Paediatric Clinical Research Infrastructure Network
PedCRIN

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Deliverable 3.8
Procedures for management of paediatric trials

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Working Package: WP3 (Tools for paediatric trials) - CVBF

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Abbreviations

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<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<td>AE</td>
<td>Adverse Event</td>
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<td>BBMRI-ERIC</td>
<td>Biobanking and BioMolecular resources Research Infrastructure - European Research Infrastructure Consortium</td>
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<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
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<td>ECRIN</td>
<td>European Clinical Research Infrastructure Network</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>GDPR</td>
<td>General Data Protection Regulation</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<td>LCAT</td>
<td>Liverpool ADR Causality Assessment Tool</td>
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<td>MIABIS</td>
<td>Minimum Information About Biobank data Sharing</td>
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<td>PedCRIN</td>
<td>Paediatric Clinical Research Infrastructure Network</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>Work Package</td>
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1. INTRODUCTION AND BACKGROUND
Managing paediatric clinical trials is more challenging due to the intrinsic characteristics of the paediatric population compared with adults and requires specific competences and infrastructures. Furthermore, paediatric clinical trials have novel complexities due to:
- The limited number of eligible patients for each condition
- The differences in pharmacokinetics and pharmacodynamics between children and adults and also among children of different ages
- Ethical considerations, including informed consent and assent issues, and the general perception that paediatric patients are vulnerable study subjects.
These challenges and complexities deter many researchers from attempting multinational trials, which are not only important for new drugs but also for available treatments which are not authorised for children but are used off-label. The Paediatric Clinical Research Infrastructure Network (PedCRIN) project brings together the European Clinical Research Infrastructure Network (ECRIN) and the most relevant European Networks and organizations in the field of paediatric clinical trials with the aim to build the necessary tools and capacity to enhance the high quality and ethical standards of multinational paediatric and neonatal clinical trials. PedCRIN work package 3 (WP3) “Tools for paediatric trials”, is specifically aimed to develop or adapt existing tools to be used for the management and set-up of the multinational neonatal and paediatric clinical trials, to disseminate tools to PedCRIN partners and to train and support partners on the use of the tools. This work package is divided into 6 tasks (Table 1) of which task 3.3 “upgrade, maintenance and sustainability of tools for paediatric trials” is focused on the upgrade and integration of the paediatric components of existing tools, and/or the creation of tools to be implemented in paediatric clinical trials particularly in areas such as regulatory submissions, pharmacovigilance, monitoring and sample management.

Table 1. Work package 3 tasks

<table>
<thead>
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<th>Task</th>
<th>Description</th>
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<tr>
<td>3.1</td>
<td>Survey on users’ needs among the paediatric community</td>
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<td>3.2</td>
<td>Gap analysis</td>
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<tr>
<td>3.3</td>
<td>Upgrade, maintenance and sustainability of tools for paediatric trials</td>
</tr>
<tr>
<td>3.4</td>
<td>Upgrade, maintenance and sustainability of tools for neonatal trials</td>
</tr>
<tr>
<td>3.5</td>
<td>Disseminate tools to members of PedCRIN and to ECRIN partners</td>
</tr>
<tr>
<td>3.6</td>
<td>Procedure for access to individual patient clinical trial data</td>
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The survey and the gap analysis were conducted by CVBF-TEDDY (European Network of Excellence for Paediatric Clinical Research) at the beginning of the project to identify the necessities of the paediatric research community in Europe and the existing gaps. The two tasks i.e. 3.1 and 3.2 highlighted a need for support expressed by people involved in ‘non-profit’ research and concluded that numerous efforts are still needed to face the paediatric research complexities and there is still a long way to go in order to cover and overcome all the existing lacks and gaps; for additional information, please refer to deliverables D3.1- Survey on infrastructure and service needs for paediatric and neonatal trials and D3.2- Gap analysis based on survey data. The development of the paediatric tools took into consideration the following topics:
- Ethical and regulatory database
- Pharmacovigilance
- Monitoring
- Biosample management
- Methodology guidelines for trial designs for small sample size
- Standard and patient-centred outcome measures database
- Certification of paediatric clinical trial units (CTUs)
The selection of these topics was based on results of the survey, the gap analysis, the resources available, and the initial plan described in the PedCRIN project. Tools related to the ethical and regulatory database, methodology guidelines for trial designs for small sample size and standard and patient-centred outcome measures database were described in deliverable D3.6-Procedures for set up of paediatric trials while the tools related to pharmacovigilance, monitoring and biosample management are described in this document, i.e., deliverable "D3.8-Procedures for management of paediatric trials".

2. TOOLS FOR THE MANAGEMENT OF PAEDIATRIC TRIALS

2.1. Pharmacovigilance

2.1.1 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 is well illustrated in the European Medicines Agency’s (EMA) "Guideline on conduct of pharmacovigilance for medicines used by the paediatric population" [2], 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 seriousness, causality and severity of an adverse event observed in the adult population and they are used both in the clinical practice and clinical trials.

2.1.1.1 Seriousness assessment

The definition of seriousness is provided in Directive 2001/20/EC [3] as "any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.” Medical and scientific judgement should be exercised in the evaluation of the seriousness of an event as important medical events that may not be immediately life-threatening or result in death or hospitalisation, may in any case require intervention [4].
assessament of seriousness of adverse events (AEs) in clinical trials is extremely important because it drives reporting to sponsors and regulatory authorities. The definition provided by regulators [4] support the medical judgement and it is itself a tool to be used for the evaluation.

2.1.1.2. Causality assessment
The assessment of causality basically comprises the evaluation of the probability that the detected untoward event is caused by a specific medication [5]. A large number of causality tools have been developed ranging from the simple to the complex [6], 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 or the Bradford-Hill criteria. These methods can be used for the evaluation of individual case reports as well as on a population scale [7,8]. For describing the degree of certainty of the assessment of causality the WHO-UMC scale is also often used [9]. Specific paediatric causality tools are not available.

