A study of regulatory challenges of pediatric oncology phase I/II trial submissions and guidance on protocol development

Lydia Beck, Ruth Witt, Martina Nesper Brock, Till Milde, Simone Hettmer, Michael C. Frühwald, Claudia Rössig, Matthias Fischer, Dirk Reinhardt, Lenka A. Taylor, Claudia Riedel, Olaf Witt, Cornelis M. Tilburg

Angaben zur Veröffentlichung / Publication details:

Beck, Lydia, Ruth Witt, Martina Nesper Brock, Till Milde, Simone Hettmer, Michael C. Frühwald, Claudia Rössig, et al. 2021. "A study of regulatory challenges of pediatric oncology phase I/II trial submissions and guidance on protocol development." *Clinical Pharmacology and Therapeutics* 110 (4): 1025–37. https://doi.org/10.1002/cpt.2319.

A Study of Regulatory Challenges of Pediatric Oncology Phase I/II Trial Submissions and Guidance on Protocol Development

Lydia Beck[1,2,3], Ruth Witt[1,2,4,5], Martina Nesper-Brock[1,2,4,5], Till Milde[1,2,4,5,6], Simone Hettmer[4,7], Michael C. Frühwald[5,8], Claudia Rössig[9], Matthias Fischer[5,10], Dirk Reinhardt[4,5,11], Lenka A. Taylor[12], Claudia Riedel[13], Olaf Witt[1,2,4,5,6] and Cornelis M. van Tilburg[1,2,4,5,6,*]

The purpose of this study was to identify key deficiencies in pediatric oncology early phase clinical trial protocols in Germany and to provide guidance for efficient trial protocol development. A systematic review of the response letters of German competent authorities (CAs) and Ethics Committees to phase I/II pediatric oncology trial submissions in the period from 2014 to 2019 was performed. Documents were requested from all five Society for Paediatric Oncology and Haematology in Germany (GPOH) phase I/II trial networks plus all nine German Innovative Therapies for Children with Consortium Cancer (ITCC) centers. A blinded dataset containing aggregated data from 33 studies was analyzed for validation. All deficiencies were reviewed, listed, and weighted using a structured matrix according to frequency, category, significance, and feasibility. In total, documents of 17 trials from 6 different sites were collected. Two hundred fifty deficiencies identified by the CAs were identified and categorized into eight categories. "Toxicity and safety" was the most prominent category (27.6%), followed by "Manufacturing and Import" (18%). The majority of deficiencies were categorized as minor and potential measures as easy to address, but an important group of major and difficult to implement deficiencies was also identified. The blinded validation dataset confirmed these findings. The majority of the EC deficiencies could be resolved by changing the wording in the patient-facing documents. In conclusion, this study was able to detect a pattern of key deficiencies. Most of the shortcomings can be anticipated by minor changes in the protocol and increased awareness can prevent time-consuming revisions, withdrawals, or even rejections. A corresponding guideline describing key regulatory aspects is provided.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ To our knowledge, the topic of regulatory challenges for phase I/II trials in pediatric oncology in Germany has not been the subject of research yet.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This is the first analysis of responses of the German competent authorities and Ethic Committees in the field of pediatric oncology. We wanted to identify recurring patterns of key deficiencies and to analyze those regarding frequency, significance, and feasibility.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We were able to identify frequent categories of deficiencies and provide a structured guidance to facilitate the submission of future pediatric oncology phase I/II clinical trials in Germany.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ We are convinced that this guidance will facilitate protocol development by highlighting important protocol requirements for pediatric oncology phase I/II trials in Germany and hopefully lead to an increased number of approved trials.

[1]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany; [2]Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]Heidelberg Medical Faculty, University of Heidelberg, Heidelberg, Germany; [4]German Cancer Consortium (DKTK), Heidelberg, Germany; [5]National Center for Tumor Diseases (NCT) Network, Heidelberg, Germany; [6]Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, Heidelberg University Hospital, Heidelberg, Germany; [7]Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Faculty of Medicine, University Medical Center Freiburg, University of Freiburg, Freiburg, Germany; [8]Swabian Children's Cancer Center, Paediatric and Adolescent Medicine, University Medical Center Augsburg, Augsburg, Germany; [9]Pediatric Hematology and Oncology, University Children's Hospital Münster, Münster, Germany; [10]Department of Experimental Pediatric Oncology, Center for Molecular Medicine (CMMC), Medical Faculty, University Hospital Köln, Cologne, Germany; [11]West German Cancer Center, Pediatrics III, University Hospital Essen, Essen, Germany; [12]Pharmacy Heidelberg University Hospital, Heidelberg, Germany; [13]The Federal Institute for Drugs and Medical Devices, Bonn, Germany.
*Correspondence: Cornelis M. van Tilburg (cornelis.vantilburg@kitz-heidelberg.de)

Received March 30, 2021; accepted May 20, 2021. doi:10.1002/cpt.2319

Pediatric cancer is rare but responsible for the death of > 6,000 young people within Europe each year. Additionally, there are between 300,000 and 500,000 Europeans who have survived some form of childhood cancer, of whom about 30% suffer from long-term sequelae of their treatment.[1] Death rates for children with cancer have continuously declined from 6.5 per 100,000 in 1970 to 2.3 in 2015 through improved therapies due to extensive research over the last decades.[2] In order to maintain this trend and reduce deaths and unintended side-effects of cancer treatment, further preclinical and clinical research are necessary. Especially the latter poses a number of challenges specific for pediatric oncology clinical trials compared with trials in the adult population, contributing to the current state of children becoming therapeutic orphans. In some therapeutic areas, unlicensed drug and off-label use adds up to 80%, with pediatric oncology being one of the areas with a particular high percentage,[3-5] indicating a need for evidence-based medicine.

