Received: 3 November 2022 | Revised: 19 December 2022 | Accepted: 13 January 2023

DOI: 10.1111/cts.13489

ARTICLE

PedCRIN tool for the biosamples management in pediatric clinical trials

Viviana Giannuzzi[1] | **Lucia Ruggieri**[1] | **Rosa Conte**[1] | **Cristina Manfredi**[2] | **Mariagrazia Felisi**[2] | **Christine Kubiak**[3] | **Mihaela Matei**[3] | **Salma Malik**[3] | **Jacques Demotes**[3] | **Adriana Ceci**[1] | **Donato Bonifazi**[4]

[1]Fondazione per la Ricerca Farmacologica Gianni Benzi Onlus, Valenzano, Italy

[2]Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF), Pavia, Italy

[3]The European Clinical Research Infrastructure Network (ECRIN), Paris, France

[4]Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF), Bari, Italy

Correspondence
Viviana Giannuzzi, Fondazione per la Ricerca Farmacologica Gianni Benzi Onlus, Via Abate Eustasio, 30, 70010 Valenzano, Italy.
Email: vg@benzifoundation.org

Funding information
European Union, Grant/Award Number: 731046

Abstract

In pediatric clinical research, it is essential to implement ethical and regulatory requirements, training, and facilities to grant the proper management of specimens, considering that blood sampling may be difficult, the number of specimens is usually limited, and all efforts should be made to minimize sample volumes. In the context of the Pediatric Clinical Research Infrastructure Network (PedCRIN) project, an easy-to-use tool has been developed to guide investigators and sponsors in managing specimens and associated data in compliance with the applicable European rules in the context of pediatric clinical trials. Key topics and research questions to properly manage biosamples and related data in the context of pediatric trials were identified by PedCRIN partners; the current European regulatory/ethical and legal resources were searched for and analyzed; the items/measures/procedures to ensure regulatory compliance of a pediatric trial with regards to biosamples were defined. A checklist of the key items to be considered for the management of biological samples in pediatric clinical trials in compliance with the European applicable rules and legislation, was prepared. It is publicly available on the PedCRIN website https://ecrin.org/projects/pedcrin. Five different topics were covered: consent and assent; minimizing harm and maximizing welfare; sampling volume; skills, training and facilities required for sampling; and long-term storage of biological material. This exercise addressed a specific need in the field of pediatric research to implement ad hoc procedures for specimen handling. In fact, specific guidance on the management of biosamples in pediatrics is not available.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Internationally agreed guidelines and recommendations on pediatric studies are available. In addition, specific tools and services on biobanking have been

developed within existing initiatives, but they do not include any guidance on the management of biological samples in pediatrics.

WHAT QUESTION DID THIS STUDY ADDRESS?

Can regulatory/legal/ethical recommendations from societies and experts be coalesced to create a comprehensive pediatric-specific tool for biospecimen collection and management?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The checklist includes specific questions to consider in order to comply with the specific requirements/qualification/standards exclusive for the pediatric setting. Therefore, a comprehensive list of the available guidance is now available open-access.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Whereas not replacing the existing applicable rules and guidelines, the checklist will help the investigators, sponsors, and other actors of clinical research to adhere to the recommended standards and design and conduct pediatric clinical trials, specifically in the management of bio-samples. National and/or local rules should be considered on a case-by-case basis.

INTRODUCTION

Biological samples, like blood, tissue, urine, and saliva cells are commonly used in biomedical research and their analyses provide key outputs in clinical trials, regarding pharmacokinetic (PK), safety, and efficacy of investigational medicinal products. For example, in pediatrics PK/pharmacodynamic (PD) analyses, which provide data on dosing, are mostly performed through blood sampling.[1] Consequently, it is essential that specimen collection, management, storage, and analysis are performed according to high standards.[2]

Moreover, the collection of biosamples, such as blood, tissues, and nucleic acids, is essential to identify and validate disease-relevant biomarkers that can be used for diagnosis, prognosis, and predicting drug responses, as well as for providing new targets for drug development. Disease-associated biomarkers (i.e., proteins, DNA, RNA, metabolites, or fatty acids), selectively or differentially expressed in diseased versus healthy tissues, can help to detect an illness at very early disease stages and may be performed during routine examination of patient blood or tissue specimens.[3]

Regulatory/legal/ethical considerations surrounding the collection and use of biospecimens in clinical trials (consent, assent, and data protection, particularly with respect to long-term storage), training and facilities required for sample collection and storage[4,5] are relevant to properly manage and use biological samples and are critical for researchers to be aware of.

