stopped or after its dosage reduced?

If your answer is **NO**, please proceed to question no. 5.

If your answer is **YES** or **UNASSESSABLE**[1], please proceed to question no. 6.

EXAMPLE 1

Suspected ADR: Diarrhoea

Suspected Medicines:

Medicine	Route	Dose	Frequency	Start date	Stop date
Cefaclor	Oral	62.5mg	TID	04/01/2009	NA

Case description:
- 8 months old female admitted with dehydration from decreased oral intake and diarrhoea
- Two weeks history of being unwell with coryzal symptoms and developed a fever six days prior to admission
- General practitioner (GP) prescribed amoxicillin one dose given 02/01/2009, patient become very hot and tachycardic, mum thought this was a reaction to the antibiotic so did not give further doses
- GP prescribed cefaclor on 04/01/2009, patient developed diarrhoea on 07/01

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[1] Un-assessable refers to situations where the medicine is administered on one occasion (e.g., vaccine), the patient receives intermittent therapy (e.g., chemotherapy) or is on medication which cannot be stopped (e.g., immunosuppressant). The event cannot be judged because information in insufficient or contradictory.

- Cefaclor stopped on admission. Patient discharged 10/01/2009, diarrhoea had stopped.

The answer to the question is **YES** or **UN-ASSESSABLE** because the antibiotic was stopped on admission and diarrhoea resolved by time of discharge.

EXAMPLE 2

Suspected ADR: Constipation

Past Medical History: Leukaemia (ALL) diagnosed February 2009; previous chemotherapy 15/10/2009.

Suspected Medicines:

Medicine	Route	Dose	Frequency	Start date	Stop date
Morphine	IV/oral	23mg/50ml; 7.5 mg	1ml/hr; 1-3 x daily	30/10/2009	04/11/2009
Dihydrocodeine	Oral	15-20mg	1-4 times daily	28/10/2009	05/11/2009
Ondansetron	Oral	4mg	Once	01/11/2009	04/11/2009

Case Summary:
- 5 years old male admitted with febrile neutropenia.
- No problems with constipation noted on admission.
- Patient was not eating very much due to pain of mucositis but was drinking adequate amounts.
- Had been on regular dihydrocodeine prior to admission since 22/10.
- On 02/11 abdomen was tender and bowel sounds were present but reduced.
- On 04/11 it was noted that he had not had his bowels open for four days so lactulose dose was increased.
- 05/11 he had still not had his bowels open so movicol added. Had bowels open early afternoon.

Current medicines / Medicines taken in the 2 weeks before admission:

Medicine	Route	Dose	Frequency	Start date	Stop date
Benzydamine hydrochloride	Topical	1 spray		28/10/2009	28/10/2009
Caphosol	Oral	N7A	1-3 times daily	03/11/2009	05/11/2009
Co-trimoxazole	Oral	360mg	1-2 times daily	31/10/2009	01/11/2009
Dexamethasone	Oral	4.5mg	1	29/10/2009	29/10/2009
Fluconazole	Oral	70mg	Once daily	02/11/2009	01/11/2009
Gentamicin	IV	160mg	Once daily	28/10/2009	02/11/2009
Lactulose	Oral	5ml, 7.5ml	1-2 times daily	02/11/2009	06/11/2009
Movicol	Oral	2 sachets	1-2 times daily	05/11/2009	06/11/2009
Paracetamol	Oral	345mg	1-2 times daily	30/10/2009	01/11/2009

Tazocin	IV	2100mgs	2-4 times daily	28/10/2009	03/11/2009

In this case the answer is **UNASSESSABLE** because laxatives were also commenced (lactulose on 02/11/2009 and movicol on 05/11/2009).

5. Was the event associated with long-lasting disability or impairment?

To answer the question, please consider the definitions reported below:

> ___Disability___*: any restriction or lack (resulting from an impairment) of the ability to perform an activity in the manner or within the range considered normal for a human being.*
> ___Impairment___*: a loss or abnormality of psychological, physiological, or anatomical structure or function.*

If your answer is **YES**, please proceed to question no. 6.

If your answer is **NO**, it is possible that the event is possibly related to the IMP.

Possible

- **Event or laboratory test abnormality, with reasonable time relationship to drug intake**
- **Could also be explained by disease or other drugs**
- **Information on drug withdrawal may be lacking or unclear**

> **What is the probability that the event was due to an underlying disease?**

6. What is the probability that the event was due to an underlying disease?

To answer this question, consider the medical history of the patient and his/her current medical status.