2.1.1.3. Severity assessment
Severity is defined as the "intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning [4]. There are a number of severity scales available. In 1975, Karch and Lasagna [10] classified severity into minor (no antidote, therapy or prolongation of hospitalization required), moderate (requires a change in drug therapy, specific treatment or an increase in hospitalization by at least 1 day), severe (potentially life threatening, causing permanent damage or requiring intensive medical care), and lethal (directly or indirectly contributes to the death of the patient). Hartwig et al. (1992), instead, categorized ADRs into seven levels as per their severity: level 1 & 2 fall under mild category, level 3 & 4 under moderate and level 5, 6 & 7 fall under severe category [11]. The NCI-Common Toxicity Criteria Adverse Event (CTCAE) criteria are another standard, often used by industry [12]. The above-mentioned instruments have been developed for the adult population while the conduct of pharmacovigilance in paediatrics requires special attention. Given the specificities of the paediatric population, it would be extremely relevant to include child-specific requirements to existing tools, and where necessary develop additional tools for paediatric pharmacovigilance, in order to maximise the information coming from the occurrence of an adverse event during a paediatric clinical trial.

2.1.2 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 [13]. 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, from 1966 to 2011 [14]. 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.

2.1.3 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%). On the other hand, no specific scales were mentioned for the assessment of severity and a further research was required. The results of this supplementary search showed that the most used tools for determining severity were the Hartwig Severity Scale and the Karch&Lasagna. An interesting new causality assessment tool was identified: the Liverpool ADR Causality Assessment Tool (LCAT) (Annex 1). 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 (Annex 2). It includes explanations of every step, together with some examples to help with evaluation of the correct responses.

2.2. Monitoring

Monitoring is “the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)” [15]. The purposes of trial monitoring are to verify that (a) the rights and well-being of human subjects are protected, (b) the reported trial data are accurate, complete, and verifiable from source documents, and (c) the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s) [15].

The practical aspects of monitoring paediatric clinical trials are equivalent to those of studies in adults. The difference between trials in the paediatric population and trials in adults lies in the way monitoring is planned, i.e., in the monitoring plan, which is the “document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial” [15]. Sponsors should prospectively identify critical data and processes, then perform a risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes, and then develop a monitoring plan that focuses on the important and likely risks to critical data and processes. When defining the monitoring strategy of a clinical trial, the sponsor should develop a systematic, prioritised, risk-based approach [16] and:

a) Identify critical data and processes that, if inaccurate, not performed, or performed incorrectly, would threaten the protection of human subjects or the integrity of the study results.

b) Perform a risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes. This assessment involves determining specific sources of risk and the effect of study errors on those risks.

c) Develop a monitoring plan that focuses on the important and likely risks to critical data and processes. The type, frequency and extent of monitoring activities usually depends on a range of factors, considered during the risk assessment, including:
- Complexity of the study design: more complex study designs may require more intensive monitoring (e.g., increased frequency and extent of review).
- Types of study endpoints: centralised monitoring may be more appropriate for objective endpoints (such as death, clinical laboratory values or standard measurements), while on-site visits may be required for more interpretative or subjective endpoints.
- Clinical complexity of the study population: a study involving a special population (e.g., seriously ill or vulnerable patients) may require more intensive monitoring and on-site monitoring visits to ensure appropriate protection is being provided.
- Geography: more intensive monitoring and on-site monitoring visits may be required when involved sites are located in areas that have different medical practice standards or patient demographics, or where there is a less established clinical trial infrastructure.
- Relative experience of the investigator and of the sponsor with the investigator: more intensive monitoring and on-site monitoring visits may be required when investigators lack significant experience in conducting and overseeing investigations; the experience of a sponsor with the investigator may also be a factor in determining an appropriate monitoring plan.
- Electronic data capture (EDC): the use of EDC systems with the capability to real-time assessment of quality metrics (e.g., missing data, data error rates, protocol violations) may help in identifying potentially higher risk sites for the purpose of targeting sites in need of more intensive monitoring.
- Relative safety of the investigational product: more intensive monitoring and on-site monitoring visits may be required for a product that has significant safety concerns or for which there is no/limited prior experience in human clinical trials to ensure appropriate oversight of subject safety.
- Stage of the study: a tapered approach to monitoring may be used, more intensive monitoring may be devoted to initiation and during early stages of a trial. Similarly, it could also be used for relatively inexperienced investigators.
- Quantity of data: centralized monitoring tools may be more useful as the quantity of collected data increases.

Most of the above-mentioned factors clearly present an higher level of complexity when performing paediatric clinical trials. The ultimate aim of the monitoring plan is to communicate the risks and monitoring procedures to everyone involved in monitoring the trial.

2.3. Biosample management

2.3.1 Introduction

Biological samples, like blood and blood fraction, tissue, urine and saliva/buccal cells, are commonly used in biomedical and clinical research [17]. Analyses from biological samples provide key outputs in clinical trials, as for pharmacokinetic, safety and efficacy evaluations of investigational medicinal products. For example, optimal dosing for paediatrics relies upon PK/PD analyses performed mostly through blood sampling [18,19]. Consequently, it is essential that sample collection, management, storage and analysis are performed according to high standards.

This is even more important in paediatrics considering that blood sampling may be difficult, the number of samples is usually limited, and all the efforts should be made to minimise sample volumes [20,21]. Moreover, collection and preservation of biological samples such as blood, tissues, and nucleic acids is essential for the identification and validation of disease-relevant biomarkers that can be used for diagnosis, prognosis, predicting drug responses and also provides new molecular targets for drug development. Disease-associated biomarker, i.e. proteins, DNA, RNA, metabolites, or fatty acids, selectively or differentially expressed in diseased versus healthy tissues, can help detect an illness at very early disease stages, and may be performed during routine examination of patient blood or tissue specimens [22]. Ethical and regulatory requirements (consent, assent and data protection, particularly
with respect to long-term storage), training and facilities required for samples collection and storage [23, 24] are relevant to grant a proper management and use of biological samples. The need for minimizing harm and maximizing welfare is a milestone in clinical research [24, 25], thus, physical and emotional pain should be prevented as much as possible while performing procedures to obtain biological samples from children. For this reason, study documents, facilities and staff expertise required for biological samples collection should comply with a series of requirements aimed at reducing distress for younger patients.