This is even more crucial in pediatrics considering that children represent a unique and vulnerable population in research for whom special considerations should be made when designing clinical trials involving biospecimens. The child appears as a "work in progress"; diseases may be different between adults and children and some diseases exist in children but not in adults. Therefore, constantly changing developmental physiology results in different drug responses and adverse reactions, blood sampling may be difficult, the number of samples is usually limited, and all the efforts should be made to minimize sample volumes.[6] The need to minimize harm and maximize welfare is a milestone in pediatric clinical research[7,8]; therefore, physical and emotional pain should be prevented as much as possible while performing procedures to obtain specimens from children. For this reason, study documents, facilities, and staff expertise required for specimen collection should comply with a series of requirements aimed at reducing distress for younger patients.

Another key aspect of research involving human subjects is informed consent. In pediatric trials, children should participate in the informed consent and assent process according to their age and understanding, receiving age-appropriate information about what will happen in the study.[7–10] The EU General Data Protection Regulation (GDPR)[11] with its guidelines[12] has endorsed and strengthened the need for informed consent that is required by the Helsinki Declaration,[13] Good Clinical Practice (GCP) guidelines,[14] and other relevant provisions.[15] When seeking consent, the use, storage, and possible future use of material should be explained. As the research advances, consent for the subsequent uses of biological material not included in

the original consent should be obtained before this secondary use begins.[14]

Considering the crucial role of biological samples and the challenges they raise for researchers planning and conducting pediatric clinical trials, PedCRIN Work Package number 3 aimed to develop a tool to support the management of biosamples and associated data in the context of pediatric clinical trials. This work was coordinated by Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) - European Network of Excellence for Pediatric Research (TEDDY) and supported by Fondazione per la Ricerca Farmacologica Gianni Benzi onlus (FGB).

Coordinated by ECRIN, the H2020 Pediatric Clinical Research Infrastructure Network (PedCRIN) project (Grant Agreement ID 731046) is a research infrastructure project designed to provide operational services to a handful of multinational investigator-initiated pediatric trials and to develop common tools to facilitate the management of multinational pediatric trials in Europe, including on biosample management (https://ecrin.org/projects/pedcrin). The PedCRIN survey on users' needs among the pediatric community[16] and the related gap analysis[17] 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,[18] MIABIS [Minimum Information About Biobank data Sharing][19]); however, no comprehensive guidance on the management of specimens in pediatrics exists.

Some guidance is available in the European Union[7,20] and in a very recent US Food and Drug Administration (FDA) document on neonatal studies[21] on the need to minimize the volume of blood samples and implement ad hoc sampling techniques for PK analyses. There is information from multiple different organizations, but no single resource provides a holistic overview. For this reason, an easy-to-use tool has been developed in the context of PedCRIN project to guide investigators, sponsors and other research actors involved in pediatric clinical trials in the management of biological samples and associated data in compliance with the applicable European rules.

The aim of the work presented here is to show how the tool was prepared based on consolidated principles in a sector where any guidance is lacking.

METHODS

For the preparation of the tool, the following steps were undertaken.

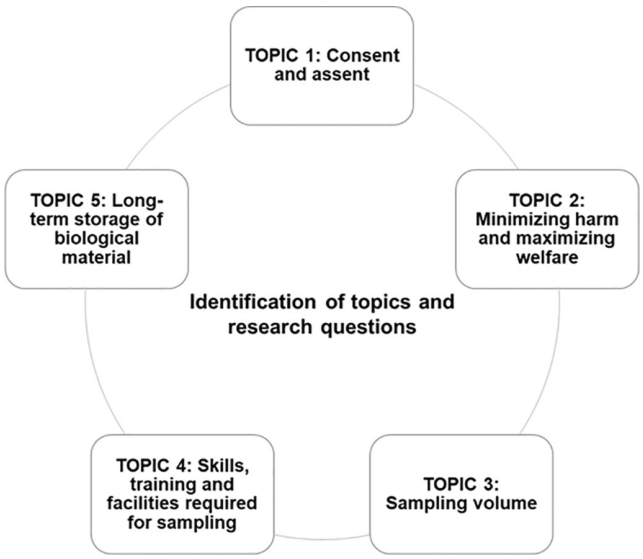

FIGURE 1 Five key topics were identified for sample management.