Although the number of pediatric oncology phase I/II trials is low in general, the number of open trials and patients participating in trials is even lower in the most populated European Union member state: Germany. From 2014 to 2019, 113 pediatric clinical trials were carried out in the United Kingdom, 93 in France and only 55 in Germany (Clinicaltrials.gov "Cancer" AND "interventional study" AND "Child (birth-17 years)" AND ("Phase 1" OR "Phase 2") for each country). These findings are in line with data provided by the Innovative Therapies for Children with Consortium Cancer (ITCC)[6] where only about 2.7% of over 2,200 patients treated in 54 pediatric oncology departments across 14 European countries between 2015 and 2019 were treated in one of the 9 participating German centers.[7]

In Germany, all clinical trials of medicinal products on humans have to be approved by one of the two federal competent authorities (CAs), the Paul-Ehrlich Institute (PEI), which is responsible for "sera, vaccines, blood preparations, bone marrow preparations, tissue preparations, tissues, allergens, advanced therapy medicinal products, xenogeneic medicinal products and blood components manufactured using genetic engineering," and the Federal Institute for Drugs and Medical Devices (BfArM), which is responsible for all other medicinal products for human use, as well as the competent Ethics Committees (ECs; §77.1–2 Medical Products Act (MPA), §40.1 MPA).[8] The federal CAs put their primary focus on the efficacy and safety of the investigated medical products, whereas the ECs focus on reviewing the trial protocol and patient-facing documents (e.g., consent forms), on ethical and legal grounds. The CAs and ECs formulate deficiency letters with regard to form and content of the trial protocol as well as for example patient-facing documents and drug labels with requests for revision.

In order to identify common regulatory hurdles, which could play a role in the relative low number of pediatric oncology phase I/II trials in Germany, we have performed a national analysis of the deficiency letters by the CAs and ECs of pediatric oncology phase I, II, or I/II trials submitted for regulatory approval. Our main focus was to identify recurring patterns of key deficiencies in order to support academic and industry sponsors in pediatric protocol development and to prevent time-consuming revision processes, trial withdrawals, or even rejections. We have performed the first systematic study of responses of the German CAs and ECs in the field of pediatric oncology and provide a structured guidance (Supplementary information) to facilitate the submission of future pediatric oncology phase I/II clinical trials in Germany.

METHODS

Pediatric oncology phase I/II trials submitted to the German CAs and ECs in the period from 2014 to 2019, regardless of approval status were included in this study. In order to be collected, the required trial documents nationwide, in all nine German ITCC centers as well as all five German phase I/II trial networks of the Society for Paediatric Oncology and Haematology in Germany (GPOH),[9,10] were asked to fill out a questionnaire with general information about the studies, attach all deficiency letters in regard to the content received from BfArM or PEI and the responsible EC, as well as the final decision of the authorities. As the requested documents contain sensible confidential information, the documents were anonymized. The deficiencies voiced by BfArM and PEI, and those by the ECs were analyzed separately as the different agencies focus on different aspects. The deficiencies identified in the deficiency letters from BfArM (primary analysis) were validated by an aggregated and blinded dataset of responses to all phase I/II pediatric oncology trials submitted to BfArM between 2015 and 2019 provided by BfArM. The validation dataset was not annotated and thus deficiencies could not be linked to a specific trial making direct interpretation of responses as performed in the primary analysis impossible.

Categorization by subject

The deficiencies identified by the CAs were divided into the following eight categories: toxicity and safety, manufacturing and import, inclusion and exclusion criteria, formalities, study population and design, risk-burden-benefit analysis, study rationale, and drug administration.

The deficiencies identified by the ECs were divided into "general deficiencies" and "deficiencies regarding the patient-facing documents" according to the structure in the EC's deficiency letters.

Categorization by significance and feasibility

The deficiencies put forward by the CAs were additionally categorized according to their significance and feasibility to improve shortcomings.

The following definitions were applied for significance:

(i) Minor deficiencies: All deficiencies that concern formalities (e.g., wording and clarification), manufacturing and import, follow-up questions on already provided information, smaller changes in the study structure (e.g., additional examination and not addressing the rationale).
(ii) Major deficiencies: All deficiencies that are important for the participant's direct safety, concern the study rationale, are not in compliance with EU regulations or German laws, concern insufficient pre-/clinical data or are mentioned as reasons for refusal of the trial.

The following definitions were applied for feasibility:

(iii) Easy to implement: All deficiencies concerning the provision of easily available information, clarification on formulations, confirmation of aspects in the trial protocol or the coherence with guidelines or laws, changes of wording, smaller changes to the study structure.
(iv) Difficult to implement: All deficiencies that cause a delay in the initiation of the trial or significant changes to its structure, design, or study population; all deficiencies that concern the provision unavailable data.

By combining the significance and feasibility, four categories were formed: (1) minor and easy to implement, (2) minor and difficult to implement, (3) major and easy to implement, and (4) major and difficult to implement. Importantly, we assumed that sponsors would accept to perform changes in the trial protocol resulting in a Germany specific version of the protocol. Categorization was done independently by two investigators (authors L.B. and C.M.v.T.). Discrepant assessments were resolved after discussion. Because the nature of the deficiencies expressed by the ECs did not fit this categorization, only "general deficiencies" and "deficiencies regarding the patient-facing documents" were differentiated.

RESULTS

In total, documents of 17 early phase pediatric oncology trials from 6 different trial sites were collected. As not all study sites provided all requested documents, 11 sets of documents regarding the deficiencies by the BfArM, 3 document sets regarding the deficiencies by the PEI, and 11 document sets regarding the deficiencies by the ECs were received (**Figure S1**). As we only received a very limited number of trial documents assessed by the PEI, we decided to omit further analysis of those deficiencies as the result would not have been representative.

The primary data set consisted of eight industry-sponsored and nine investigator-initiated trials. Eight industry sponsored trials were part of a Paediatric Investigation Plan (PIP) of the European Medicines Agency (EMA). Of the 17 trials, 2 were declined by the BfArM, 2 were withdrawn by the sponsor, and 2 trials were approved, but only with major restrictions (e.g., age groups or entities). The data on declined or withdrawn PIPs did not allow for systematic evaluation but in the following issues were important for the BfArM: patient burden (of e.g., safety investigations), need for preclinical juvenile data and the rationale pediatric age group, and the prerequisite for the availability for adult data. Of the four trials not started in Germany (one part of a PIP), all four had been approved by the CAs of at least one other European member state at the time of trial submission. In total, 13 of the analyzed trials were approved by both the CA and EC.

