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Deficiencies in paediatric research applications delaying ethics committee approval

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Summary

BACKGROUND: A clinical research application must be submitted for approval by a competent ethics committee (EC) before a study can be executed. There is very limited information on how such submissions could be optimised, especially regarding research in children and adolescents, which requires particular caution and age-adapted patient information.

METHODS: We assessed all research applications from the University Children's Hospital Zurich submitted to the EC of the Canton of Zurich in 2014–2015, i.e., in the first two years after Switzerland's new Human Research Act came into effect. Moreover, we validated our findings by assessing a randomly selected sample of applications from the same hospital in 2018–2019.

RESULTS: We assessed a total of 86 applications from 2014–2015, originating from 29 departments and sub-specialties. The EC judged that it was not responsible for three applications and declined an assessment for another three because the studies had already been conducted. Thus, we included 80 applications in the present analysis (18 clinical trials, 52 research projects, 10 further use projects). Applicants withdrew four applications before the EC's final decision and the EC rejected two after assessment. The EC had objections in 46 (62%) of the remaining 74 applications. Formal, including formal legal, objections (n = 503) and legal objections (n = 287) accounted for the vast majority of objections. There were also 71 ethical and 82 scientific objections. The most frequent formal and formal legal objections were incomplete or missing age-adapted patient information (49%) and incorrect templates for informed consent and signature forms (46%). A review of the 20 randomly selected applications from 2018–2019 confirmed that four out of the five most frequent deficiencies relating to informed consent were identical to those observed in the 2014–2015 applications.

CONCLUSIONS: Careful preparation of submission documents by the investigators and close adherence to formal and legal requirements have the potential to considerably optimise and expedite the EC review process, and thus the commencement of the clinical research.

Keywords: *age-adapted patient information, formal deficiencies, legal deficiencies, ethical deficiencies, scientific deficiencies*

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Introduction

Ethical approval of a clinical research study is essential before it can start [1], and the legal requirements for such approval may differ between countries [2]. In Switzerland, research in humans is regulated at the national level by the Human Research Act (HRA) and three associated ordinances, which came into effect on 1 January 2014 [3]. Legal requirements for clinical studies with pharmaceuticals and medical devices were for the most part transferred from the Therapeutic Products Act (TPA) to the HRA and its ordinances. The new law generated changes for investigators and ethics committees (ECs). The Swiss HRA differentiates between clinical trials, which evaluate an intervention and are regulated by the Ordinance on Clinical Trials (ClinO) [4], and research projects, i.e., the collection of health-related personal data and the sampling of biological material, which are regulated by the Ordinance on Human Research, also called the Human Research Ordinance (HRO) [5]. The HRO also regulates the further use of existing data and biological material for research purposes. Hence, the HRA regulates various kinds of research in humans. Since the HRA uses a risk-based approach, clinical research is segregated into risk categories, with gradated requirements for authorisation, monitoring and reporting.

The preparation of applications for EC approval is thus demanding due to the legal requirements, and enthusiastic investigators tend to underestimate the administrative and legal duties associated with research in humans. Therefore, a cumbersome submission of a planned clinical study for EC approval may delay or, in the worst case, in prevent the commencement of the research. Writing applications for clinical research in paediatrics is even more demanding, since the vulnerability of children and their age-adapted information must be considered [6].

The primary aim of this study was to identify the most common objections to paediatric applications made by the EC of the Canton of Zurich in the first two years after the new HRA came into effect. Our results will provide guidance to investigators on optimising future paediatric research applications.

Materials and methods

We reviewed all research applications submitted from the University Children's Hospital Zurich to the EC of the Canton of Zurich in 2014–2015. We extracted relevant data from the EC's electronic database Evidence® on the basis of pre-defined categories. These included the medical discipline of origin, the nature of the research and the potential objections by the EC, segregated into formal (including formal legal), legal, ethical and scientific items (total 41). Two authors (HÖ; EB) reviewed the ECs' responses in a first step, and all the authors discussed and verified the responses in a second step.

In order to evaluate the validity of our findings, we assessed a sample of 20 randomly selected paediatric research applications from 2018–2019. We extracted the data from the electronic submission platform Business Administration System for Ethics Committees (BASEC), which has been used by all ECs in Switzerland as an information and management system since 2016. Initially, one author (PK) reviewed the applications from 2018–2019 using the above procedure. Then two other authors (EB and DN) verified the EC's responses.

Cooperation between the University Children's Hospital Zurich and the EC of the Canton Zurich was agreed in writing. Data extraction took place in the offices of the EC. Confidential handling of the data was assured throughout. The management of the University Children's Hospital consented in writing to the reviewing of all applications.

The present study required no ethics committee approval.