Identification of topics and research questions

Using a co-creation approach, PedCRIN partners (CVBF, Fondazione per la Ricerca Farmacologica Gianni Benzi onlus, INSERM, ECRIN, and BBMRI-ERIC) were asked to identify the key topics and research questions to be dealt with in order to properly manage samples and related data in the context of pediatric trials. Five key topics were identified in order (Figure 1). Each key topic included specific research questions that consider the specific requirements/qualification/standards exclusive to the pediatric setting.

TOPIC 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 this content should be detailed in the information material for the child and in the assent form?
- How should samples be handled when the subject (minor) reaches the age of legal competence to consent?
- If the subject withdraws consent when they reach 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?

TOPIC 2: Minimizing harm and maximizing welfare

- How do we deal with the most critical procedures to get biological material from pediatric patients (e.g., repeated sampling and hospitalization, invasive procedures, like venipuncture or tissue biopsy)?
- How can we reduce in particular painful procedures to get biological material in pediatric clinical trials (e.g., using micro-sampling)?
- Which procedures/tools are specific to manage and measure the level of pain in children?

TOPIC 3: Sampling volume

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

TOPIC 4: Skills, training, and facilities required for sampling

- What the professional expertise and qualifications are required for the personnel collecting blood/other biological material in pediatric clinical trials?
- What are the requirements for facilities for the collection of blood/other biological material in pediatric clinical trials?
- What are the quality standards for the collection and management of blood/other biological materials in pediatric clinical trials?

TOPIC 5: Long-term storage of biological material

- How long can biological samples derived from pediatric clinical trials be stored for?
- Which aspects should be considered to reuse samples collected in a pediatric clinical trial?
- Which rules regulate the cross-border transfer of biological samples (provider's legislation, recipient's legislation, both...)?

Search and analysis of the existing provisions

For each research question, the following sources were consulted to identify the provisions ruling the handling of specimens in pediatric research:

- EudraLex (e.g., Regulations, Directives, Recommendations, etc.)[22];
- International Conference on Harmonization (ICH)[23];
- European Medicines Agency (EMA) guidelines, concept papers, reflection papers, other releases[24];
- Council for International Organizations of Medical Sciences (CIOMS)[25];
- World Health Organization (WHO)[26];
- European Committee for Standardization[27];
- International Organization for Standardization.[28]

In cases where the above-mentioned sources did not contemplate any provision for a specific topic or research question, experts from PedCRIN partners were asked to provide advice on relevant recommendations or guidelines released at national level or from scientific societies/research consortia.

Preparation of the checklist

A checklist was prepared based on the identified topics and research questions listed above. The items/measures/procedures to ensure regulatory compliance of a pediatric trial with regard to specimens to the European applicable rules and legislation were listed for the five already identified topics.

RESULTS

The research team identified the existing guidelines and recommendations applicable to each research question topic, including the current European regulatory/ethical and legal framework (Tables 1–5).

Based on these sources, a checklist describing measures/procedures for each item in the five identified domains was developed.

For each item/measure/procedure, the user will tick the box "Yes" if its pediatric clinical trial has implemented the measure/procedure and noted any necessary actions for complying with the applicable requirements.

The checklist does not replace the reference rules/guidelines, but it is intended as a support to design and

TABLE 1 Consent and assent (Topic 1).

Research question	Sentences to be included in the checklist	Sources
Which aspects must be detailed in the information sheet and consent form? 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, organizational, 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 authorization and to withdraw consent or authorization at any time	EC Ethical Recomm. 2017[7]; GDPR[11]; Art 29 WP guidelines[12]
a. 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., pseudonymization, 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[11]; Art 29 WP guidelines[12]
a. Measures for data/biological material destruction if the consent is withdrawn	• Data processing actions must stop and data not fully anonymized (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 • The person who has withdrawn consent has the right to have the samples and associated data either destroyed or anonymized, according to the provisions specified in the original consent	CIOMS/WHO 2016[5]; GDPR[11]; Art 29 WP guidelines[12]; Recomm. CM/Rec (2016)6[29]
How and which of this content 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, and computer programs). Among the items recommended to be covered: "What will happen to any samples taken from my body?," "for which purpose will these samples be taken?" and where applicable for patients >10 years, "Will any genetic tests be done?"	EC Ethical Recomm. 2017[7]; GDPR[11]; Art 29 WP guidelines[12]
If the subject withdraws consent when they reach the age of legal competence to consent, what will happen to the biological material already collected?	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 anonymized	GDPR[11]; Art 29 WP guidelines[12]; Recomm. CM/Rec (2016)6[29]; Regulation (EU) 536/2014[9]