BfArM submissions

Overall, 250 deficiencies were identified from 11 different trials assessed by the BfArM and subsequently categorized into 8 different subject categories with a median of 16 (range 2–78) deficiencies per trial. "Toxicity and safety" was the category to which most deficiencies were attributed (27.6%), followed by "Manufacturing and import" (18%) and "Inclusion and exclusion criteria" (14%). In addition, 384 deficiencies from the cumulative blinded dataset obtained from the BfArM itself were analyzed accordingly and a similar distribution of deficiencies to the 8 categories could be observed (**Table 1**) confirming our initial results.

Subsequently, the deficiencies were further divided into subcategories in order to detect the most common fields of shortcomings within the categories. For each subcategory, considerations to address the respective deficiencies are provided to serve as guidance for improved protocol writing and submissions. Deficiencies that could not all be attributed to corresponding subcategories, were allocated to "other."

Table 1 BfArM deficiencies

	Toxicity and safety	Manufacturing and import	Inclusion and exclusion criteria	Formalities	Study population and design	Risk- burden - benefit analysis	Study rationale	Drug administration	Total
Number of deficiencies in 11 BfArM response letters	69 (27.6)	45 (18)	35 (14)	29 (11.6)	26 (10.4)	22 (8.8)	14 (5.6)	10 (4)	250 (100)
Number of deficiencies in blinded dataset from BfArM	102 (26.6)	98 (25.5)	46 (12)	38 (9)	34 (8.9)	26 (6.8)	27 (7)	13 (3.4)	384 (100)

Attribution of deficiencies from 11 BfArM deficiency letters and from the blinded BfArM dataset to subject categories with number of deficiencies (%).
BfArM, Federal Institute for Drugs and Medical Devices.

Toxicity and safety

The category "Toxicity and safety" includes all deficiencies that concern the wellbeing of the trial participant by minimizing and evaluating possible risks in advance. This category was dived into the subcategories provided in **Table 2**.

Manufacturing and import

This category comprises deficiencies regarding the aspects of drug manufacturing and can be further divided into the subcategories provided in **Table 3**.

Inclusion and exclusion criteria

The category "Inclusion and exclusion criteria" includes deficiencies related to the inclusion and exclusion criteria of the trial. **Table 4** displays the different subcategories.

Formalities

This category comprises deficiencies due to formal issues, such as the submission of faulty (34.5%) or outdated (13.8%) documents, or the nonsubmission of necessary documents (20.7%; **Table S1**). Many of the deficiencies in this category seem to occur on an individual basis, so that only limited general recommendations can be given regarding this category. In order to avoid deficiencies in this category, all documents should be controlled for their accuracy and completeness before submission. In addition, all documents should be submitted in their most current version, in particular Investigator Brochure (IB) and Summary of Products Characteristics (SmPC). Other (31%) deficiencies included the need to confirm that all nonclinical studies required to comply with Good Laboratory Practice, were performed in the Organisation for Economic Co-operation and Development (OECD) countries or countries, who signed "OECD Mutual acceptance of Data" agreement.

Study population and design

This category includes deficiencies regarding the planned trial design and structure and was further divided into the subcategories displayed in **Table 5**.

Risk-burden-benefit analysis

This category includes deficiencies due to an insufficient risk-benefit analysis. It was further divided into the subcategories listed in **Table 6**.

Study rationale

This category includes deficiencies regarding the trial rationale with a focus on the compliance with MPA §40.4.4. The subcategories are displayed in **Table 7**.

Drug administration

The category "drug administration" includes all deficiencies dealing with aspects related to drug administration. Common deficiencies are that the investigated medical product is not available in an adequate drug formulation for the intended study population and that the trial protocol does not include a comprehensive administration plan. Considerations to avoid respective deficiencies are listed in **Table S2**.

Significance and feasibility

In order to weigh the identified deficiency with respect to significance and feasibility aspects, we grouped all deficiencies into the categories "easy to implement" and "difficult to implement" as well as "minor" and "major."

The majority, 129 of the 364 deficiencies (51.6%), were attributed to category 1 (minor and easy to implement) and 92 (36.8%) were placed in category 3 (major and easy to implement). Only 8 deficiencies (3.2%) were attributed to category 2 and 21 to category 4 (8.4%) (**Table S3**). Although the considerable majority of deficiencies can be implemented into the trial protocol relatively easy by providing additional information or introducing smaller changes to the trial protocol, a small part of deficiencies is more difficult to comply with (categories 2 and 4). Deficiencies in category 2 deal with, for example, the transition from phase I to phase II. Although all these deficiencies can lead to delays in the trial or complicate procedures, they do not fundamentally hinder the proposed trial, as is the case with deficiencies in category 4. The implementation of category 4 deficiencies poses certain challenges as they often require fundamental changes of the study structure or question the trial itself. For instance, many deficiencies deal with the study rationale (e.g., inclusion of minors), and the study population (e.g., restriction of inclusion criteria). Another relevant topic is missing preclinical juvenile animal data, which, if not available, can lead to the rejection of the trial.

Ethics committees

In total, 260 deficiencies by the ECs were identified within the 11 analyzed trials with a median of 19 (6–55) per trial. The deficiencies were divided into two main areas: (i) general deficiencies (13.9%), excluding patient-facing documents, and (ii) deficiencies concerning the patient-facing documents, which account for the majority of EC deficiencies (86.1%).

Among the general deficiencies, formality issues (25%) were the most common deficiencies. Recurring deficiencies were, for example, outdated or missing documents but also typographical errors. Other frequent deficiency subjects were "Toxicity and Safety" (22.2%) and "Data Protection" (22.2%). The remaining deficiencies concerned primarily topics that were also addressed by the BfArM (e.g., burden of protocol specific measures and inclusion of minors). For further details see **Table S4**.

