THIS IS PART 1 OF A 2-PART ARTICLE. PLEASE SEE THE JUNE 2017 ISSUE OF PEDIATRICS FOR PART 2.

Ethical Conduct of Research in Children: Pediatricians and Their IRB (Part 1 of 2)

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As human experimentation continues to grow into an ever more complex and sophisticated endeavor, the relevant ethical and regulatory structures become more intricate. When pediatricians and general practitioners are invited by pharmaceutical companies to enroll their offices in a clinical trial or a multicenter observational study or when they develop their own research questions, they frequently find themselves at a loss in the human research environment. The legal and regulatory complexity may have an unintended deterring effect at a time when office-based high quality pediatric research is urgently needed to support evidence-based medicine. Unfortunately, in many instances, unaware practitioners become involved in low-risk research activities without knowing it and become entangled in legal, auditing, and compliance procedures. This paper, written in 2 parts, aims at providing a general guidance on the principles that regulate human research with a focus on pediatrics. Part 1 discusses the history, the legal framework, and the consent process and highlights some practical aspects of initial protocol submission, continued review, and institutional review board determinations with the main focus on multicenter clinical trials (industry-sponsored research). Part 2 focuses on pediatric research regulation, also known as subpart-D, and minimal risk research, which encompasses many research activities aimed at addressing questions that may emerge in pediatricians' practices (investigator-initiated research).

HISTORY AND GENERAL PRINCIPLES

On December 9, 1946, a historical event that was to define the course and nature of permissible human research took place at the Nuremberg Palace of Justice, Room 600. It was part of the so called "follow-up trials," conducted by a military tribunal constituted by the victorious United States and Allied Forces at the end of the Second World War. In his opening statement, Brigadier General Telford Taylor, chief counsel for the prosecution, enumerated the crimes and formulated the charges for the 23 defendants (20 of them doctors), initiating what would become known as "The Doctors' Trial."[1,2] The crimes included subjecting Jews and others imprisoned in Nazi death camps to experiments involving exposure to simulated high altitudes, freezing, malaria, and mustard gas; the Ravensbrueck experiments on sulfanilamide, muscle and nerve regeneration, and bone transplantation; the sea water, epidemic jaundice, typhus, poison and incendiary bomb experiments; and the creation of the Jewish skeleton collection. Referring to the defendants, Taylor declared: "...They are not ignorant men. Most of them are trained physicians and some of them are distinguished scientists. Yet

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these defendants, all of whom were fully able to comprehend the nature of their acts, and most of them were exceptionally qualified to form a moral and professional judgment in this respect, are responsible for wholesale murder and unspeakable cruel tortures…"[1]

The ensuing indictment, framed in 4 counts, was delivered on August 20, 1947. Fifteen of the 23 defendants were found guilty and sentenced to death by hanging. The indictment contained a list of conditions required for the conduction of "permissible human experiments," which would come to be known as the Nuremberg Code,[2] a list of 10 principles with 2 of them explicitly dealing with the obligation to obtain and maintain consent. The document remains the cornerstone of ethical human research and it is a template for all consent forms. I hope this article will help readers alter their view of clinical research as a burdensome process of countless pushbacks, stipulations, deferrals, and revisions emanating from offices known as institutional review boards (IRBs) or research ethics committees. IRBs have the difficult task of advancing knowledge while guarding individuals' rights, a task even harder in pediatric research, where self-determination is exercised by proxy (parents and guardians).

Between 1932 and 1972 the US Public Health Service (PHS) studied the natural history of untreated syphilis in ~300 indigent African American sharecroppers residing in Macon County, Alabama. The study was headquartered in Tuskegee, AL, hence, this infamous study came to be known as the Tuskegee Study. Penicillin became available in the 1940s. Soon after, it was known to be effective for syphilis. Treatment was not offered to the research subjects, who were misled into believing that the multiple examinations, including regular spinal taps, were performed to their benefit. The Public Health Service stopped the study in 1972, 25 years after the Nuremberg code was drafted, and 8 years after the first version of the declaration of Helsinki by the World Medical Association.[3] It took an additional 25 years for the US government, represented at the time by President Bill Clinton, to produce a formal apology to the survivors and the families of the deceased.