Abbreviations: CIOMS, Council for International Organizations of Medical Sciences; GDPR, General Data Protection Regulation; WHO, World Health Organization.

conduct pediatric clinical trials. Moreover, national and/or local rules should be considered on a case-by-case basis.

TOPIC 1: Consent and assent

A series of EU provisions[5,7,9,11,12,29] rule the information to be detailed in the information sheet, consent, and assent forms.

Information concerning the biosamples management (handling, use, storage, data protection, and destruction if consent is withdrawn and reconsenting on reaching legal age) must be detailed clearly in the information sheet and consent form. Table 1 shows the list of points to be considered. They are intended to be customized according to the patient age and understanding, as shown in a recently published guide on informed consent and assent in pediatric trials in Europe.[10]

TABLE 2 Minimizing harm and maximizing welfare: technical, ethical, and methodological measures (Topic 2).

Research question	Sentences to be included in the checklist	Sources
How to deal with the most critical procedures to get biological material from pediatric patients (e.g., repeated sampling, hospitalization, invasive procedures, like venipuncture or tissue biopsy)?	Physical and emotional pain are prevented and minimized 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	EC Ethical Recomm. 2017[7]; Regulation (EU) 536/2014[9]
How to reduce in particular painful procedures to get biological material in pediatric clinical trials (e.g., using micro-sampling)?	• Using size−/age-appropriate assays, material and devices • Using validated noninvasive 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 • Minimizing pain and distress as appropriate (e.g., by using anesthetic plasters or sampling from indwelling catheters), in particular where repeated 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	EC Ethical Recomm. 2017[7]; WHO guideline on phlebotomy 2010[31]
Which procedures/tools are specific to manage and measure the level of pain in children?	Starting at about age 3 or 4 years, children can reliably use pain scales If a child is not capable of self-reporting because of their age or condition, healthcare providers will use behavioral and composite measures • Pediatric Pain Questionnaire • Pain diary • Behavioral 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 behavior as well as the context and possible symptoms of pain	SickKids tools 2009[32]

Abbreviation: PPQ, Pediatric Pain Questionnaire.

TOPIC 2: Minimizing harm and maximizing welfare

Infants and children are particularly vulnerable to pain. If unmanaged, children between the ages of 5 and 10 could experience short- and long-term physiological, psychological, and emotional consequences following a bad needle experience.[30] Therefore, physical and emotional pain should be prevented and minimized as much as possible, constantly monitored,[7,9] and effectively treated when unavoidable. For example, painful procedures can be eased by using size−/age-appropriate devices.[31] Appropriate guidelines, techniques, and procedures should be followed for children who cannot express themselves.[7,32]

Starting at about age 3 or 4 years, children can reliably use pain scales. Alternatively, healthcare providers should consider using behavioral composite measures.[32] All points to be considered are shown in Table 2.

TOPIC 3: Sampling volume

Micro-volumes and micro-assays should be used for blood and tissue assays or developed when not available. Likewise, if micro-assays are not applied, then it should be justified in the protocol.[7] Per individual, the study-related blood loss should not exceed 3% of the total blood volume over a period of 4 weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 80–90 mL/kg body weight with, 3% being 2.4 mL blood per kg body weight. Table 1 of the EC Recommendations 2017 detail the maximum allowable research-related blood sample volumes.[7] All points to be considered are shown in Table 3.

TOPIC 4: Skills, training, and facilities required for sampling

Pediatric trials should comply with the same quality standards as those of the adults to collect blood and other biological materials.[14,33–42] The only specific provision was on blood sampling (need for demonstrated proficiency on the specific methods used and for experienced/trained phlebotomist for venipuncture).[31] No specific requirement was found for the other biological materials. Table 4 provides an example of a checklist of points to be considered.

TOPIC 5: Long-term storage of biological material

Provisions for the storage of biological material for future use and for the possible cross-border transfer of specimens[11,12,29,43–45] are not specific to pediatric trials. This means that those applicable for adult trials should also be followed also for pediatrics, as detailed in Table 5.