Another key aspect of research involving human subjects is the informed consent. In paediatric trials, children should participate in the informed consent and assent process according their age and understanding, receiving age-appropriate information about what will happen in the study and therefore about the handling of biological samples and personal data [25-30]. The new EU General Data Protection Regulation (GDPR) [26] has endorsed and strengthened the need for informed consent that is required by the Helsinki Declaration [31], Good Clinical Practice (GCP) guidelines [15] and other relevant provisions [28]. When seeking consent, the use, storage and possible future use of material should be explained. As the research advances, consent for subsequent uses of biological material not included in the original consent should be obtained before this secondary use begins [27].

Considering the crucial role of biological samples and the challenges they raise for researchers planning and conducting paediatric clinical trials, PedCRIN WP3 aimed to develop a tool to support the management of biological samples and associated data in the context of paediatric clinical trials. The survey on users’ needs among the paediatric community (task 3.1) and the related gap analysis (task 3.2) showed that specific tools and services on biobanking have been developed within the Biobanking and BioMolecular resources Research Infrastructure – European Research Infrastructure Consortium (BBMRI-ERIC), e.g., Common service ELSI, MIABIS (Minimum Information About Biobank data Sharing), Human Sample Exchange Regulation Navigator (http://www.bbmri-eric.eu/services/other-services/), but that they do not include any guidance on the management of biological samples in paediatrics.

2.3.2 Objective

This document has been developed with the aim to provide investigators with a checklist of key items to be considered for the management of biological samples in paediatric clinical trials, in compliance with the European applicable rules and legislation. This checklist will favour the adherence to the recommended standards and will allow to release an easy-to-use tool to help the investigators, sponsors and other researchers involved in paediatric clinical trials in the management of bio-samples.

2.3.3 Methodology

The methodology described below has been applied for the preparation of the tool.

2.3.3.1 Identification of topics and research questions

PedCRIN partners and experts from BBMRI-ERIC, were asked to identify the key topics and research questions to be dealt with in order to properly manage sample and related data in the context of paediatric trials.

2.3.3.2 Search and analysis of the existing provisions

In addition to the bibliographic search the current European regulatory/ethical and legal framework has been reviewed to identify the provisions ruling the management of biosamples in the paediatric research. Other relevant international guidelines and texts were also taken into account. The following sources have been consulted:

- EudraLex (e.g. Regulations, Directives, Recommendations, etc.): https://ec.europa.eu/health/documents/eudralex_en;
PedCRIN has received funding from the European Union’s Horizon 2020 programme under grant agreement number 731046

2.3.3 Preparation of the checklist
A list of the items/measures/procedures to ensure regulatory compliance of a paediatric trial with regards to biosamples on the basis of the European applicable rules and legislation.

Please note that the checklist does not replace the reference rules/guidelines, but it is intended as a support to design and conduct paediatric clinical trials. Moreover, national and/or local rule should be considered on a case by case basis.

2.3.4 Results
2.3.4.1 Identification of topics and research questions
Five key topics were identified in order to properly manage samples and to properly collect and store data in the context of paediatric trials. Each key topic includes specific research questions that consider the specific requirements/qualification/standards exclusive for the paediatric setting.

2.3.4.1.1 Consent and assent
- Which aspects must be detailed in the information sheet and consent form (e.g., on handling and use of biological material, including possible storage for future uses, measures for data protection, and measures for data/biological material destruction if the consent is withdrawn)?
- How and which of these contents should be detailed in the information material for the child and in the assent form?
- How to handle samples when the subject (minor) reaches the age of legal competence to consent?
- If the subject withdraws the consent when he/she reaches the age of legal competence to consent, what will happen to the biological material already obtained? Can “already obtained data” prior to withdrawal be used?

2.3.4.1.2 Minimizing harm and maximizing welfare
- How to deal with the most critical procedures to get biological material from paediatric patients (e.g. repeated sampling and hospitalisation)?
- How to reduce painful procedures to get biological material in paediatric clinical trials (e.g., using micro-sampling)?
- In which cases, analgesia is required?

2.3.4.1.3 Sampling volume
- What is the maximum volume of blood that is allowed to be withdrawn in paediatric clinical trials (single sampling/repeated sampling for each population)?
- Is the use of micro sampling techniques (e.g., capillary microsampling, dried blood/plasma spots, volumetric absorptive microsampling) always recommended in paediatric clinical trials (e.g. for blood and bone marrow sampling, biopsy)?

2.3.4.1.4 Skills, training and facilities required for sampling
- Which are the professional expertise and qualifications required for the personnel collecting blood/other biological material in paediatric clinical trials?
- Which are the requirements for the facilities for the collection of blood/other biological material in paediatric clinical trials?
- Which are the quality standards for the collection and management of blood/other biological material in paediatric clinical trials?

2.3.4.1.5 Long-term storage of biological material
- How long biological samples deriving from a paediatric clinical trial can be stored for?
- Which aspects should be considered to reuse samples collected in a paediatric clinical trial?
- Which rules regulate the cross-border transfer of biological samples (provider’s legislation, recipient's legislation, both...)?
### Table 2: Consent and assent (Topic-1)