The Tuskegee scandal profoundly influenced the drafters of the 1978 Belmont Report, named after the meeting room where the proceedings took place.[4] This document was the final work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, created by the National Research Act of 1974, after hearings led by Senator Edward Kennedy in 1973. The report enumerates the 3 ethical principles under which human research ought to be conducted: (1) respect for persons (also known as autonomy or self-determination), (2) beneficence, and (3) justice. These 3 principles are not unique to biomedical research; they draw from entire philosophical systems and schools of ethics' developed over the last 2 centuries. Respect for persons is self-explanatory; humans cannot be treated as means, only as ends. This notion was championed by the German enlightenment philosopher Immanuel Kant, who in the second formulation of his categorical imperative devised the image of humanity as a "Kingdom of Ends." This principle constitutes the foundation of the consent process, which must be differentiated from the *c*onsent document itself. "Process" implies that consent should be conducted under adequate conditions by providing sufficient time and an appropriate environment, and by enabling an exchange of questions and the assessment of comprehension by the person obtaining consent. Consent should be by trained professionals familiar with the research protocol and the ethical principles of human experimentation.

Justice always entails the notion of equality. It informs research project designers, trialists, funding institutions, and IRBs, who should neither target nor exclude minorities, genders, or social classes from either participating in or benefitting from clinical research without scientific justification (eg, because a disease affects only 1 sex). Incentives to industry to fund pediatric clinical trials and rules requiring an explicit justification when women are not eligible for a study are applications of the justice principle. Research studies must be widely inclusive when it comes to participant selection. Making an experimental drug available at the end of a trial to participants who benefited from it are other ways of honoring the principle of justice. On the contrary, targeting poor countries, disadvantaged communities, inmates, or institutionalized patients just for convenience or perceived acquiescence are forms of violating this principle.

There can be justifiable modifications of the justice principle. For example, it may be justifiable to conduct trials in a poor country to establish less costly or complex therapeutic regimens that may be more locally appropriate. Jeremy Bentham enunciated the utilitarian principle of the "greatest happiness for the greatest numbers," but his disciple, the British liberal thinker John Stuart Mill, created the philosophical school known as utilitarianism. Utilitarianism informs public policy to assign and prioritize distribution of limited resources. IRBs use utilitarianism to balance decisions when confronted with the fact that complete equity is not always attainable.

Finally, there is beneficence, the most respected of the notions guiding IRBs, the principle that

makes IRBs the proxy for those protected by its mandate. No harm can be intentionally inflicted (nonmalificence) to research subjects ever. Risk of harm can be acceptable if it is balanced by the prospect of direct benefit (beneficence), or in adult research by honoring individual altruism.

These principles are not abstractions. They can collide with each other and can be taken to harmful extremes; beneficence can become paternalism, overprotection, and mission creep. Justice can be radicalized to a point that no research protocol would ever be approved, blocking important beneficial research, and autonomy can allow for a laissez-faire approach, whereby the consent document becomes a legalistic contract and the signature of the participant a virtual authorization to accept any risk. IRBs deal with these tensions every day.

The IRB's mission is clear; researchers working with human subjects are not blind to context. As bombs fell over hospitals in war torn places indiscriminately maiming and killing children, pediatricians need not to see photographs to know that children's special status as a vulnerable population is far from being respected. Protecting research participants can seem a small drop in a sea of injustice and abuse. As physicians, we find ourselves tending to the small bruise or the ear infection, while elsewhere thousands of children die of preventable diseases, dehydration, or just plain murder. That is the trick with ethics, a visceral emotion modulated by attention to facts and data. Every protocol, consent, or adverse event is considered by using the same set of 3 principles and is subject to the laws emanating from them.

The following more recent examples show why independent oversight of research activities continues to be necessary. Scientific curiosity and the sense of "mission" among scientific pioneers and research leaders are required traits, yet human research requires oversight to avert wrongs.