When analyzing the deficiencies with regard to patient-facing documents, nine frequently addressed topics were identified (**Table S5**). The remaining deficiencies were summarized under "Other."

The most frequent topic was "Comprehensibly," which accounted for 35.3% of all deficiencies in regard to patient-facing documents, followed by "Study samples and data" (17.4%) and "Risk-burden-benefit" (16.5%).

DISCUSSION

In comparison with other European countries, Germany is lagging behind in the number of phase I/II pediatric oncology trials conducted as well as with regard to the number of recruited patients. We hypothesized that the regulatory challenges in pediatric early phase clinical drug development could be an important contributing

Table 2 "Toxicity and safety" deficiencies

Category: Toxicity and safety		
Subcategories	**Common deficiencies**	**Considerations to avoid respective deficiencies**
Screening and follow-up (23.2%, *n* = 16)	Request to implement additional examination, e.g., laboratory values, e.g., due to suspected drug related side effects or inclusion/exclusion criteria	The IMPs **IB** and/ or **SmPC** should be thoroughly reviewed for **possible toxicities** and the **examinations/investigations** performed during screening and follow up aligned accordingly
Contraception and pregnancy (15.9%, n = 11)	In case of embryotoxic or teratogenous IMPs:	
	Only highly effective contraception methods should be used, and these should be stated and explained in the study protocol	"CTFG recommendation related to contraception and pregnancy testing in clinical trial,"[15] which describes in what situations pregnancy test and contraception are necessary, how often pregnancy test should be performed, for how long contraception is necessary, as well as highly effective contraception methods
	Frequency of pregnancy test is not sufficient	The highly effective contraception methods and the duration of contraception for female and male study subjects should be clearly stated in the trial protocol
Drug dosage and escalation (13%; *n* = 9)	No scientific rationale for intended drug dosages was provided	Rationale for starting dose and dose escalation should be provided and supported by preclinical and clinical data
Recommendation of toxicity management (13%, *n* = 9)	The IB recommends certain measures in order to prevent toxicities, which are not stated in the protocol Recommended measures need to be clarified	Measures recommended in the IB should be stated in the protocol in sufficient detail to provide guidance There should be clear objective criteria for treatment modifications
Discontinuation criteria (8.7%, *n* = 6)	The criteria for trial discontinuation of an individual subject or the complete trial are inconclusive or formulated in a too general manner	Provide definitions for unacceptable toxicities including a list expended risk and predefined limits Formulation regarding **individual subject discontinuation** to be added to the trial protocol, e.g., "trial therapy in the individual will be halted as soon as pregnancy is suspected or licensed drug becoming available for the patient, retroactive failure to fulfil inclusion/exclusion criteria, significant non-compliance, loss of contact, relocation, negative benefit/ risk assessment for the whole trial; Institutional Review Boards, ECs, or relevant authority's request" Criteria **for complete trial discontinuation:** · Occurrence of an **unjustifiable risk**, such as "an AE, which is new in terms of its nature or severity or frequency of occurrence compared with the known risk profile," "a change in scientific knowledge with a negative impact on the assessment of the benefit-risk balance" · **Request** of the sponsor or competent authorities · If the planned recruitment cannot be completed within the indicated time period · If the **authorization** for manufacture or import of the **IMP** is **withdrawn** · Finding **study sites** to be **unsuitable** (by the sponsor, authorities, or ethics committee) · **Deviations** from the **approved statistical analysis** plan or not achieving statistical objectives

(Continued)

Table 2 (Continued)

Category: Toxicity and safety		
Subcategories	**Common deficiencies**	**Considerations to avoid respective deficiencies**
Clinical data (7.2%, *n* = 5)	No or insufficient clinical data was provided The provided data is outdated	All available data in regard to efficacy, safety and pharmacokinetics from other clinical trials of the IMP should be provided If data is only available from adult trials, **justification for transferability** should be provided as well The data should be **up-to-date** and also include information from **recently published papers** on the IMP
Nonclinical data (5.8%, *n* = 4)	The provided preclinical data was insufficient, e.g., due to missing data from juvenile animal trials	Preclinical data should include toxicity dataset, pharmacokinetic value estimations according to recognized models for each age-group, pharmacology, and pharmacodynamic In order to provide data on the possible influence of the IMP on the development of pediatric trial subjects**, data from trials in juvenile animals** should be provided; if no data are available, it should be stated why such data is not of relevance for the population under study →This can, e.g., be discussed in a "kick-off meeting" with the BfArM before protocol submission
Adverse events (5.8%, *n* = 4)	The definitions of AEs, adverse reaction and expected/ unexpected adverse events are not in line with the current guidelines	ICH guideline E2, "Communication from the Commission-detailed guidance on the collection, verification and presentation of adverse event/reaction, reports arising from clinical trials on medical products for human use"[16] and Directive 2001/20/EC §2 and §16,[17] which include: · **Definitions of relevant terms** · **Reporting and monitoring guidelines**, including time frames
	Abnormal laboratory values are only defined as AEs in case of e.g., treatment modification or clinical symptoms, which is not in line with current guidelines	Each **deterioration of laboratory values or vital signs** has to **documented as AE if it is clinically significant**, whether or not considered related to the IMP Toxicities should be described at least as precise as in the current version of the **CTCAE**[18]
Other (7,2%, *n* = 5)	Additive toxicities due to interaction of the IMPs need to be discussed An emergency ID card should be provided to trial participants	-

Summary of "Toxicity and Safety" subcategories and considerations to avoid the respective deficiencies. Percentage (%) indicates the relative contribution of each subcategory to the category "Toxicity and Safety" and "*n*" the total number of deficiencies in this subcategory. Bold values represent issues or findings of key importance.
AE, adverse event; BfArM, Federal Institute for Drugs and Medical Devices; CTCAE, Common Toxicity Criteria for Adverse Events; CTFG, Clinical Trial Facilitation Group; EC, Ethics Committee; IB, Investigator Brochure; ICH, International Conference on Harmonization; IMPs, Investigational Medical Products; SmPC, Summary of Products Characteristics.