<table>
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<tr>
<th>Research question</th>
<th>Sentences to be included in the checklist (see Annex 3)</th>
<th>Sources</th>
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| **a. Handling and use of biological material, including possible storage for future uses** | **Information to detail:**  
- the initial purposes of the processing of samples and data and the future purposes (where applicable) and adequate legal basis;  
- the conditions applicable to the storage of samples and data;  
- any relevant conditions governing the use of samples;  
- the period for which the personal data will be stored, or if that is not possible, the criteria used to determine that period;  
- the applicable safeguards (appropriate technical, organisational and de-identification measures) to be applied during the storage period taking into account the nature, scope and purposes of the processing or categories of processing;  
- the transfer policies according to local and national laws;  
- the recipients/recipient categories of data;  
- the tools and guarantees regarding the transfer personal data to a third country (where applicable);  
- the right to refuse consent or authorisation and to withdraw consent or authorisation at any time. | EC Ethical Recomm. 2017 [25]; GDPR [26]; Art 29 WP guidelines [27]; Giannuzzi, Landi et al. 2018 [28]. |
| **b. Measures for data protection**                                               | - the identity and contact details of the data controller;  
- purpose;  
- legal basis;  
- the type of data and of planned de-identification measures (e.g. pseudonymisation, encryption);  
- the contact details of the data protection officer (if applicable);  
- the right to request access to data;  
- the right to data portability, as applicable;  
- the right to lodge a complaint with a supervisory authority;  
- the right to rectification or erasure of personal data or restriction of processing concerning the data subject;  
- the existence of automated decision-making (if any). | GDPR [26]; Art 29 WP guidelines [27]; Giannuzzi, Landi et al. 2018 [28]. |
| **c. Consent validity**                                                            | The consent given by the parent(s)/legal representative for the processing of personal data of the child expires once the data subject reaches the legal age of consent, as detailed below.                                                                                                                      | No reference available                                                                 |
| **d. Measures for data/biological material destruction if the consent is withdrawn** | - Data processing actions must stop and data not-fully-anonymised, i.e. personal data and biological samples, cannot be further used;  
- All operations based on consent and done before the withdrawal of consent remain lawful;                                                                                       | CIOMS/WHO 2016 [24]; GDPR [26]; Art 29 WP guidelines [27]. |
PedCRIN has received funding from the European Union’s Horizon 2020 programme under grant agreement number 731046

How and which of these contents should be detailed in the information material for the child and in the assent form?

Children should receive separate information material appropriate for their maturity and age (drawings, pictures, cartoons, DVD’s, computer programmes). Among the items recommended to be covered, the followings should be addressed: “What will happen to any samples taken from my body?” and where applicable, “Will any genetic tests be done?”

How to deal with the most critical procedures to get biological material from paediatric patients (e.g. repeated sampling, hospitalisation)?

- Painful procedures are minimized;
- Risk threshold, degree of distress and number of attempts to take a blood sample and failure escalation are defined in the protocol;
- Risk threshold, degree of distress and physical pain are constantly monitored;
- Effective treatment of pain is administered and reviewed regularly.

How to reduce painful procedures to get biological material in paediatric clinical trials (e.g. using micro-sampling)?

- Using size-/age-appropriate assays, material and devices;
- Using validated non-invasive procedures;
- Making sure to use a needle of the appropriate size;
- Coordinating timing of sampling to avoid repeated withdrawals;
- Possibly treating physical pain and discomfort intensity according to guidelines, particularly in children who cannot express it verbally;
- Minimising pain and distress as appropriate (e.g. by using anaesthetic plasters or sampling from indwelling catheters), in particular where repeated sampling is necessary.

Table 3: Minimizing harm and maximizing welfare: technical, ethical and methodological measures (Topic-2)

<table>
<thead>
<tr>
<th>Research question</th>
<th>Sentences to be included in the checklist (see Annex 3)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>How to deal with the most critical procedures to get biological material from paediatric patients (e.g. repeated sampling, hospitalisation)?</td>
<td>Physical and emotional pain are prevented and minimised as much as possible, and effectively treated when unavoidable. More in detail:</td>
<td>EC Ethical Recomm. 2017 [25]; Regulation (EU) 536/2014 [30].</td>
</tr>
<tr>
<td>How to reduce painful procedures to get biological material in paediatric clinical trials (e.g. using micro-sampling)?</td>
<td>- Using size-/age-appropriate assays, material and devices;</td>
<td>EC Ethical Recomm. 2017 [25]; WHO guideline on phlebotomy 2010 [32].</td>
</tr>
</tbody>
</table>
PedCRIN has received funding from the European Union’s Horizon 2020 programme under grant agreement number 731046.

- Using methods such as population approaches and sparse sampling for pharmacokinetic data, in order to reduce the number of blood samples in each child.

**Which procedures/tools are specific to manage and measure the level of pain in children?**

Starting at about age three or four, children can reliably use pain scales. If a child is not capable of self-reporting because of their age or condition, health-care providers will use behavioural and composite measures.

- Pediatric Pain Questionnaire (PPQ)
- Pain diary
- Behavioural assessment methods (e.g., Faces, Legs, Activity, Cry, Consolability - FLACC - scale,)
- Self-report measures (self-report scales, visual analogue or faces scales)
- Postoperative and critical care assessment scales (i.e., CHEOPS, FLACC scale, COMFORT scale and PPPM)
- Composite measures, which consider a child’s behaviour as well as the context and possible symptoms of pain.

<table>
<thead>
<tr>
<th>Research question</th>
<th>Sentences to be included in the checklist (see Annex 3)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Which is the maximum volume of blood that is allowed in paediatric clinical trials (single sampling/repeated sampling for each population)?</strong></td>
<td>Per individual, the study-related blood loss (including any losses in the manoeuvre) should not exceed 3% of the total blood volume over a period of four weeks, and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight. Table 1 of the <a href="#">EC Recommendations 2017</a> shows the maximum allowable research-related blood sample volumes.</td>
<td>EC Ethical Recomm. 2017 [25], including Table 1.</td>
</tr>
<tr>
<td><strong>Is the use of blood micro sampling techniques always recommended in paediatric clinical trials (e.g. for blood and bone marrow sampling, biopsy)?</strong></td>
<td>Micro-volumes and micro-assays should be used for blood and tissue assays or developed when not available. In particular:  - Micro-sampling allows to use low sample volume (≤ 50 µL plasma or serum);  - Micro-methods on dry spots and scavenged blood remnants should be used whenever possible, since they reduce trial-related blood loss. Not using micro-assays should be justified in the protocol.</td>
<td>EC Ethical Recomm. 2017 [25].</td>
</tr>
</tbody>
</table>
**Table 5: Skills, training and facilities required for sampling (Topic-4)**