Investigators at the Willowbrook State School, a facility for children with intellectual disability in New York, conducted an experiment on infectious hepatitis between 1955 and 1970. This study involved intentional infection of children by feeding them a solution of feces of infected children. Newly admitted children were infected to test the efficacy of the previous injection of antibodies hypothesized to be protective. The investigators soon noted that there are 2 strains of hepatitis of different oral transmissibility, and labeled them hepatitis A and B. This study was approved by the New York University School of Medicine, the New York State Department of Hygiene, and the New York State Department of Public Health. Infection rates were as high as 80%, making the additional risk of experimental transmission numerically less significant; the fact that doctors infected healthy children for the purpose of gaining scientific information would be unthinkable now. The parental consent document lacked any detailed enumeration of risks. In addition, the study involved undue inducement because the infected children were admitted to a new facility that was better staffed and better equipped. The main investigator, Dr S. Krugman presented his findings at the American Academy of Pediatrics spring meeting. *Pediatrics* published the results in 1958.[5] Reading the paper is educational; the Methods section describes the procedure for titration of the concentration of infective material required to induce hepatitis.

As recently as 1999, we were confronted with a scenario that also disturbs our moral compass and illustrates not only the limits of the current consent process, but also the need for continual vigilant oversight of human research activities. This incident, still fresh in our collective memory, took place at one of the world's most prestigious institutions, the University of Pennsylvania. Jesse Gelsinger who suffered from partial ornithine transcarbamylase deficiency volunteered to participate in a gene therapy experiment that would have benefited others with more severe disease. In this study, the OTC gene was incorporated into an attenuated adenovirus vector, which was injected in the hepatic artery of research volunteers. The research team understated the risks in the consent form by not considering the death of primates in preclinical experiments or serious related adverse events observed in previous human recipients (Jesse was participant 19 of the third cohort of patients). No doubt the consent process was not as flagrantly flawed as in Willowbrook, but the difference is in magnitude, not in essence. Not only were the adverse events not captured within the risk section of the consent form, but those events were reported neither to the Food and Drug Administration (FDA) nor the IRB when they occurred, as mandated by the protocol. It is plausible that such reporting would have led to a hold of the study. Jesse died of an unusual inflammatory response to the vector with multiple organ failure just 4 days after the infusion.[6–8]

A FEW HIGHLIGHTS ON THE WORLD OF DRUG DEVELOPMENT AND CLINICAL TRIALS

In this article, I focus on research conducted in the United States, but similar principles and rules apply in other countries. Investigators are urged to familiarize themselves with their local laws, rules, and customs. The process of drug development typically involves a preclinical and a clinical phase. During the preclinical phase, researchers test potential compounds or biologic agents for efficacy and safety

using in vitro, ex vivo, or animal experiments. At the end of that process, the investigators apply to the FDA for an investigational new drug designation. Negotiations and exchanges between the FDA and the drug developer ensue, culminating in a proposed research plan for human experimentation that constitutes the clinical phase. This phase involves 4 additional phases (I to IV). A phase I study can involve normal healthy volunteers or patients suffering from a significant disease when the drug being tested is known to be toxic (eg, a new cancer chemotherapeutic agent). A phase I study is meant to generate basic safety and pharmacokinetic data. It is not designed to test efficacy, but may offer some early sense of efficacy. These types of studies also involve dose escalations in sequential cohorts to identify a maximum tolerable dose as well as the study of the pharmacodynamics of the medication. Agents that yield reasonable safety and pharmacokinetic data can progress to a phase II study. In phase II, a small group of patients suffering from the disease in question is tested for a preliminary sense of efficacy, with additional testing for safety, pharmacokinetics, and pharmacodynamics. This phase commonly has a dose seeking component with ≥2 administration schemes and is typically placebo controlled. Phase II studies can be multicenter or single center, depending on the rarity of the disease and the complexity of the required testing. Agents that are successful in a phase II study can progress to a phase III trial, which is usually a large multicenter effort conducted to test efficacy, to enable licensing the new drug; they are also known as pivotal trials. Phase III studies declare in advance a primary end point or set of end points to be met by study results. Phase IV studies are postapproval studies that can take the form of an extension trial, whereby data on efficacy, but mainly on safety, continue to be collected sometimes for many years. The drug is usually not provided by the drug company, but other study costs may be covered. In its approval decision, the FDA sometimes mandates phase IV trials. The FDA relies on such studies as a valuable tool to detect unforeseen safety signals when the drug becomes available and large populations are exposed to it.