If your answer is **HIGH** or **UNSURE**, please proceed to question no. 7.

If your answer is **LOW,** please proceed to question no. 8.

EXAMPLE

Suspected ADR: Diarrhoea

Suspected Medicines:

Medicine	Route	Dose	Frequency	Start date	Stop date
Cefaclor	Oral	62.5mg	TID	04/01/2009	NA

Case description:
- 8 months old female admitted with dehydration from decreased oral intake and diarrhoea
- Two weeks history of being unwell with coryzal symptoms and developed a fever six days prior to admission
- General practitioner (GP) prescribed amoxicillin one dose given 02/01/2009, patient become very hot and tachycardic, mum thought this was a reaction to the antibiotic so did not give further doses
- GP prescribed cefaclor on 04/01/2009, patient developed diarrhoea on 07/01
- Cefaclor stopped on admission. Patient discharged 10/01/2009, diarrhoea had stopped.

The answer is **UNSURE** because there is a 2 weeks history of coryzal symptoms and 6 days history of fever, however diarrhoea did not start until after antibiotics was started.

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7. Is there any objective evidence supportive of the causal ADR mechanism?

Examples of objective evidence:
- positive laboratory investigations of the causal ADR mechanism (not those merely confirming the adverse reaction);
- supra-therapeutic drug levels;
- good evidence of dose-dependent relationship with toxicity in the patient.

If your answer is **YES**, please proceed to question no. 9.

If your answer is **NO**, it is *possible* that the event is causally related to the IMP.

Possible

- **Event or laboratory test abnormality, with reasonable time relationship to drug intake**
- **Could also be explained by disease or other drugs**
- **Information on drug withdrawal may be lacking or unclear**

8. Was there a positive rechallenge?

The question evaluates the information related to rechallenge and should be translated with:

Did the event reappear after drug reintroduction?

If your answer is **NO**, please proceed to question no. 9.

If the reaction reappeared when the drug was re-administered, your answer is **YES**; it is *definite* that the event is causally related to the IMP.

Definite

- **Event or laboratory test abnormality, with plausible time relationship to drug intake**
  - **Cannot be explained by disease or other drugs**
  - **Response to withdrawal plausible (pharmacologically, pathologically)**
  - **Event definitive pharmacologically or phenomenologically (An objective and specific medical disorder or a recognised pharmacological phenomenon)**
  - **Rechallenge (if necessary)**

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Is there a past history of the same event with this drug in this patient?
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9. Is there a past history of the same event with this drug in this patient?

To reply to this question, you need to verify if the patient had a similar reaction to a medicinal product belonging to the same class of drugs of the IMP during a previous exposure.

If your answer is **NO**, please proceed to question no. 10.

If your answer is **YES**; it is *definite* that the event is causally related to the IMP.

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Definite
</div>

- **Event or laboratory test abnormality, with plausible time relationship to drug intake**
    - **Cannot be explained by disease or other drugs**
    - **Response to withdrawal plausible (pharmacologically, pathologically)**
    - **Event definitive pharmacologically or phenomenologically (An objective and specific medical disorder or a recognised pharmacological phenomenon)**
    - **Rechallenge (if necessary)**

10.Has the event previously been reported with this drug?

To answer this question, you need to consult the reference safety information of the IMP provided by the Sponsor (i.e., SmPC or IB).

If your answer is **NO**, it is *possible* that the event is causally related to the IMP.

Possible

- **Event or laboratory test abnormality, with reasonable time relationship to drug intake**
- **Could also be explained by disease or other drugs**
- **Information on drug withdrawal may be lacking or unclear**

If your answer is **YES**; it is *probable* that the event is causally related to the IMP.

Probable

- **Event or laboratory test abnormality, with reasonable time relationship to drug intake**
- **Unlikely to be attributed to disease or other drugs**
- **Response to withdrawal clinically reasonable**
- **Rechallenge not required**

SCHEMATIC REPRESENTATION OF THE FINAL CAUSALITY ASSESSMENT OF AN EVENT:

UNLIKELY	NO reasonable possibility of relatedness with study medications	Serious Adverse Event (SAE)
POSSIBLE	Reasonable possibility of relatedness with study medication	Serious Adverse Reaction (SAR)
PROBABLE	Reasonable possibility of relatedness with study medication	Serious Adverse Reaction (SAR)
DEFINITE	Reasonable possibility of relatedness with study medication	Serious Adverse Reaction (SAR)

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