Material should not be stored for longer than is necessary. The duration of storage for biosamples should be specified in the consent. If consent has not been given for retention beyond the end date of the study, the material should be destroyed upon completion of that study.[11,43]

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 in purpose of a collection should be subject to an independent examination and if appropriate consent or authorization is required.

DISCUSSION

In pediatric clinical research, it is essential that the collection, management, storage, and analysis of specimens are performed according to high standards.[2] Study documents, facilities, and staff expertise required for biological samples collection should comply with a series of ethical and regulatory requirements be sourced from different provisions, not limited to GCP.[46] Furthermore, specific guidance on the management of biosamples in pediatrics is not available. The creation of the checklist presented in this work fills a current need for sponsors and researchers to implement ad hoc procedures for specimen handling in pediatric research and their possible successful implementation in clinical studies.[47–49] In fact, such a checklist was built aggregating all available existing resources and using expert opinion to fill in any gap.

Our work identified specific measures and procedures to be applied to five topics: consent and assent; minimizing harm and maximizing welfare; sampling volume; skills, training, and facilities required for sampling; and the long-term storage of biological material. Some of these measures and procedures are specific to pediatric studies: content of the assent material, possibility to withdraw parental consent once the subject reaches the age of legal maturity and the related consequences for the handling of collected biospecimens, procedures and facilities to withdraw blood samples and to measure the level of pain and expertise for venipuncture in pediatrics.

On the other hand, we found other measures that are not pediatric-specific but should be sourced from adult ones: contents for informed consent material (handling and use of biological material, including possible storage for future uses), measures for data protection and data/

TABLE 3 Sampling volume (Topic 3).

Research question	Sentences to be included in the checklist	Sources
What is the maximum volume of blood that is allowed in pediatric clinical trials (single sampling/repeated sampling for each population)?	Per individual, the study-related blood loss (including any losses in the maneuver) should not exceed 3% of the total blood volume over a period of 4 weeks, and should not exceed 1% at any single time. The total volume of blood is estimated at 80–90 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	EC Ethical Recomm. 2017,[7] including Table 1
Is the use of blood micro-sampling techniques always recommended in pediatric clinical trials (e.g., for blood and bone marrow sampling, biopsy)?	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, because they reduce trial-related blood loss Not using micro-assays should be justified in the protocol	EC Ethical Recomm. 2017[7]

biological material destruction if the consent is withdrawn, quality standards of medical/laboratory/technical procedures/tests to collect biological material other than blood, the duration of biospecimens storage, and the requirements for possible cross-border transfer of specimens.

Further insight may be needed to check whether these areas need further pediatric-specific regulatory guidance and should take into account any age-related differences.

Therefore, even if the majority of samples collected on a pediatric clinical trial is blood, other samples, including biopsies, require unique skills to collect. However, we did not find any specific requirements for pediatric trials, as the only reference on expertise and facilities for sample collection was found in a WHO guideline on phlebotomy from 2010.[31]

This exercise confirmed that a unique source cannot cover all of the key aspects to be considered while planning and conducting a pediatric clinical study that foresees the collection of biosamples. The most relevant and complete provisions released in the European Union is Ethical Recommendations,[7] which is able to cover most of the necessary requirements. In fact, this document contains specific requirements on informed consent and assent, measures to minimize harm and the use of minimal volumes for blood sampling; in contrast, these recommendations do not provide any specific provision on the long-term storage of biological material. This issue is rather dealt by the EU Recommendations on research on biological materials of human origin[29] and other documents released at the European Union[2,45] and national[43] levels. GDPR[11] and related guidelines remain the main reference for data processing in the European Union.

In this way, our work does fill a gap in the pediatric-specific guidance. The tool presented in this work was developed to help investigators, sponsors, and other research actors involved in pediatric clinical trials in this effort. It is publicly available on the PedCRIN website https://ecrin.org/projects/pedcrin. The checklist represents an easy-to-use document to verify that all key aspects are taken into consideration to properly manage samples and collect and store data in the context of pediatric trials on the basis of the European applicable rules and legislation. It is intended to be used during the planning and set up of pediatric trials, including the preparation of the protocol and related documents as well as material for informed consent and assent, to properly address all the relevant topics and requirements as well as during the trial to check whether the foreseen provisions are complied with.