Results

A total of 86 research applications from 29 departments and sub-specialties from the University Children's Hospital, Zurich were submitted during the 2-year period 2014–2015. The EC declined an assessment for three of these applications, as the studies had already been conducted, and judged that it was not responsible for three other applications. Thus, we included 80 applications in this analysis: 18 clinical trials, 52 research projects and 10 further use projects. The majority of applications were monocentric (n = 58; 72.5%); the EC Zurich was the leading committee in 12 of the 22 multicentre trials (10 clinical trials, 10 research projects and 2 further use projects).

Applicants withdrew four applications before the EC's final decision and the EC rejected two after assessment. The EC had objections in 46 (62%) of the remaining 74 applications. The EC requested a second assessment for seven (9.2%) applications, three of which were eventually rejected, and a third assessment for one application.

Table 1 lists the most frequent formal (including formal legal), legal, ethical and scientific/medical objections made by the EC to the 74 applications used for analysis. "Formal" objections addressed deficiencies in the form of the application and included the lack of a signature, omissions in the list of co-workers, linguistic weaknesses and missing documents. "Formal legal" objections addressed deficiencies related to the letter of the law and included, e.g., faults in the process of encryption and anonymisation of data. "Scientific/medical" objections included aspects surrounding the research question, such as the inclusion and exclusion criteria or the description of the study population. The vast majority of objections were formal and legal ones.

Table 2 presents the frequencies with which modifications regarding parent/patient information or informed consent were requested by the EC in all 74 applications. Objections regarding parent/patient information were the most frequent, followed by objections regarding the consent form. Almost half the applications provided incomplete or no age-adapted patient information, and in 45% of applications, information about the anonymisation of the data generated and the destruction of biological material once the study was completed, including for those who withdrew from the study prematurely, was either not given or was incorrect.

Table 1: Objections regarding formal and formal legal deficiencies and ethical, legal or scientific requirements in the 74 submissions analysed.

Objections (total n)	Description of the most frequent objections
Formal and formal legal deficiencies (n = 503)	Confusion of encryption and anonymisation
	Addressing minors or parents incorrectly on the information sheet
	Unclear specification of different age groups
	Wrong use of terms when custodian, guardian or legal representative is meant
	Use of overly technical language not understandable by laypersons in the information sheet
Non-fulfilment of ethical requirements (n = 71)	Freedom of choice as to whether or not a research subject wants to be informed about incidental findings missing
	Inadequate reflection period between informing about a research project and seeking written consent
	Insufficient information about study procedures and what is expected of the research subjects
	Benefit-risk relationship too positive or potential risks underestimated in the informed consent form
	Preselection of research subjects by a person not authorised to access medical record without having obtained informed consent
Non-fulfilment of legal requirements (n = 287)	Insufficient description in the protocol of data encryption or anonymisation processes, storage of the code and data access rights
	No consideration of adolescents' right to legally consent in research with only minimal risks
	Non-separation of consent to a specific research project and consent to the further use of data/samples in future research projects
	Documentation of identifying information in the case record forms, e.g. full date of birth
	Deficient or unclear instructions with respect to contraception
Non-fulfilment of general scientific requirements (n = 82)	No specification of inclusion/exclusion criteria
	Lack of medically relevant exclusion criteria
	Lack of declaration of the radiation dose in projects with radiological examinations

Apart from shortcomings concerning informed consent, the two most frequent *ethical objections* were information about study intervention and handling of/information about unexpected findings. The most frequent *legal objections* requiring revision concerned data protection, data retention and procedure in the case of consent revocation. Objections concerning further use of data beyond the study, instructions about contraception in applications for clinical trials, involvement of children/adolescents capable of judgement and anonymisation in research projects were less frequent. The most frequent *medical or scientific objections* were related to the risks or description of the proposed intervention, the description of the study population, and follow-up intervention. In applications for research projects, the most frequent *medical or scientific objections* were inclusion/exclusion criteria, description of study population, risks of the intervention and description of the intervention.

The 20 paediatric applications from 2018–2019 that were selected randomly to validate the data from 2014–2015 showed a proportional distribution of application types (eight further use projects; seven projects involving persons; five clinical studies) comparable to those from 2014–2015. The analysis of the 2018–2019 applications revealed that the most common deficiencies concerned the data encryption or anonymisation process, the storage of the code and the data access rights, as observed in the analysis of the 2014–2015 applications. Furthermore, four out of the five most frequent deficiencies with respect to informed consent had already been observed in the analysis of the 2014–2015 applications (table 3 and data not shown).

Discussion

Our analysis reveals that the EC eventually approved the vast majority of applications, but that more than one in two submissions were returned to the applicants for modification with multiple objections, mostly of a formal, formal legal or legal nature. Thus, careful preparation of the submission documents by the investigators has the potential to considerably expedite final approval by the EC and the commencement of the clinical research.