<table>
<thead>
<tr>
<th>Research question</th>
<th>Sentences to be included in the checklist (see Annex 3)</th>
<th>Sources</th>
</tr>
</thead>
</table>
| **Which are the professional expertise and qualifications required for the personnel collecting blood/other biological material in paediatric clinical trials?** | - Demonstrated proficiency on the specific methods used, e.g. sampling, venous, arterial and capillary blood sampling;  
  - Venepuncture requires an experienced and trained phlebotomist. If a trained phlebotomist is not available, the physician may need to draw the specimen. | **WHO guideline on phlebotomy 2010** [32].                                                  |
| **Which are the requirements for the facilities for the collection of blood/other biological material in paediatric clinical trials?** | - Facilities appropriate to childcare to minimize pain, discomfort and fear;  
  - Trial hosted in a familiar environment - including appropriate furniture, toys, activities, and where appropriate, school attendance;  
  - In inpatient areas and wards with curtain at the patient’s bedside, close the bed, to offer privacy and ensure that blood sampling is done in a private and clean manner;  
  - A dedicated phlebotomy small workplace in an outpatient department or clinic;  
  - Children concerns addressed by skilled personnel. | **EC Ethical Recomm. 2017** [25];  
**WHO guideline on phlebotomy 2010** [32].                                              |
| **Which are the quality standards for the collection and management of blood/other biological material in paediatric clinical trials?** | Paediatric trials should comply with the same quality standards as adult ones. Before the trial starts, documents on certification or accreditation or quality control of medical/laboratory/technical procedures/tests should be provided, appropriately documented and traceable and be publicly available. European and International standards recommending standardized processes for the handling, documentation and processing of various human specimen types, intended for molecular in vitro diagnostic purposes, i.e. FFPE Tissue, Snap Frozen Tissue, Venous Whole Blood and Serum/Plasma and Urine for the intended purpose of isolating various profiles of molecules during the pre-analytical phase. The following Technical Standards (TS) are available at cen.eu or iso.org: ISO 20387:2018, CEN/TS 16826-1:2015, CEN/TS 16826-2:2015; CEN/TS 16827-1:2015, CEN/TS 16827-2:2015, CEN/TS 16827-3:2015, CEN/TS 16835-1:2015, CEN/TS 16835-2:2015, CEN/TS 16835-3:2015, CEN/TS 16945:2016. BBMRI-ERIC complementary self-assessment checklists (Self-Assessment-Surveys) can be used to verify compliance with the standard requirements: http://www.bbmri-eric.eu/services/self-assessment-survey/ Standardised collection, processing, shipment, storage and analyses of biological samples. Use of the correct gauge of hypodermic needle to prevent haemolysis or abnormal results. | **WHO guideline on phlebotomy 2010** [32];  
**ICH-GCP** [15];  
**ISO 20387:2018** [35];  
**CEN guidelines** [36-44];  
Peplies et al. 2010 [45]. |
### Table 6: Long-term storage of biological material (Topic-5)

<table>
<thead>
<tr>
<th>Research question</th>
<th>Sentences to be included in the checklist (see Annex 3)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How long biological samples deriving from a paediatric clinical trial can be stored for?</strong></td>
<td>Material should not be stored for longer than is necessary, i.e., if consent has not been given for retention beyond the end date of a specified research project then the material should be destroyed on completion of that project. The duration of storage for biosamples may vary between 24 hours up to 30 years, depending on local regulations, sample type, available storage conditions. The storage period should be specified in the donor consent.</td>
<td>GDPR [25]; Irish Council for Bioethics Recomm. [49].</td>
</tr>
</tbody>
</table>
| **Which aspects should be considered to reuse samples collected in a paediatric clinical trial?** | In general, biological material to be used for future research should be stored in a structured manner, i.e. organized and stored according to a predefined format and to the relevant requirements. The patient concerned should be provided with comprehensible information as mentioned above (topic 1).  
- Sponsors should check with the local regulatory authorities and ethics committees if any change of purpose of a collection should be subject to an independent examination and if appropriate consent or authorisation is required. Compliance with GDPR should be checked as well. | GDPR [26]; Art 29 WP guidelines [27]; Giannuzzi, Landi et al. 2018 [28]; Recomm. CM/Rec (2016)6 [29]; DH-BIO/INF Recomm. 2015 [50]. |
| **Which rules regulate the cross-border transfer of biological samples (provider’s legislation, recipient’s legislation, both...)?** | No specific requirements for paediatric trials are available. Points to consider are:  
- Ensure that the appropriate safety and confidentiality conditions are put in place and that the transfer is in accordance with the original consent.  
- Comply with the regulatory and legal framework in force in the country regarding the transfer and protection of biospecimens and personal data.  
- Apply de-identification measures.  
- Divide samples from associated data.  
- Transfer biological material only to a Country where an appropriate level of protection is either ensured by the law or by legally binding and enforceable instruments adopted and implemented by the parties involved in the transfer for future research activities.  
- Put in place a data sharing and material transfer agreement between the provider of the biological material and related data and the recipient. Appropriate consent or authorisation, including any relevant restriction should be included in the agreement. | GDPR [26]; Recomm. CM/Rec (2016)6 [29]; Directive 2004/23/EC [51]; COM (2016)223 - Implementation of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC [52]. |
2.3.4.2 Preparation of the checklist

This checklist represents an easy-to-use document to help the researchers, sponsors and other research actors involved in paediatric clinical trials to verify that all key aspects are taken into consideration to properly manage samples and collect and storage data in the context of paediatric trials on the basis of the European applicable rules and legislation. It has been prepared on the basis of the topics and research questions listed above and the relevant items retrieved in the listed sources. For each item/measure/procedure, the user will tick the box ‘Done’ if its paediatric clinical trial has implemented the measure/procedure and note whatever necessary action for complying with the applicable requirement.

3 REFERENCES


23. Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples 2010 EMA/INS/GCP/532137/2010 GCP Inspectors Working Group.


29. Recommendation CM/Rec (2016)6 of the Committee of Ministers to member States on research on biological material of human origin (Adopted by the Committee of Ministers on 11 May 2016.