The tool was built in the context of academic research, because PedCRIN aims to develop capacity for the management of multinational pediatric non-commercial

TABLE 4 Skills, training, and facilities required for sampling (Topic 4).

Research question	Sentences to be included in the checklist	Sources
What the professional expertise and qualifications are required for the personnel collecting blood/other biological material in pediatric clinical trials?	• Demonstrated proficiency on the specific methods used (e.g., sampling, venous, arterial, and capillary blood sampling) • Venipuncture 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[31]
What are the requirements for facilities for the collection of blood/other biological material in pediatric 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[7]; WHO guideline on phlebotomy 2010[31]
What are the quality standards for the collection and management of blood/other biological materials in pediatric clinical trials?	Pediatric 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/ The collection, processing, shipment, storage and analyses of biological samples should be standardized Use of the correct gauge of hypodermic needle to prevent hemolysis or abnormal results	WHO guideline on phlebotomy 2010[31]; ICH-GCP[14]; ISO 20387:2018[33]; CEN guidelines.[34–42]

Abbreviations: ICH-GCP, International Conference on Harmonization-Good Clinical Practice; WHO, World Health Organization.

TABLE 5 Long-term storage of biological material (Topic 5).

Research question	Sentences to be included in the checklist	Sources
How long can biological samples derived from pediatric clinicals trial be stored for?	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 h up to 30 years, depending on local regulations, sample type, and available storage conditions. The storage period should be specified in the donor consent	GDPR[11]; Irish Council for Bioethics Recomm[43]
Which aspects should be considered to reuse samples collected in a pediatric 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 authorization is required. Compliance with GDPR should be checked as well	GDPR[11]; Art 29 WP guidelines[12]; Recomm. CM/Rec (2016)6[29]; DH-BIO/INF Recomm. 2015[44]
Which rules regulate the cross-border transfer of biological samples (provider's legislation, recipient's legislation, both...)?	No specific requirements for pediatric 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 authorization, including any relevant restriction should be included in the agreement	GDPR[11]; Recomm. CM/Rec (2016)6[29]; Directive 2004/23/EC[2]; COM (2016)223 - Implementation of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC.[45]

Abbreviations: EC, European Commission; GDPR, General Data Protection Regulation.

clinical trials. However, the tool could also be useful for commercial trials and we can expect the pharmaceutical industry to use this checklist.

The limits of this instrument are correlated with the challenges encountered to standardize the retrieved information where we found no pediatric-specific provision.

The checklist on biosamples management for pediatric trials was included in a project deliverable and published as freely available.[17]

Therefore, this tool can be directly used in pediatric research because it is a comprehensive checklist specifically dealing with pediatric themes. The methods used to

prepare such a tool demonstrate the feasibility of creating an "expert guide" on the basis of consolidated principles in a sector where guidance is lacking.

Such specific tools and services are necessary to conduct pediatric studies. Considering the continuous advancing of science and innovation in the biomedical research field and the resulting continuous updates in the regulatory and ethics field, such an instrument would need periodical updates. For example, new methods for collecting informed consent and assent or their updates (e.g., digital consent and assent), for collecting blood samples or other types of biological material, possibly reducing pain, discomfort, and distress, could be discovered and implemented.

Important input may derive from the actions and initiatives undertaken by the EMA's Innovation Task Force (ITF) and the pharmaceutical strategy for Europe,[50] which support the uptake of innovative methods in clinical trials and more generally in the development of medicines.

Pediatric networks, such as c4c (conect4children, a large collaborative European network aimed at facilitating the development of new drugs and other therapies for the entire pediatric population), TEDDY, speciality pediatric networks and the other members of the European Network of Pediatric Research at the European Medicines Agency (Enpr-EMA), as well as pan-European Research Infrastructures such as ECRIN, BBMRI, and EPTRI, could contribute to such updates.

AUTHOR CONTRIBUTIONS

V.G. and J.D. wrote the manuscript. V.G., L.R., R.C., M.F., S.M., C.K., and A.C. designed the research. L.R. and R.C. performed the research. V.G., C.M., M.M., A.C., and D.B. analyzed the data.