In a clinical trial, study methods are described in detail in a protocol, typically devised by the drug sponsor, usually a pharmaceutical company although sometimes it will be an individual researcher (sponsor-investigator) or a device manufacturer, with input from the FDA. Local investigators receive an investigator brochure, which contains additional preclinical and early phase clinical information not usually included in the protocol. There is also a manual of operating procedures. The investigator should study these documents carefully. The sponsor is responsible for rapidly reporting serious unforeseen adverse events and providing a thorough review of the progress of the study to FDA at least annually. The sponsor oversees the conduct of the study at the research sites. This oversight is conducted by specially trained individuals known as monitors, who initially conduct a site preactivation visit to review credentials and inspect facilities and perform follow-up visits to review research records. Sponsors can conduct the study directly or contract with third party organizations known as clinical research organizations. For the individual site, there is only 1 person ultimately responsible for the conduct of the study: the site principal investigator (PI) who supervises coordinators, coinvestigators, study nurses, research pharmacists, and laboratory technicians. The site investigator signs a contract with the sponsor that states responsibilities, payment for time and effort, study budget agreements, publication rules, and management of proprietary information. These contracts usually fall within the purview of the office for sponsored research in institutions and universities, but this author strongly recommends future investigators to get directly involved in this phase. Individual investigators should be very involved when the candidate site is the private office. Investigators should carefully consider the terms of any contract with a sponsor and how that contract may affect their own ethical principles (eg, limits on publication).

An underresourced study is a recipe for failure. The time to negotiate for adequate resources is before signing a study agreement. Remember the site PI is ultimately and only responsible for the conduct of the study. Be accurate and realistic when invited to respond to a feasibility questionnaire. Think about your time availability and patient population when you estimate your recruiting capacity and make sure funding is sufficient. Studies can look easy, but are often not. Performing objective feasibility analysis of your site is crucial; take your time and think. Recall that you are not only responsible to your patients, the sponsor, your institution, and its IRB, but also directly to the FDA. As a local investigator you will be signing a form known as form 1572, which lists a series of commitments you make when you agree to become the local PI.[9] The FDA can conduct audits at your site either randomly or for cause, so be prepared and make sure your site is well resourced in both facilities (laboratory, phlebotomy, pharmacy, storage) and personnel. One crucial member of the team is the study coordinator; make sure there is adequate funding for a well-trained and experienced individual with adequate time to dedicate to the trial.

Other entities help oversee Phase III studies, notably the Data and Safety Monitoring Board or Committee (DSMB or DMC). This is an independent board constituted by experts in the field as well as biostatisticians who are met with periodically to examine data collected in the study. DSMBs can recommend protocol amendments or continuation, interruption, or conclusion of a study. A recommendation to end a study could result from safety concerns or to avoid a futile study when an end point has been met or it is anticipated will not be met.

IRB CONSTITUTION AND OPERATIONS: IMPLEMENTING THE PRINCIPLES

On August 19, 1991, Title 45 CFR 46 became the effective law that regulates human research in the United States. Initially covering research funded by the US Department of Health and Human Services, it was eventually adopted by all funding federal agencies and hence came to be known as the Common Rule. An almost identical law (Title 21, Part 56) was enacted to regulate research under FDA jurisdiction. The FDA regulates research related to drugs, biologics, or medical devices. Clinical trials therefore have to comply with both laws, Title 45 CFR 46 and Title 21 CFR 56. Both laws define and rely strongly on the IRB as the foundation for research oversight and defined its composition, jurisdiction, and obligations.[10,11]