38. CEN/TS 16827-1:2015 Specifications for Pre-examination processes for FFPE tissue – Part 1: Isolated RNA.
41. CEN/TS 16835-1:2015 Specifications for Pre-examination processes for Venous whole blood – Part 1: Specifications for Pre-examination processes for Isolated cellular RNA.
42. CEN/TS 16835-2:2015 Specifications for Pre-examination processes for Venous whole blood – Part 2: Isolated genomic DNA.
50. COMMITTEE ON BIOETHICS (DH-BIO). Draft Recommendation on research on biological material of human origin. DH-BIO/INF (2015).
ANNEX 1: 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
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.

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.
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.

**EXAMPLE:**

**Suspected ADR:** Vomiting

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

**Suspected Medicines:**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Route</th>
<th>Dose</th>
<th>Frequency</th>
<th>Start date</th>
<th>Stop date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>IV</td>
<td>2g</td>
<td>1-2 times daily</td>
<td>28/10/2009</td>
<td>30/10/2009</td>
</tr>
<tr>
<td>Amikacin sulphate</td>
<td>IV</td>
<td>800mg</td>
<td>Once daily</td>
<td>28/10/2009</td>
<td>01/11/2009</td>
</tr>
<tr>
<td>Drug</td>
<td>Route</td>
<td>Dosage</td>
<td>Frequency</td>
<td>Start Date</td>
<td>End Date</td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>---------</td>
<td>----------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>IV</td>
<td>1g</td>
<td>1-3 times daily</td>
<td>30/10/2009</td>
<td>02/11/2009</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Oral</td>
<td>750mg</td>
<td>Twice daily</td>
<td>30/10/2009</td>
<td>05/11/2009</td>
</tr>
</tbody>
</table>

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

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.
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.

- 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
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, please proceed to question no. 6.

**EXAMPLE 1**

**Suspected ADR:** Diarrhoea

**Suspected Medicines:**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Route</th>
<th>Dose</th>
<th>Frequency</th>
<th>Start date</th>
<th>Stop date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefaclor</td>
<td>Oral</td>
<td>62.5mg</td>
<td>TID</td>
<td>04/01/2009</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

---

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 is insufficient or contradictory.
EXAMPLE 2

Suspected ADR: Constipation

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

Suspected Medicines:

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

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:

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Route</th>
<th>Dose</th>
<th>Frequency</th>
<th>Start date</th>
<th>Stop date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzydamine hydrochloride</td>
<td>Topical</td>
<td>1 spray</td>
<td></td>
<td>28/10/2009</td>
<td>28/10/2009</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>Oral</td>
<td>360mg</td>
<td>1-2 times daily</td>
<td>31/10/2009</td>
<td>01/11/2009</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Oral</td>
<td>4.5mg</td>
<td>1</td>
<td>29/10/2009</td>
<td>29/10/2009</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Oral</td>
<td>70mg</td>
<td>Once daily</td>
<td>02/11/2009</td>
<td>01/11/2009</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>IV</td>
<td>160mg</td>
<td>Once daily</td>
<td>28/10/2009</td>
<td>02/11/2009</td>
</tr>
<tr>
<td>Lactulose</td>
<td>Oral</td>
<td>5ml, 7.5ml</td>
<td>1-2 times daily</td>
<td>02/11/2009</td>
<td>06/11/2009</td>
</tr>
<tr>
<td>Movicol</td>
<td>Oral</td>
<td>2 sachets</td>
<td>1-2 times daily</td>
<td>05/11/2009</td>
<td>06/11/2009</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Oral</td>
<td>345mg</td>
<td>1-2 times daily</td>
<td>30/10/2009</td>
<td>01/11/2009</td>
</tr>
<tr>
<td>Tazocin</td>
<td>IV</td>
<td>2100mgs</td>
<td>2-4 times daily</td>
<td>28/10/2009</td>
<td>03/11/2009</td>
</tr>
</tbody>
</table>

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.

- 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
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:**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Route</th>
<th>Dose</th>
<th>Frequency</th>
<th>Start date</th>
<th>Stop date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefaclor</td>
<td>Oral</td>
<td>62.5mg</td>
<td>TID</td>
<td>04/01/2009</td>
<td>NA</td>
</tr>
</tbody>
</table>

**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.
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.

- 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.

- 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)
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.

- 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)
Has the event previously been reported with this drug?

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.

- 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.

- 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:

<table>
<thead>
<tr>
<th>UNLIKELY</th>
<th>Reasonable possibility of relatedness with study medications</th>
<th>Serious Adverse Event (SAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSSIBLE</td>
<td>Reasonable possibility of relatedness with study medication</td>
<td>Serious Adverse Reaction (SAR)</td>
</tr>
<tr>
<td>PROBABLE</td>
<td>Reasonable possibility of relatedness with study medication</td>
<td>Serious Adverse Reaction (SAR)</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>Reasonable possibility of relatedness with study medication</td>
<td>Serious Adverse Reaction (SAR)</td>
</tr>
</tbody>
</table>
ANNEX 3: BIOSAMPLE MANAGEMENT CHECKLIST

This checklist represents an easy-to-use tool for guiding investigators, sponsors and other research actors involved in paediatric clinical trials in the management of biological samples and associated data. It is not intended to replace official rules/guidelines and complementary national/local legislative framework should be considered as well.

Specific measures and procedures are provided for five different topics:
1. Consent and assent
2. Minimizing harm and maximizing welfare
3. Sampling volume
4. Skills, training and facilities required for sampling
5. Long-term storage of biological material

This tool is intended to be used during the plan and set up of the paediatric trial, including the preparation of the protocol and related documents, material for informed consent and assent, to properly address all the relevant topics and requirements as well as during the trial conduct to check if the foreseen provisions are complied with. Not all the aspects might be pertaining for the specific trial that is going to be designed/conducted.