ACKNOWLEDGMENTS

The research leading to these results was done in context of the Pediatric Clinical Research Infrastructure Network (PedCRIN) project funded by European Commission Horizon 2020 Programme under Grant Agreement 731046. Authors acknowledge the contribution given by the European Network of Excellence for Pediatric Research (TEDDY) providing access to its regulatory database. This paper is part of a collaborative research project in the context of a publicly funded research project that required the preparation of public deliverables. These deliverables are available on the project website (https://ecrin.org/paediatric-tools). The tool is also published in the project website: https://cordis.europa.eu/project/id/731046/results.

FUNDING INFORMATION

The research leading to these results has received funding from the European Union's Horizon 2020 Programme under grant agreement number 731046 (PedCRIN). Sole responsibility lies with the authors. The funding body, the European Commission, is not responsible for any use that may be made of the information contained therein and has no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

ORCID

Viviana Giannuzzi https://orcid.org/0000-0002-2534-6783
Lucia Ruggieri https://orcid.org/0000-0001-9820-3890
Rosa Conte https://orcid.org/0000-0003-2049-8929
Cristina Manfredi https://orcid.org/0000-0002-3755-0474
Mariagrazia Felisi https://orcid.org/0000-0002-7315-0857
Christine Kubiak https://orcid.org/0000-0002-1505-8622
Jacques Demotes https://orcid.org/0000-0002-0807-0746
Adriana Ceci https://orcid.org/0000-0002-8778-3612
Donato Bonifazi https://orcid.org/0000-0003-2636-9159

REFERENCES

1. Barker CIS, Standing JF, Kelly LE, et al. Pharmacokinetic studies in children: recommendations for practice and research. *Arch Dis Child*. 2018;103:695-702.
2. DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.
3. Sarojini S, Goy A, Pecora A, Suh KS. Proactive biobanking to improve research and health care. *J Tissue Sci Eng*. 2012;3:116.
4. 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.
5. Council for International Organizations of Medical Sciences (CIOMS) in Collaboration with the World Health Organization (WHO). *International Ethical Guidelines for Health-Related Research Involving Humans*. Council for International Organizations of Medical Sciences; 2016.
6. Committee for Medicinal Products for Human Use (CHMP). Role of pharmacokinetics in the development of medicinal products in the paediatric population; 2006. EMEA/CHMP/EWP/147013/2004.
7. European Commission. Ethical considerations for clinical trials on medicinal products conducted with minors. Recommendations of the expert group on clinical trials for the implementation of 12 Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use; 2017.