The Common Rule defines research as a systematic investigation, including research development, testing, and evaluation designed to develop or contribute to generalizable knowledge. A human subject means a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. This definition helps us explain why the IRB may not claim jurisdiction on individual case reports (not systematic) or on quality improvement projects (not intended to contribute generalizable knowledge). The Common Rule definition of human subject as a living human being or his/her private information explains why IRBs are involved in research performed on medical records or existing samples, but not on research on the deceased, or on samples collected for other purposes that have been stripped of identifying information, such as samples of blood discarded by a clinical laboratory that are no longer linked to patients. Research on such samples can be considered "not human subjects research," but most institutions require that an IRB make that determination after a specific request by the investigator planning to use such samples in research.

A third important piece of legislation for IRB operations is the Health Insurance Portability and Accountability Act, better known as HIPAA, which contains a section devoted to the protection of research participants' privacy.[12] HIPAA is relevant to all research activities involving the collection or disclosure of private health information, defined as private by being linked to any of 18 listed identifiers. HIPAA governs the protection of research databases and sample repositories used in research and the rules of disclosure of data to sponsors. HIPAA extends its protection to the deceased, and IRBs usually function as the HIPAA-mandated institutional privacy board. The language dealing with protections to research participant's privacy as regulated by HIPAA usually populates the sections on privacy and confidentiality included in consent forms.[12,13]

The Common Rule and FDA Title 21 require that IRBs be independent bodies and include at least 5 members, including a nonscientific and an unaffiliated member. IRBs maintain diverse memberships by fostering gender, ethnicity, racial, and educational background diversity. The decisions of IRBs are informed mainly by ethics, but also science. Additional expertise may be obtained from consultants within or without the institution. Pediatric membership is required from those IRBs that regularly review pediatric research. IRBs consult the literature, and can contact investigators for clarifications. IRBs can (but rarely do) contact other IRBs in multicenter studies or require investigators to do so. IRBs need to see the final determination and communications with the DMCs or DSMBs. Similarly, IRBs may request clarifications or changes from the sponsor. The investigator typically serves as the link between IRBs, DSMBs, and sponsors. IRBs communicate directly with the FDA when necessary. Some friction points between IRBs and sponsors can include language of the consent document (sponsors may understate or overstate the potential benefit or risk, include exculpatory language, limit liability on costs, or provide language that appears too legalistic), availability of experimental product posttrial, safety-related tests, or volume of blood sampling for research testing. Pharmaceutical and device manufacturing companies sponsoring research may lack expertise in pediatrics and may be unaware of the nuances associated with approvability of research in children.

IRBs are registered with the federal government under a Federalwide Assurance, whereby IRBs assure the federal government represented by the Office of Human Research Protection that human research is being performed in compliance with the existing federal regulations and provide an updated roster of members and officials. It should be noted that a supplemental body of institutional policy and

procedures is a basic requirement for research institutions and that protections under those policies can be more (but not less) stringent than protections granted by the law. The Federalwide Assurance provides the option to grant an equal level of protection to federally funded and non–federally funded research, because the Common Rule strictly speaking applies only to federally funded research. Specific oversight responsibilities for federally versus non–federally funded research can vary from institution to institution. IRBs can also subject themselves to a rigorous review system that provides certification. Credentialing provided by Association for the Accreditation of Human Research Protection Programs is one of the most comprehensive and is used by institutions worldwide. The most recent tally as of July 2016 puts the total number of accredited institutions at 231, of which 35 are outside the United States.

IRB JURISDICTION: WHAT NEEDS TO BE SUBMITTED?