Table 3 "Manufacturing and import" deficiencies

Category: Manufacturing and import		
Subcategories	**Common or relevant deficiencies**	**Considerations to avoid respective deficiencies**
Formalities (22.2%, *n* = 10)	Missing or faulty documents, such as manufacturers' declaration, batch overview or application form	If possible, an IMP manufacturer with clinical trial experience should be on board; otherwise, involvement of a consulting party might be supportive
Synthesis process and quality (22.2%, *n* = 10)	The analytical methods for the drug substance have not been validated yet	All applied **analytical methods have to be validated** according to corresponding ICH guideline Q2 (R1) "Validation of analytical procedures"[19] and data of validation should be submitted
	The specifications regarding the synthesis process are not extensive enough	**Description of synthesis** has to include the following for each process step • Starting materials and intermediate products • Solvents • Catalyzers • Reagents • Any relevant process controlsThis information should be found in the Active Substance Master File, which should be submitted to the authorities together with the Letter of Access by the active ingredient manufacturer; the description of synthesis is also necessary for all excipients not listed in the European Pharmacopoeia
	For capsule manufacturing: weight limits need to be defined	
Stability (17.8%, *n* = 8)	The stability data is not extensive enough to justify the foreseen shelf-life, so that additional data has to be provided or the shelf-life shortened	
	The provided stability data is not extensive enough to justify an independent extension of shelf-life	In order to be able to extent shelf-life **without a substantial amendment** a stability plan committing to generate more stability data parallel to the trial has to be defined in the IMPD and submitted to the BfArM before trial initiation; more information regarding stability commitment can be found in ICH guideline Q1A (R2)[20]
Impurities and composition (15.6%, *n* = 7)	Stating only the total amount of impurities is not sufficient Reporting of only the biggest impurities is not sufficient	Besides the overall amount of impurities, **all impurities**, known and unknown, above the reporting limit **have to be reported**; the values **threshold limits** for new substance are stated in "ICH Q3A (R2) Impurities in new drug substances"[20] Updated documents on manufacturing and quality have to be submitted if the foreseen drug dosage exceeds the **threshold limit for impurities**
Labeling (13.3%, *n* = 6)	The label does not contain all the relevant information	Specifications for **labels of investigational drugs** are given in Annex 13 of the EU GMP[21] and has to include information about the drug intake, the storage conditions and the durability after opening If a drug is available in **various dosages**, draft labels for each dosage have to be submitted
Other (8.6%, *n* = 4)		-

Summary of "Manufacturing and Import" subcategories and considerations to avoid the respective deficiencies. Percentage (%) indicates the relative contribution of each subcategory to the category "Manufacturing and Import" and "*n*" the total number of deficiencies in this subcategory. Bold values represent issues or findings of key importance.
BfArM, Federal Institute for Drugs and Medical Devices; EU GMP, European Union Good Manufacturing Practice; ICH, International Conference on Harmonization; IMPD, Investigational Medicinal Product Dossier; IMPs, Investigational Medical Products; SmPC, Summary of Products Characteristics.

Table 4 "Inclusion and exclusion" deficiencies

Category: Inclusion and exclusion criteria		
Subcategories	**Common deficiencies**	**Considerations to avoid respective deficiencies**
Clarification and specification (22.9%, *n* = 8)	The criterion is not clear and needs specification	All inclusion and exclusion criteria should be clear and unambiguous
Biomarker (20%, *n* = 7)	For each biomarker used a scientific rationale should be given	For trials in which biomarker status is an inclusion criterion a **scientific rationale for each biomarker** should be provided in the trial protocol
	Description of *in vitro* diagnostics used to measure the biomarker and data to demonstrate sufficient technical validation of methods are missing	Provision of information on the performed *in vitro* diagnostics and biomarker validation
Threshold values (17.1%, *n* = 6)	"Normal" values should be defined according to age-appropriate threshold values	For IMPs that potentially cause QTc problems: for the definition of a **normal QTc interval** the BfArM refers to German Pediatric Cardiology guideline "Pädiatrische Kardiologie: Tachykarde Herzrhythmusstörungen im Kindes- und Jugendalter,"[22] which recommends the following: • QTc < 440 ms = normal range • QTc > 460 ms = prolongation • Use of the Bazett formula for the correction of QTc intervals in children
Allergy (8.6%, *n* = 3)	Patients with hypersensitivity to the IMP or any components of the drug need to be excluded from the trial	One exclusion criterion should state that all patients with known or suspected **hypersensitivity** against the active substance or any of the ingredients of **the IMP** will be **excluded from trial participation**
Other (31.4%, *n* = 11)	The sponsor has to ensure that the trial participant does not miss out on any established treatments due his or her participation	One inclusion criterion should state that **only those patients** will be included in the trials which have **received all possible standard of care treatment** (including potentially available second or even third line therapies) appropriate for their tumor type and stage of disease as laid down in the respective treatment guidelines or for which further licensed treatment options are contraindicated
	Scientific rationale for certain inclusion criteria is not clear	
	According to MPA §40.4.3 the assent of the minor is needed if he/she is capable of understanding the situation	One inclusion criterion should state that if a minor is capable of understanding the nature, meaning and scope of the clinical trial **the minor has assented**
	The exclusion criteria should reflect the toxicity profile	All contraindicated drugs listed in an IMP's IB should be exclusion criteria

Summary of "Inclusion and exclusion criteria" subcategories and considerations to avoid the respective deficiencies. Percentage (%) indicates the relative contribution of each subcategory to the category "Inclusion and exclusion criteria" and "*n*" the total number of deficiencies in this subcategory. Bold values represent issues or findings of key importance.
BfArM, Federal Institute for Drugs and Medical Devices; IB, Investigator Brochure; IMPs, Investigational Medical Products; QTc, corrected QT.

