Paediatric Clinical Research Infrastructure Network

Procedures for the management of paediatric trials

Collection, storage and use of biological samples and related data in paediatric clinical trial

Description	A checklist developed to help researchers, sponsors, and other affiliated personnel actors to verify that all key aspects required to properly manage samples and related data in the context of paediatric trials are taken into consideration.
Key words	Paediatric clinical trials, biosamples management, ethical and regulatory requirements

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

FLACC	Faces, Legs, Activity, Cry, Consolability scale
GDPR	General Data Protection Regulation
PedCRIN	Paediatric Clinical Research Infrastructure Network
PIPP	Premature Infant Pain Profile
PPQ	Pediatric Pain Questionnaire
TS	Technical Standards

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1. Introduction

Biological samples are commonly used in biomedical and clinical research.

Ethical and regulatory requirements, training and facilities required for samples collection and storage are relevant to grant a proper management and use of biological samples. 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.

An easy-to-use tool has been developed in the context of PedCRIN to guide investigators, sponsors and other research actors involved in paediatric clinical trials in the management of biological samples and associated data in compliance with the applicable European rules.

This 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. Methodology

For the preparation of the tool,

- key topics and research questions to properly manage sample and related data in the context of paediatric trials were identified;
- the current applicable European regulatory/ethical and legal provisions were searched and analysed;
- the items/measures/procedures to ensure regulatory compliance of a paediatric trial with regards to biosamples were included in a checklist as divided in 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.

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3. Checklist

Topic 1 - Consent and assent				
Item – measure - procedure	***Yes***	***No***	***Not applicable***	***Source/evidence and notes***
Are the following aspects detailed in the information sheet and informed consent form for parents/legal representatives?				
a) Handling and use of biological material, including possible storage for future uses				
- The initial purposes of the processing of samples and the future purposes (where applicable) and adequate legal basis.				
- The conditions applicable to the storage of samples.				
- Any relevant conditions governing the use of samples.				
- The transfer policies according to local and national laws.				
- The right to refuse consent or authorisation and to withdraw consent or authorisation at any time.				
b) Measures for data protection				
- The identity and contact details of the data controller.				
- The initial purposes of the processing of data and the future (where applicable) and adequate legal basis.				
- The period for which the personal data will be stored, or if that is not possible, the criteria used to determine that period.				
- The type of data and of planned de-identification measures (e.g., pseudonymisation, encryption).				
- The recipients/recipient categories of data.				
- The contact details of the data protection officer (if applicable).				
- 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 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 tools and guarantees regarding the transfer personal data to a third country (where applicable).				
c) Measures for data/samples destruction, in case 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.				

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Topic 1 - Consent and assent				
Item – measure - procedure	***Yes***	***No***	***Not applicable***	***Source/evidence and notes***
- 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 and in the assent form for the child? Children should receive separate information material appropriate for their maturity and age (drawings, pictures, cartoons, DVD's, computer programmes).				
- What will happen to any samples taken.				
- Genetic tests (where applicable).				
Do you handle biological material already obtained as follows if the subject withdraws the consent when he/she reaches the age of legal competence to 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				
Item – measure - procedure	***Yes***	***No***	***Not applicable***	***Source/evidence and notes***
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 appropriately 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.				
- 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.				
- Using methods such as population approaches and sparse sampling for pharmacokinetic data, in order to reduce the number of blood samples in each child.				
Have you dealt with the most critical procedures to get biological material from paediatric patients with the following procedures (e.g., repeated sampling, and hospitalisation)? Physical and emotional pain are prevented and minimised as much as possible, and effectively treated when unavoidable.				
- 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.				

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Topic 2 - Minimizing harm and maximizing welfare: technical, ethical and methodological measures				
Item – measure - procedure	***Yes***	***No***	***Not applicable***	***Source/evidence and notes***
- Risk threshold, degree of distress and physical pain are constantly monitored.				
- Effective treatment of pain is administered and reviewed regularly.				
Do you apply specific procedures/tools to manage and measure the level of pain in children?				
- Pediatric Pain Questionnaire (PPQ).				
- Pain diary.				
- 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).				
If a child is not capable of self-reporting because of their age or condition, health-care providers will use behavioural and composite measures.				
- Behavioural assessment methods (e.g., Faces, Legs, Activity, Cry, Consolability - FLACC – scale).				
- 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).				

Topic 3 - Sampling volume				
Item – measure - procedure	***Yes***	***No***	***Not applicable***	***Source/evidence and notes***
Is the following maximum volume of blood foreseen in the trial (single sampling/repeated sampling for each population)[1]?				
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.				
If applicable, are blood micro-sampling techniques (e.g. for blood and bone marrow sampling, biopsy) used in the trial according the following procedures? 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.				

[1] As included in the clinical study protocol.

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Topic 4 - Skills, training and facilities required for sampling				
Item – measure - procedure	***Yes***	***No***	***Not applicable***	***Source/evidence and notes***
Have professional expertise and qualification for personnel collecting blood/other biological material required in the trial been selected according the following criteria? -				
- 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.				
Do the facilities to collect blood/other biological material in the trial respond to the following requirements?				
- 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 area 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.				
Have you implemented quality standards for the collection and management of blood/other biological material in the trial?				
- 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. Technical Standards (TS) are available at cen.eu or iso.org. BBMRI-ERIC complementary self-assessment checklists (Self-Assessment-Surveys) can be used to verify compliance with the standard requirements:				

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Topic 4 - Skills, training and facilities required for sampling				
Item – measure - procedure	***Yes***	***No***	***Not applicable***	***Source/evidence and notes***
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.				

Topic 5 - Long-term storage of biological material				
Item– measure–procedure	***Yes***	***No***	***Not applicable***	***Source/evidence and notes***
Have you foreseen the following measures on the storage duration of biological samples deriving from the trial? 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.				
Have you considered the following aspects to reuse samples collected in the 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 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 consent or authorisation. Compliance with GDPR should be checked as well.				
- 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.				
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.				

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Topic 5 - Long-term storage of biological material				
Item– measure–procedure	***Yes***	***No***	***Not applicable***	***Source/evidence and notes***
- 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.				

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4. References

1. EudraLex: https://ec.europa.eu/health/documents/eudralex_en
2. International Conference on Harmonisation (ICH): https://www.ich.org/home.html;
3. European Medicines Agency (EMA) guidelines, concept papers, reflection papers, other releases: https://www.ema.europa.eu/en;
4. Council for International Organizations of Medical Sciences (CIOMS): https://cioms.ch/;
5. World Health Organization (WHO): https://www.who.int/;
6. European Committee for Standardisation: https://www.cen.eu/;
7. International Organization for Standardization (iso.org): https://www.iso.org/.

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