8. Giannuzzi V, Altavilla A, Ruggieri L, Ceci A. Clinical trial application in Europe: what will change with the new regulation? *Sci Eng Ethics*. 2016;22(2):451-466. doi:10.1007/s11948-015-9662-0
9. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
10. Lepola P, Kindred M, Giannuzzi V, et al. Informed consent and assent guide for paediatric clinical trials in Europe. *Arch Dis Child*. 2022;107(6):582-590. doi:10.1136/archdischild-2021-322798
11. European Parliament and Council of the European Union. Regulation (EU) 2016/679 Of The European Parliament And Of The Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). Official Journal of the European Union. May, 2016.
12. Article 29 Working Party on the Protection of Individuals with Regard to the Processing of Personal Data. Article 29 Working Party Guidelines on consent under Regulation 2016/679.
13. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310:2191-2194.
14. European Medicines Agency. Guideline for good clinical practice E6(R2). Step 5. EMA/CHMP/ICH/135/1995. 1 December 2016. 2016. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf. Accessed September 26, 2019.
15. Giannuzzi V, Landi A, Bartoloni F, Ceci A. A review on impact of general data protection regulation on clinical studies and informed consent. *J Clin Res Bioeth*. 2018;9(3):327. doi:10.4172/2155-9627.1000327
16. Ruggieri L, Ceci A, Bartoloni F, et al. Paediatric clinical research in Europe: an insight on experts' needs and perspectives. *Contemp Clin Trials Commun*. 2021;10(21):100735. doi:10.1016/j.conctc.2021.100735
17. https://ecrin.org/projects/pedcrin/wp-activities/7. Accessed August 18, 2022.
18. http://www.bbmri-eric.eu/services/common-service-elsi/. Accessed August 18, 2022.
19. Norlin L, Fransson MN, Eriksson M, et al. A minimum data set for sharing biobank samples, information, and data: MIABIS. *Biopreserv Biobank*. 2012;10(4):343-348. doi:10.1089/bio.2012.0003
20. Committee For Medicinal Producs For Human Use (CHMP) and Paediatric Committee (PDCO). Guideline on the investigation of medicinal products in the term and preterm neonate. EMEA/536810/2008.
21. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry, July 2022.
22. https://health.ec.europa.eu/medicinal-products/eudralex_en. Accessed August 18, 2022.
23. https://www.ich.org/. Accessed August 18, 2022.
24. https://www.ema.europa.eu/en. Accessed August 18, 2022.
25. https://cioms.ch/. Accessed August 18, 2022.
26. https://www.who.int/. Accessed August 18, 2022.
27. https://www.cen.eu/. Accessed August 18, 2022.
28. https://www.iso.org/. Accessed August 18, 2022.
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.
30. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg*. 2007;105(1):205-221. doi:10.1213/01.ane.0000268145.52345.55
31. WHO Guidelines on Drawing Blood. *Best Practices in Phlebotomy*. World Health Organization; 2010.
32. SickKids. Tools for measuring pain; 2009. https://www.aboutkidshealth.ca/Article?contentid=2994&language=English#. Accessed August 18, 2022.
33. International Standard ISO 20387:2018 Biotechnology – Biobanking – General requirements for biobanking.
34. CEN/TS 16826-1:2015 Specifications for Pre-examination processes for snap frozen tissue – Part 1: Isolated RNA.
35. CEN/TS 16826-2:2015 Specifications for Pre-examination processes for snap frozen tissue – Part 2: Isolated proteins.
36. CEN/TS 16827-1:2015 Specifications for Pre-examination processes for FFPE tissue – Part 1: Isolated RNA.
37. CEN/TS 16827-2:2015 Specifications for Pre-examination processes for FFPE tissue – Part 2: Isolated proteins.
38. CEN/TS 16827-3:2015 Specifications for Pre-examination processes for FFPE tissue – Part 3: Isolated DNA.
39. 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.
40. CEN/TS 16835-2:2015 Specifications for Pre-examination processes for Venous whole blood – Part 2: Isolated genomic DNA.
41. CEN/TS 16835-3:2015 Specifications for Pre-examination processes for Venous whole blood – Part 3: Isolated circ cell-free DNA from plasma
42. CEN/TS 16945:2016. Specifications for Pre-examination processes for metabolomics in urine, serum and plasma.
43. Irish Council for Bioethics. Human Biological Material Recommendation for Collection, Use & Storage in Research; 2014. https://health.gov.ie/wp-content/uploads/2014/07/Human_Biological_Material1.pdf. Accessed August 18, 2022.
44. COMMITTEE ON BIOETHICS (DH-BIO). *Draft Recommendation on Research on Biological Material of Human Origin*. DH-BIO/INF; 2015.
45. COM(2016)223 – Implementation of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC setting standards of quality and safety for human tissues and cells.
46. Giannuzzi V, Devlieger H, Margari L, et al. The ethical framework for performing research with rare inherited neurometabolic disease patients. *Eur J Pediatr*. 2017;176(3):395-405. doi:10.1007/s00431-017-2852-9
47. Giannuzzi V, Felisi M, Bonifazi D, et al. Ethical and procedural issues for applying researcher-driven multi-national paediatric clinical trials in and outside the European Union: the challenging experience of the DEEP project. *BMC Med Ethics*. 2021;22(1):49. doi:10.1186/s12910-021-00618-2
48. Parker SL, Wallis SC, Fourie C, et al. Evaluation of low-volume plasma sampling for the analysis of meropenem in

clinical samples. *Anal Bioanal Chem*. 2022;414(6):2155-2162. doi:10.1007/s00216-021-03851-1

49. Napiórkowska-Orkisz M, Gutysz-Wojnicka A, Tanajewska M, Sadowska-Krawczenko I. Evaluation of methods to minimize pain in newborns during capillary blood sampling for screening: a randomized clinical trial. *Int J Environ Res Public Health*. 2022;19(2):870. doi:10.3390/ijerph19020870
50. European Commission. COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS Pharmaceutical Strategy for Europe. {SWD(2020) 286 final} COM(2020) 761 final. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=SWD:2020:286:FIN. Accessed August 18, 2022.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Giannuzzi V, Ruggieri L, Conte R, et al. PedCRIN tool for the biosamples management in pediatric clinical trials. *Clin Transl Sci*. 2023;16:797-809. doi:10.1111/cts.13489