Table 5 "Study population and design" deficiencies

Category: Study population and design		
Subcategories	**Common deficiencies**	**Considerations to avoid respective deficiencies**
Study population (34.6%, *n* = 9)	Gender and age allocation have to be justified and specified	According to GCP ordinance §7[16] 10[23] and European Regulation No. 536/2014 Art. 17 (y)[24] **gender and age allocation** have to be justified; the trial protocol should mention • The age groups that will be treated, including **age and sample size limits**, and the rationale for treating those age groups • **Gender distribution**; if this is not possible due to too small sample sizes, it should also be mentionedAccording to ICH guideline E6 Art. 6.9.2[25] the trial protocol should mention the **number of subjects planned to be enrolled** as well as the number per trial side in multicenter trials; the rationale for sample size calculations (per age group) should also be included
	Sample size or chosen cohorts are not adequate to allow assessment of security and efficacy of the IMP	If a wide range of age groups is to be included, particularly when differences in metabolism and pharmacokinetics of the IMP are to be expected for those groups, the allocation in subgroups, e.g., age or tumor entities, should be considered and discussed in the protocol; if this is not possible, an explanation should be given e.g., low prevalence If the patient collective is inhomogeneous, an increase in sample size should be considered and described in the protocol
Study design (19.2%, *n* = 5)	The trial protocol does not state in which order the different age-groups will be treated in phase I	In phase I an **age-staggered approach** should be used as younger children are seen as more vulnerable as older children; the start of the next-younger-cohort is only allowed if a substantial amendment has been approved by the BfArM If the number of patients does not allow an age-staggered approach, alternatives should be discussed in the protocol and can be discussed with the BfArM, in a "kick-off-meeting"
Transition from phase I/II (7.7%, *n* = 2)	Phase II is only to begin after positive evaluation of substantial amendment, which has to be filed after phase I completion and included an interim report	The **interim report** should include • Updated safety, tolerability and efficacy data • Updated benefit-risk assessmentAn interim report **for each cohort** has to be provided
Other (38.5%, *n* = 10)	An independent DMC has to be implemented as young children are planned to be included in the trial	A DMC should be complied with **"Guideline on Data Monitoring Committees"**[26]: A DMC is indicated when dealing with **life-threatening illnesses**, a **pediatric population**, or a complex study design The finalized and sometimes signed **DMC charter** should be submitted to the BfArM

Summary of "Study population and design" subcategories and considerations to avoid the respective deficiencies. Percentage (%) indicates the relative contribution of each subcategory to the category "Study population and design" and "*n*" the total number of deficiencies in this subcategory. Bold values represent issues or findings of key importance.
BfArM, Federal Institute for Drugs and Medical Devices; DMC, Data Monitoring Committee; GCP, Good Clinical Practice; ICH, International Conference on Harmonization; IMP, Investigational Medical Product.

Table 6 "Risk-burden-benefit" deficiencies

Category: Risk-burden-benefit analysis		
Subcategories	**Common deficiencies**	**Considerations to avoid respective deficiencies**
Insufficient benefit-risk analysis (50%, *n* = 11)	No risk-benefit evaluation was provided Risk-burden benefit analysis is insufficient (for other reasons than mentioned below)	Risk-benefit evaluation should include a **critical discussion of the anticipated and known risks and benefits** (ICH E6 (R2) 6.2.3) based on all pre-/clinical data and be compared with alternative therapies Risk assessment should include • The risks of the tested IMP • The risk of withholding active treatment • The risk of the disease itself • Illustration of medical need with survival data of specific pediatric oncology disease(s) • Rationale for dose (escalation); in case of combination: the rationale for dose (escalation) of the drug combination with all available preclinical and clinical toxicity data • Risk management aspects of the trial design and an explanation on the guidance provided in the protocol for toxicity management • Explanation how continuous review of safety data by the sponsor is guaranteed • Overview of the potential benefit for patients (e.g., on the basis of the study rationale) • Integrated risk assessment paragraph summarizing the above at the endA separate risk-benefit evaluation is needed for each phase, arm and age group of the trial
Degree of burden (27.3%, *n* = 6)	Noncompliance with MPA § 40.4.4, which states that the degree of burden and the risk threshold to which a trial participant is subjected during the trial must be defined in the study protocol and measured constantly	Include statement that every investigator is obliged to **reduce pain and discomfort** for all trial subjects as much as it is reasonably possible Include that all examinations will be adapted to the age of the child Intensity, frequency, and type of required investigational procedures should be compared with standard of care If more investigational procedures compared to standard of care are necessary, explain reasoning
Specific measures in the pediatric population (22.7%, *n* = 5)	In order to comply with MPA §40.4 the following information should be added to the trial protocol: · Description of all measures in order to reduce pain and stress · Required blood volumes, taking into account the maximum limits for the individual blood draw and for a period of 4 weeks for specific age-groups · Estimation of the glomerular filtration rate using the appropriate formula · Adjustment of laboratory limits not expressed as a multiple deviation from standard values to the normal values in the different age groups	Possible measures to reduce pain and discomfort • Venipunctures should be reduced to minimum and a maximum number of attempts should be defined • The use of local anesthetics should be considered prior venipunctures • Routine examinations should be adapted to the age of the patient, e.g., sedation for imaging "Ethical considerations for clinical trials on medicinal products conducted with minors,"[27] which recommends: • Per individual, the research related blood loss (including any waste) as a general rule should not exceed 3% of the total blood volume over a period of 4 weeks, and should not exceed 1% at any single timeIt should be stated that the trial will only be opened at sites with profound pediatric expertise

Summary of "Risk-burden-benefit" subcategories and considerations to avoid the respective deficiencies. Percentage (%) indicates the relative contribution of each subcategory to the category "Risk-burden-benefit" and "*n*" the total number of deficiencies in this subcategory. Bold values represent issues or findings of key importance.
ICH, International Conference on Harmonization; IMP, Investigational Medical Product.