### Topic 1 - Consent and assent

<table>
<thead>
<tr>
<th>Item – measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Source/evidence and notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are the following aspects detailed in the information sheet and consent form for parents/legal representatives?</td>
<td></td>
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<tr>
<td>a) biological material handling and use including possible storage for future uses</td>
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<tr>
<td>- The initial purposes of the processing of samples and data and the future purposes (where applicable) and adequate legal basis.</td>
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<td>- The conditions applicable to the storage of samples and data.</td>
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<tr>
<td>- Any relevant conditions governing the use of samples.</td>
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<td>- The period for which the personal data will be stored, or if that is not possible, the criteria used to determine that period.</td>
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<tr>
<td>- The applicable safeguards (appropriate technical, organisational and de-identification measures) to be applied during the storage period taking into account the nature, scope and purposes of the processing or categories of processing.</td>
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<td>- The transfer policies according to local and national laws.</td>
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<td>- The recipients/recipient categories of data.</td>
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<tr>
<td>- The tools and guarantees regarding the transfer personal data to a third country.</td>
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<tr>
<td>- The right to refuse consent or authorisation and to withdraw consent or authorisation at any time.</td>
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<tr>
<td>Are the following aspects detailed in the information sheet and consent form for parents/legal representatives?</td>
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</table>
### Topic 1 - Consent and assent

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<tr>
<th>Item – measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Source/evidence and notes</th>
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</thead>
<tbody>
<tr>
<td><strong>b) Measures for data protection</strong></td>
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<tr>
<td>- The identity and contact details of the data controller.</td>
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<tr>
<td>- Purpose.</td>
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<tr>
<td>- Legal basis.</td>
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<tr>
<td>- The type of data and of planned de-identification measures (e.g., pseudonymisation, encryption).</td>
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<tr>
<td>- The contact details of the data protection officer (if applicable);</td>
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<tr>
<td>- The right to request access to data.</td>
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<tr>
<td>- The right to data portability, as applicable.</td>
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<tr>
<td>- The right to lodge a complaint with a supervisory authority.</td>
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<tr>
<td>- The right to rectification or erasure of personal data or restriction of processing concerning the data subject.</td>
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<tr>
<td>- The existence of automated decision-making process, e.g., randomisation (if any).</td>
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</table>

**Are the following aspects detailed in the information sheet and consent form for parents/legal representatives?**

**c) consent validity**
The consent given by the parent(s)/legal representative for the processing of personal data of the child expires once the data subject reaches the legal age of consent, as detailed below.

**Are the following aspects detailed in the information sheet and consent form for parents/legal representatives?**

**d) measures for data/samples destruction if the consent is withdrawn**
- Data processing actions must stop and data not-fully-anonymised, i.e., personal data and biological samples, cannot be further used. If there is no lawful basis justifying the processing (e.g., further storage) of the data, they should be deleted.

- All operations based on consent and done before the withdrawal of consent remain lawful.

- When identifiable biological samples are stored for research purposes only, the person who has withdrawn consent has the right to have the samples and associated data either destroyed or anonymised.

**Are the following contents detailed in the information material for the child and the assent form?**
Children should receive separate information material appropriate for their maturity and age (drawings, pictures, cartoons, DVD's, computer programmes). Among the items recommended to be covered: “What
### Topic 1 - Consent and assent

<table>
<thead>
<tr>
<th>Item – measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Source/evidence and notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will happen to any samples taken from my body? and where applicable, &quot;Will any genetic tests be done?&quot;</td>
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</tbody>
</table>

**Do you handle biological material already obtained as followings if the subject withdraws the consent when he/she reaches the age of legal competence to consent?**

The consent given by the parent(s)/legal representative for the processing of personal data of the child expires once the subject reaches the legal age of consent. Consent could be confirmed, modified or withdrawn. From that day forward, the controller must inform the subject about these possibilities and should obtain valid consent from the subject him/herself. If he/she does not take any action, consent given by the parent(s)/legal representatives remains valid. If the subject withdraws consent, samples and associated data must be destroyed or anonymised.

### Topic 2 - Minimizing harm and maximizing welfare: technical, ethical and methodological measures

<table>
<thead>
<tr>
<th>Item – measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you deal with the most critical procedures to get biological material from paediatric patients with the following procedures (e.g., repeated sampling, and hospitalisation)?</td>
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</table>
| Physical and emotional pain are prevented and minimised as much as possible, and effectively treated when unavoidable. More in detail:  
- Painful procedures are minimized.  
- Risk threshold, degree of distress and number of attempts to take a blood sample and failure escalation are defined in the protocol.  
- Risk threshold, degree of distress and physical pain are constantly monitored.  
- Effective treatment of pain is administered and reviewed regularly. |     |     |                |       |

**Do you apply the following procedures to reduce painful procedures to get biological material in paediatric clinical trials (e.g., using micro-sampling)?**

- Using size-/age-appropriate assays, material and devices.
- Using validated non-invasive procedures.
- Using appropriate sized needle.
- Coordinating timing of sampling to avoid repeated sampling.
- Possibly treating physical pain and discomfort intensity according to guidelines, particularly in children who cannot express it verbally.
### Topic 2 - Minimizing harm and maximizing welfare: technical, ethical and methodological measures

<table>
<thead>
<tr>
<th>Item – measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Minimising pain and distress as appropriate (e.g. by using anaesthetic plasters or sampling from indwelling catheters), in particular if repeated blood sampling is necessary.</td>
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<tr>
<td>- Using methods such as population approaches and sparse sampling for pharmacokinetic data, in order to reduce the number of blood samples in each child.</td>
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<tr>
<td><strong>Do you apply specific procedures/tools to manage and measure the level of pain in children?</strong></td>
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<tr>
<td>- Pediatric Pain Questionnaire (PPQ).</td>
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<tr>
<td>- Pain diary.</td>
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<td>- Self-report measures (self-report scales, visual analogue or faces scales).</td>
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<tr>
<td>- Postoperative and critical care assessment scales (i.e., CHEOPS, FLACC scale, COMFORT scale and PIPP).</td>
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<tr>
<td>If a child is not capable of self-reporting because of their age or condition, health-care providers will use behavioural and composite measures:</td>
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<tr>
<td>- Behavioural assessment methods (e.g., Faces, Legs, Activity, Cry, Consolability - FLACC – scale);</td>
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<tr>
<td>- Composite measures, which consider a child’s behaviour as well as the context and possible symptoms of pain (e.g. the premature infant pain profile (Premature Infant Pain Profile – PIPP –, CRIES Score).</td>
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</table>