Policies vary among institutions, but if there is a question about the need to submit to the IRB consider that the definition of research is quite wide and any systematic activity involving living humans or their data with the intent of producing generalizable knowledge is research and needs review. If it is not clear, it is better to consult first. Quality improvement projects are sometimes hard to distinguish from research. Most IRBs offer a determination of nonresearch activity and have written procedures on how to obtain such determination. Similarly, single case reports typically do not require IRB review. Yet, they must comply with HIPAA, so no identifiers in your published reports are permitted. Consult with your IRB; recall that institutions can have policies that provide higher level of protections than that required by the Common Rule. There are research activities that are considered exempt, and the Common Rule provides 6 specific exempt categories.[1] Typically, the determination of exempt research is done by the IRB. In practical terms, what that means is that no additional oversight is required; therefore, no continued review is needed. Remember that a determination of exemption is only valid for the protocol as submitted. If you amend the study, you will need to submit to your IRB to reconfirm your exempt status.

IRB OPERATIONS: SOME HIGHLIGHTS ON APPROVAL BY CONVENED MEETING

Unless the study meets 1 of the 9 criteria for expedited review (review not involving the full convened IRB meeting) listed in the Common Rule,[1] the review of the study has to wait for a full committee meeting with the corresponding quorum (50% + 1 of the members). An institution cannot supersede disapproval by the IRB; however, an institution can block a study approved by its IRB. IRBs can approve studies subject to stipulations. If these stipulations are minor, the chair or designee can sometimes approve them without referral back to committee. Major revisions usually become deferrals, because the required response to stipulations may not be black and white and may be beyond what a chair or designee can decide. A deferred protocol goes back to the full IRB. Investigators are usually given a period to respond to stipulations; I recommend investigators act quickly so the protocol is fresh in the memory of the reviewers. A disapproved protocol needs resubmission as a new protocol.

IRBs can only approve protocols for 1 calendar year, hence the need for continued review. Applications should be submitted for continued review early enough to ensure that approval does not lapse. IRBs usually publish submission deadlines. IRB reviewers need enough time to enable meaningful review. IRB administrators need time to make sure the submission is complete before sending it to reviewers. Investigators should be aware of submission deadlines. No research can be conducted after the expiration, and approval may be conditional to stipulations. If the study has expired, research must stop. Usually a hold on a study allows for already enrolled participants to continue receiving research intervention and for data to be collected because research participants' wellbeing is a priority. During the hold period, new recruitment must stop.

Consents are stamped and/or bar-coded with an expiration date. A common violation involves the use of expired consent forms for newly recruited participants. Investigators should destroy expired consent forms to prevent this common audit finding. Researchers and the research team are usually required to have updated proof of human research training certification. Researchers also have to sign a conflict of interest and financial disclosure form with new submissions.

WHAT IS INCLUDED IN A SUBMISSION PACKAGE?

Investigators often receive additional requests for documentation and modifications from IRBs after submission. An incomplete submission may prevent review at the next meeting. Table 1 lists the usually required documents for a new submission and Table 2 lists the usually required documents for continued review (policies and requirements vary among institutions).

WRITING CONSENTS

Get directly involved in the preparation of the consent document.

You will have to fuse 2 documents: the IRB template and the sponsor consent. You need to know the protocol in depth to create a consent that provides a complete yet succinct description of the study, readable at a reasonable reading level, and not a collage of cut and paste paragraphs that repeat or contradict each other. Think of yourself as the person who needs to read it before consenting to have their child be a study subject. Be aware of your institutional policies regarding industry-sponsored research. Consult with your IRB in advance if you have questions. Don't think of the consent as a legal contract, but as an informing transparent document and be sure there is no exculpatory language in it.

TABLE 1 Minimal Document Requirement for Initial Review Application (Clinical Trial Site)

Cover letter
Application for new study
Addenda for biologic, drug, or device
Protocol
Investigator brochure
Research team agreement, disclosure, attestation form (investigators and coordinators)
Parental permission form
Informed consent (if participants are ≥18 y)
Adolescent assent
Child assent
Short form (if few non-English speakers expected) or professionally translated consents (if significant number of non-English speakers expected)[a]
Recruitment tools
Approvable flyers[b]
Web site social media postings
TV radio ads
Scripts for telephone recruitment
Outcome assessment tools (questionnaires, checklists)
Proof of radiation committee approval
Proof of human research protection training for all team members
Proof of biosafety committee approval
Letter of support from Department chair and institutional collaborators (core facilities, etc)
If applicable, merit review committee approval
Pharmacy approval
Curriculum vitae of investigator(s)

Some IRBs may require diaries and summary of the manual of operating procedures.
[a] Cost of translations can be negotiated with sponsor.
[b] Usually, dollar figures for participant incentives are not permitted.