Table 7 "Study rationale" deficiencies

Category: Study rationale		
Subcategories	**Common deficiencies**	**Considerations to avoid respective deficiencies**
Inclusion of minors (57.1%, *n* = 8)	According to MPA §40.4.4 clinical trials on minors are only allowed if clinical trials performed on adults or other research methods cannot be expected to produce satisfactory test results according to medical knowledge • The trial rationale does not indicate why substantial differences in effect and tolerability between the application of the IMP in children or adults are to be expected; indeed, it is expected that sufficient results could be achieved on adults so that minors have to be excluded from the trial	In order to comply with **MPA §40.4.4** a comprehensive justification why the trial has to be performed on minors should be included in the trial protocol; relevant aspects are • Point out the insufficiency of data generated on adults by highlighting the biological differences between the pediatric and the adult malignancy[28] • Limited occurrence, e.g., embryonal tumors • IF there is a **PIP** for the respective IMP, assure that the trial protocol is in alignment with the PIP
	According to MPA §41.2.1.2b, the research must be absolutely necessary in order to confirm data obtained in clinical trials on other persons or by means of other research methods; • The IMP has not shown any antitumor activity in "x" in adults; provide rationale for the use of the IMP in pediatric "x" • As there is only insufficient clinical data on the efficacy of the IMP for the indication "x" available at the moment, the clinical trial is hence not absolutely necessary to confirm data obtained in other persons	In order to justify a clinical trial in minors, **safety and efficacy data** generated on adults has to be provided • If the data of the IMP for indication "x" in adults is insufficient, the rationale for use in the pediatric indication should be explained and supported by data
Justification of drug for drug combination (14.3%, *n* = 2)	No rationale for the combination of the two IMPs was provided	The combination of different IMPs should be supported by preclinical and clinical data regarding safety and efficacy
Other (28.6%, *n* = 4)	The trial protocol does not contain a justification for the use of a placebo	If a placebo is used, a rationale should be provided

Summary of "Study rationale" subcategories and considerations to avoid the respective deficiencies. Percentage (%) indicates the relative contribution of each subcategory to the category "Study rationale" and "*n*" the total number of deficiencies in this subcategory. Bold values represent issues or findings of key importance.
IMP, Investigational Medical Product; PIP, Paediatric Investigation Plan.

factor. In addition, other potential factors could also contribute to this observation: first, in Germany, the pediatric oncology healthcare system is less centralized in comparison with other countries and, thus, phase I/II trials requiring a dedicated infrastructure and competence are more difficult to implement. To overcome this, the GPOH has established five regional early phase-trial networks for pediatric oncology aimed to facilitate referral of patients, to enable a high-quality trial patient care nationwide, and to provide a central entry point for sponsors.[10] Second, the decentralized structure also interferes with the support and professionalization of parent representative organizations for pediatric oncology early phase clinical trials, whereas in countries with a more centralized healthcare system, they often have parent initiatives who provide strong support for innovative early phase clinical trials (e.g., Imagine for Margot in France and Kick Cancer in Belgium). This becomes especially clear if one compares the level of funding between the United States and Europe.[11] Third, the German health insurance companies are very generous in granting reimbursement for off-label treatment in comparison with other healthcare systems providing access to innovative medicine outside of clinical trials, thereby reducing the need to open early phase clinical trials.

This study is the first systematic analysis to identify key deficiencies in pediatric oncology early phase clinical trial protocols at regulatory submission. In our series, a significant proportion (6/17) of trial protocol submissions were either rejected or only accepted following major protocol modifications. Importantly, although the majority of deficiencies identified were classified as "minor" and relatively easy to implement into the submission documents, a smaller but important group classified as major and difficult to implement (8.4%) were identified, which can lead to rejection or withdrawal of the trial. This report identifies recurrent submission deficiencies and provides a guidance document (Supplementary information) on how to address these to support optimal protocol development for adherence to regulatory requirements. This is highly relevant for the planning and submission of future phase I/II pediatric oncology trials in Germany and possibly other countries to facilitate successful submission processes for academic and industry sponsors. In addition, many recommendations also apply for trials with systemic treatments in other pediatric diseases, especially concerning diseases with a limited survival prognosis.

Although we were only able to analyze about a third of all trials submitted to the BfArM during the time period of investigation (2014–2019), a cumulative, blinded data set of all trials submitted during this period was used to validate and confirm our findings and therefore we believe that the results presented here are representative. Unfortunately, no systematic analysis of deficiencies

identified by PEI was possible due to a low number of study documents available for this paper. The lower number of studies submitted to PEI is in accordance with the lower number of studies in pediatric oncology in the field of immune, cell, and gene therapy. The deficiencies detected by the ECs were mostly in regard to the patient-facing documents and could be solved by minor changes in wording or description of procedures. Therefore, we conclude that these deficiencies do not usually hinder trial approval.

Dullweber *et al*.[12] reported on regulatory challenges of pediatric trial protocols focusing on EC deficiencies across all pediatric subspecialties and trial phases in Germany. Although they found similar reoccurring deficiency areas (e.g., concerning Art. 40.4 MPA and contraception), the number of deficiencies reported in our study are much more diverse and detailed. This could possibly be due to broader and more systematic inclusion of competent authority reviews focusing on pediatric oncology and therefore a significantly higher number of investigated deficiencies. Due to the large amount of data, we were not only able to categorize the deficiencies into different subgroups and thereby highlighting common fields of deficiencies, but also to provide guidance to overcome these.

A comprehensive overview of the deficiencies can be found in the form of a guidance document as Supplementary information. The important group of major but difficult to implement deficiencies are especially problematic as they can lead to rejection or withdrawal of a trial if implementation of deficiencies is not feasible. One example is the need to provide additional nonclinical data from juvenile animal studies, which is not available, and which would take a long time period to generate, hence delaying any clinical trials in children. Avoiding these deficiencies plays a crucial role in increasing the number of pediatric oncology phase I/II trials in Germany. Potential hurdles for trial approval should therefore be addressed before submission and not only when the trial protocol is finalized, for example, in a kick-off-meeting at the BfArM, also involving parent/patient representatives, in order to find a suitable solution.[13] Many of the major deficiencies are due to nonadherence to relevant laws and their interpretation by the CAs. This applies in particular to Art. 40.4 MPA, which states that clinical trials in children should only be performed if "clinical trials performed on adults or other research methods cannot be expected to produce satisfactory test results according to medical knowledge" and as long as the trial participants suffer as "little burden and other foreseeable risks as possible."[8] This particular article is the basis for numerous identified deficiencies. It is therefore important to emphasize particularities about the nature and biology of pediatric cancers compared with adult tumors to underscore the necessity for a pediatric-specific trial protocol. Although these principles can also be found in other countries as well, German authorities apply a narrower interpretation and request more information, therefore setting the regulatory bar at a relatively high level and resulting in relatively low phase I/II trials in Germany. This is supported by our data, which demonstrates that trials not approved in Germany did get approval from other European CAs.