An important observation here is that the overwhelming majority of the objections raised by the EC were of a formal or formal legal nature and due to the legal requirements not being fulfilled. This implies that many of the EC's objections could be prevented by the investigators considering the formal issues and legal requirements more carefully. Considering legal requirements such as data protection, retention or further use, for which clear acts or rules exist, requires less effort than considering issues such

Table 2: Frequencies of modifications requested by the ethics committee regarding parent/patient information or the consent form from a total of 74 submissions.

	n (%)
Parent/patient information (PI)	
Age-adapted patient information incomplete or missing	36 (49)
Information about anonymisation of data generated and destruction of biological material once the study was completed, including for those who withdraw from the study prematurely, not given or wrong	33 (45)
Insufficient/misleading (scientific, organisational) information	24 (32)
Inapt information on who decides about communication of unexpected results	9 (12)
No information about right of patients/parents to withdraw from study at any time	8 (11)
No information about right of patients/parents to be informed at any time	6 (8)
Missing information about costs	5 (7)
Superfluous information	4 (5)
Phone number/e-mail address of medical contact person not provided	3 (4)
Stationery on form incorrect	3 (4)
Informed consent (IC) – signature form	
Template form for parents/paediatric patients not correctly adapted or wrong example form used	33 (45)
Version of patient/parent information used not stated or incorrect	13 (18)
Paragraph regarding information about unexpected results incorrect	7 (9)
Missing example of general consent	3 (4)
Stationary on form incorrect	3 (4)
Missing statement about version of signature form	2 (3)

Table 3: Most frequent overall deficiencies or deficiencies with respect to informed consent in 20 randomly selected submissions from 2018–2019 in descending order.

Deficiencies	Specification
Overall	**Deficiencies in the data encryption or anonymisation process, storage of the code and data access rights**
	Protocol not signed by all parties or study sites
	Unclear status of informed consent to further use of data or samples for research purposes
	Statement that legal requirements in CH are respected missing or incomplete (primarily international projects)
	Deficiencies with respect to handling of data/samples after withdrawal of consent
With respect to informed consent	**Use of overly technical language not well understood by laypersons in the information sheet**
	Benefit-risk relationship too positive or potential risks underestimated in the informed consent form
	Freedom of choice as to whether a research subject wants to be informed about incidental findings or not missing
	Deficiencies in the information sheet with respect to data protection rights
	Non-separation of consent to a specific research project and consent to the further use of data/samples in future research projects

Bold text = deficiencies that were also frequently observed in 2014 and 2015

as patient information and informed consent, which may need meticulous phrasing and editing. These latter are especially challenging in paediatric studies as they require additional, age-adapted patient information or informed consent. Nevertheless, addressing patients and volunteers with linguistic correctness independently of their age, as well as communicating clearly with them, are important prerequisites for successful recruitment to and enhanced compliance during a study. A subsequent analysis of randomly selected applications from four years later revealed that formal (including formal legal) or legal deficiencies similar or identical to those observed in 2014–2015 were still among the most frequent objections. Importantly, the application samples from 2014–2015 and 2018–2019 are broadly comparable. Therefore, time invested in preparing study documents for ECs will pay dividends by allowing a clinical study to be executed more quickly.

A motivating factor for investigators is our observation that the EC rejected only a very small proportion of submissions. Few investigations have so far addressed the performance of ECs, and research is needed to understand how ECs accomplish their objectives, what issues they consider important, the quality of the EC review process, and how effective ECs are at protecting human research participants [7–11]. Nevertheless, here the EC very rarely opposed the execution of a study. In contrast, the EC review process most often resulted in objections regarding formal and formal legal issues only, of which age-adapted patient information and issues related to informed consent were by far the most frequent. Linguistic improvements to informed consent, however, have been a matter of debate, as they may reduce patient enrolment but not increase patients' understanding [12]. It is of note that the EC did not here raise fundamental ethical questions relating to the context of paediatric research, particularly participants' safety. The criticisms voiced do not mirror poor design or ill formulation by the investigators, but rather alert them to inconsistencies. Investigators are in most cases more proficient in their specific research topics than EC members.

Our study has limitations as a retrospective study at just one University Children's Hospital and the single corresponding competent EC. The latter might be a more important limitation, as ECs may differ in their judgment. This may impact on the formal and medical/scientific issues, but is unlikely to affect the legal issues and is even less likely to affect the ethical issues. Thus, our results can be generalised with respect to legal and ethical issues.

Improved, more careful preparation of submission documents, thereby respecting well-defined legal issues, and editing texts with the support of Clinical Trial Units may substantially help investigators to optimise and expedite their clinical research and thus benefit patients. Notably, swissethics, the umbrella organisation of all seven research ethics committees in Switzerland, has generated templates for all types of clinical research (www.swissethics.ch/templates.html). This reflects an acknowledgment of the most frequent objections issued by the ECs and aims to support clinical investigators. From a more general point of view, the help of patients' and parents' organisations should be sought whilst engineering a research project and phrasing the patient information.

Disclosure statement

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