### Topic 3 - Sampling volume

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<tr>
<th>Item – measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td><strong>Is the following maximum volume of blood foreseen in the trial (single sampling/repeated sampling for each population)?</strong></td>
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<tr>
<td>Per individual, the study-related blood loss (including any losses in the manoeuvre) should not exceed 3% of the total blood volume over a period of four weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight. Table 1 of the EC Recommendations 2017 shows the maximum allowable research-related blood sample volumes.</td>
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<tr>
<td><strong>If applicable, are blood micro-sampling techniques (e.g. for blood and bone marrow sampling, biopsy) used in the trial according the following procedures?</strong></td>
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2 As included in the clinical study protocol.
### Topic 3 - Sampling volume

<table>
<thead>
<tr>
<th>Item – measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Micro-volumes and micro-assays should be used for blood and tissue assays or developed when not available. In particular:</td>
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<tr>
<td>- Micro-sampling allows to use low sample volume (≤ 50 µL plasma or serum).</td>
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<tr>
<td>- Micro-methods on dry spots and scavenged blood remnants should be used whenever possible, since they reduce trial-related blood loss.</td>
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<tr>
<td>Not using micro-assays should be justified in the protocol.</td>
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</table>

### Topic 4 - Skills, training and facilities required for sampling

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<tr>
<th>Item – measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td><strong>Have professional expertise and qualification for personnel collecting blood/other biological material required in the trial been selected according the following criteria?</strong></td>
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<tr>
<td>- Demonstrated proficiency on the specific methods used, e.g., sampling, venous, arterial and capillary blood sampling.</td>
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<tr>
<td>- Veneupuncture requires an experienced and trained phlebotomist. If a trained phlebotomist is not available, the physician may need to draw the specimen.</td>
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<tr>
<td><strong>Do the facilities to collect blood/other biological material in the trial respond to the following requirements?</strong></td>
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<tr>
<td>- Facilities appropriate to childcare to minimize pain, discomfort and fear.</td>
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<tr>
<td>- Trial hosted in a familiar environment - including appropriate furniture, toys, activities, and where appropriate, school attendance.</td>
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<tr>
<td>- In inpatient areas and wards with curtain at the patient's bedside, close the bed, to offer privacy and ensure that blood sampling is done in a private and clean manner.</td>
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<tr>
<td>- A dedicated phlebotomy small workplace in an outpatient department or clinic.</td>
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<td>- Children concerns addressed by skilled personnel.</td>
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<tr>
<td><strong>Have you implemented quality standards for the collection and management of blood/other biological material in the trial?</strong></td>
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<tr>
<td>- Before the trial starts, documents on certification or accreditation or quality control of medical/laboratory/technical procedures/tests</td>
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</table>
### Topic 4 - Skills, training and facilities required for sampling

<table>
<thead>
<tr>
<th>Item – measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Notes</th>
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<tbody>
<tr>
<td>should be provided, appropriately documented and traceable and be publicly available.</td>
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<tr>
<td>- European and International standards recommending standardized processes for the</td>
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<tr>
<td>handling, documentation and processing of various human specimen types, intended for</td>
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<tr>
<td>molecular in vitro diagnostic purposes, i.e. FFPE Tissue, Snap Frozen Tissue, Venous</td>
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<tr>
<td>Whole Blood and Serum/Plasma and Urine for the intended purpose of isolating various</td>
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<td>profiles of molecules during the pre-analytical phase. Technical Standards (TS) are</td>
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<td>available at cen.eu or iso.org. BBMRI-ERIC complementary self-assessment checklists</td>
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<tr>
<td>(Self-Assessment-Surveys) can be used to verify compliance with the standard requirements:</td>
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<tr>
<td>- Standardised collection, processing, shipment, storage and analyses of biological</td>
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<td>samples;</td>
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<tr>
<td>- Use of the correct gauge of hypodermic needle to prevent haemolysis or abnormal results.</td>
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### Topic 5 - Long-term storage of biological material

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<th>Item – measure – procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Have you foreseen the following measures on the storage duration of biological samples deriving from the trial?</strong>&lt;br&gt;Material should not be stored for longer than is necessary, i.e. if consent has not been given for retention beyond the end date of a specified research project then the material should be destroyed on completion of that project. The duration of storage for biosamples may vary between 24 hours up to 30 years, depending on donor consent, local regulations, sample type and available storage conditions.</td>
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<tr>
<td><strong>Have you considered the following aspects to reuse samples collected in the trial?</strong>&lt;br&gt;- In general, biological material to be used for future research should be stored in a structured manner, i.e. organized and stored according to a predefined format and to the relevant requirements.</td>
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<tr>
<td>- The person concerned should be provided with comprehensible information as mentioned above (topic 1). Any change of purpose of a collection should be subject to an independent examination and, where necessary, may require appropriate</td>
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</table>
### Topic 5 - Long-term storage of biological material

<table>
<thead>
<tr>
<th>Item - measure - procedure</th>
<th>Yes</th>
<th>Not</th>
<th>Not applicable</th>
<th>Notes</th>
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<tbody>
<tr>
<td>consent or authorisation. Compliance with GDPR should be checked as well.</td>
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<tr>
<td>- Biological material should only be obtained or stored for future research having the potential to produce, in the absence of direct benefit to the person concerned, benefit to other persons in the same age category or afflicted with the same disease or disorder or having the same condition, and if the aims of the research could not reasonably be achieved using biological material from persons able to consent.</td>
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**Have you implemented the following rules on the cross-border transfer of biological samples?**

No specific requirements for paediatric trials are available. In general:

- Appropriate safety and confidentiality conditions in accordance with the original consent or authorisation.

- De-identification measures and legal/ethical framework in force in the country regarding the transfer of biospecimens and personal data should be considered.

- Associated data should not be transported together with samples.

- Biological material should only be transferred to another State if an appropriate level of protection is either ensured by the law of that State or by legally binding and enforceable instruments adopted and implemented by the parties involved in the transfer for future research activities.

- A data sharing and material transfer agreement between the provider of the biological material and related data and the recipient should be signed. Appropriate consent or authorisation, including any relevant restriction should be included in the agreement.