It will be interesting to see how the introduction of the European Regulation 536/2014 will impact on this. The launch of an associated new electronic EU-portal will provide more transparency regarding the approval process of different national Cas, including information on which countries did not give approval and the reasons why. However, in order to grant children across Europe the same access to innovative therapies, further harmonization of national regulations and assessment criteria are necessary as they currently pose a barrier and lead to delays in pediatric drug development.[11] The renewal of the regulation provides the perfect opportunity to improve interaction between national CAs and the EMA also in regard to PIPs in order to avoid that PIPs get approved by the EMA but not or only partially by the national CAs. Notably, the number early phase pediatric oncology trials is significantly higher in the United States compared with the European Union.[14] Discrepancies between national CA regulatory requirements are challenging for sponsors, many of which are located in the United States resulting in protocol development according to American regulations but frequently lacking specific aspects required in European protocols.[11] Therefore, a kick-off-meeting at a CA like the BfArM represents a very good opportunity to harmonize protocol development at an early stage.

Access to novel therapy is particularly important for pediatric patients with cancer eligible for phase I/II trials, because this patient population typically has exhausted standard therapy options to control their deadly disease. An intensified dialogue between the EMA and national CAs discussing the interpretation of the acceptable burden under the special circumstances of children with life-threatening diseases should be encouraged and could also lead to a less restrictive application of MPA §40.4. Many innovations in the adult cancer drug development have not been translated into pediatric early phase clinical trials yet and children should equally be offered a chance to benefit from new innovative trials in all countries.[10]

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTERESTS

C.M.v.T. participated in advisory boards of Novartis and Bayer. O.W. participated in advisory boards of Novartis, Janssen, BMS, Roche, Bayer, Astra Zeneca, and DayOne. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript and analyzed data. L.B., R.W., M.N.-B., C.M.v.T., and O.W. also performed research. L.B., C.M.v.T. and O.W. also designed the research.

1. Vassal, G. *et al*. Challenges for children and adolescents with cancer in Europe: the SIOP-Europe agenda. *Pediatric Blood Cancer* **61**, 1551–1557 (2014).
2. Siegel, R.L., Miller, K.D., & Jemal, A. Cancer statistics, 2018. *CA A Cancer J. Clinicians* **68**, 7-30 (2018).
3. Pandolfini, C. & Bonati, M. A literature review on off-label drug use in children. *Eur. J. Pediatrics* **164**, 552–558 (2005).
4. Paolucci, P., Jones, K.P., del Carmen Cano Garcinuno, M., Catapano, M., Iolascon, A. & Ceci, A. Challenges in prescribing drugs for children with cancer. *Lancet Oncol.* **9**, 176–183 (2008).
5. Conroy, S. *et al*. Survey of unlicensed and off label drug use in paediatric wards in European countries. *British Med. J.* **320**, 79–82 (2000).
6. https://www.itcc-consortium.org
7. https://www.itcc-consortium.org/our-structure.php
8. Federal Ministry of Justice and Consumer Protection. Medical Products Act. (2019).
9. https://www.gpoh.de/fachgremien-arbeitsfelder/klinische-studien/
10. Nesper-Brock, M. *et al*. Molekulare tumortherapie: Phase-I/II-netzwerkstruktur der gesellschaft für pädiatrische onkologie und hämatologie. *Der Onkologe* **27**(5), 447–457 (2021).
11. Vassal, G. *et al*. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. *Eur. J. Cancer* **51**, 218–224 (2015).
12. Dullweber, F., Riedel, A. & Böhler, S. Genehmigungsanträge für pädiatrische klinische Studien. *Monatsschrift Kinderheilkunde* **160**, 662–668 (2012).
13. Rei Bolislis, W. *et al*. Optimizing pediatric medicine developments in the European union through pragmatic approaches. *Clin. Pharmacol. Ther.* **110**, 871–879 (2021).
14. European Medicines Agency (EMA).10-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation (2016).
15. CTFG. Recommendations related to contraception and pregnancy testing in clinical trials, Version 1.1. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf
16. European Commission. Communication from the Commission - Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use. (2011).
17. European Parliament. Directive 2001/20/EC of the European Parliament and of the Council. (2001).
18. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events Version 5.0. (2017).
19. International Conference on Harmonization Guideline (ICH).Validation of analytical procedures: text and methodology. *Q2 (R1)* **1**, 5 (2005).
20. International Conference on Harmonization (ICH) Guideline. Q3A (R2), Impurities in New Drug Substances. ICH Steering Committee (2006).
21. European Commission. EU Guideline to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use: Annex 13. (2010).
22. Deutsche Gesellschaft für Pädiatrische Kardiologie und Angeborene Herzfehler e.V. Tachykarde Herzrhythmusstörungen im Kindes, Jugend- und jungen Erwachsenenalter. AWMF-Register Nr. 023/022. (2018).
23. Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for use in humans (GCP Ordinance - GCP-V)*. (ed. Federal Ministry of Health and Social Security, Federal Ministry of Economics and Labour) 6 (2004).
24. European Parliament and Council. Regulation (EU) No 536/2014 on medicinal products of human use, and repealing Directive 2001/20/EC (2014).
25. Committee for Human Medicinal Products. Guideline for good clinical practive E6 (R2). (2016).
26. EMA. Guideline on Data Monitoring Committees. (2005).
27. European Union. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. *Eur. J. Health Law* **15**, 223–250 (2008).
28. Gröbner, S.N. *et al*. The landscape of genomic alterations across childhood cancers. *Nature* **555**, 321–327 (2018).