WHAT COULD HAVE MADE THE IRB DISAPPROVE A STUDY?

What needs to happen for a study to be approvable? A list of required items taken from a typical reviewer's checklist is shown in Table 3. Sometimes industry-sponsored studies have a marketing rather than a scientific purpose, and drugs to treat conditions of dubious nature or that are not innovative or represent real advance may be rejected too. Unnecessary risks involving a wash out period with discontinuation of effective therapy and unnecessary placebo arms are some of the merit issues an IRB will look at. Perfectly written research studies with a dubious research question or hypothesis may be disapproved. Studies may be so poorly written that IRBs become concerned about the ability of the research team to carry on safe research. IRBs may feel compelled to disapprove a study with competitive recruitment among sites or with too high an incentive, particularly for risky research procedures, but incentives can depend on local factors; an incentive that appears modest in the setting of a rich country can be highly coercive in a setting where subsistence is a daily challenge. Concerns of insufficient benefit can apply to a wide range of research scenarios from Phase I oncology trials in children with advanced disease to pharmacokinetic research involving too short treatment arms to be of benefit.

TABLE 2 Minimal Document Requirement for Continued Review Application

Cover letter
Application for continued review (usually contains a section for listing unreported minor adverse events and deviations)
Consent forms if updated from last approval (some IRBs require submission of consents even if unchanged)
Any new research-related documents
DSMB or DMC reports
Study-wide reports/updates
Manuscripts or citations of manuscripts or presentations

TABLE 3 Criteria for the Approvability of Human Research (Checklist)

Physical, psychological, legal, and economic risks are minimized by using procedures consistent with sound research and do not subject participants to unnecessary risks
Risks are minimized by using procedures, when appropriate, already being performed for diagnostic or treatment purposes
Risks are reasonable in relation to anticipated benefits, if any, and the importance of the knowledge expected to result from the study
The selection of participants is equitable
The research plan makes provisions for monitoring the data collected to ensure the safety of participants
Privacy of participants is protected
Confidentiality of the data collected is protected
Additional safety measures are in place

Adapted from the Nemours IRB initial IRB review checklist.

STIPULATIONS

Respond promptly and comprehensively to IRB stipulations. IRBs will communicate in writing. Read the stipulations carefully and respond respectfully. A cooperative rather than a confrontational relationship with your IRB is always preferable. When you respond to stipulations, think the same way you do when responding to reviewers of manuscripts. Work with a cover letter in which you transcribe the stipulations and explain the actions taken, point by point. If you need to rebut, provide the rationale. It is fine to consult with the sponsor, but when responding to your IRB, do it from your prospective; don't simply forward the sponsor's response to the IRB. Elaborate and explain. The IRB knows you and would rather work with you than with a sponsor's representative. Changes required in consent forms should be submitted with tracked changes versions as well as clean copies so the reviewers can easily find the revisions.

FROM PATIENT TO RESEARCH PARTICIPANT

Be aware that your patient, who you have taken care of until now and whose best interest has been guiding all of your decisions, is about to become a research participant. The patient's best interest becomes entangled with the interest of the experiment, and you are partially suspending your role as a doctor to become an investigator. Consent forms should contain language that explains the role of the physician during their patient's participation in the clinical trial. This scenario and its consequences are known as therapeutic misconception.[14] The IRB system has been put in place precisely to cover that gap or "suspension". The review of the consent document and the description in the protocol of the consenting process are the main tools the IRB has to carry on its mission: the development of a transparent, informative, concise, and readable document administered in a context that respects fully the participant's right to self-determination.

ABBREVIATIONS

DSMB or DMC: Data and Safety Monitoring Board or Committee
FDA: Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
PI: principal investigator

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