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

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

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In part 1 of this series, we discussed the historical, ethical, and legal background that provides justification for the current system of protection of subjects of human experimentation. We also discussed briefly the implementation of those principles in institutional review board (IRB) operations. In part 2, we focus on legislation dealing with pediatric research, the rules and ethics of assent, and then turn our attention to minimal-risk studies. To that end, we discuss the minimal-risk threshold and the process of balancing benefit and risk in IRB decisions for pediatric studies. We define the notion of consent waiver as well as the procedures for expedited review, management of adverse events, and amendments to approved protocol. Finally, we mention some miscellaneous issues, including central and commercial IRB, reliance agreements, biobanks, and sample shipping regulations.

THE COMMON RULE AND PEDIATRIC RESEARCH: SUBPART D

Children are considered a vulnerable population and are granted extra legal protections. These protections are mainly included in Subpart D of the Common Rule (Title 45 CFR 46) and Food and Drug Administration (FDA) (Title 21, Part 50)[1,2] and are anchored on the notion of limited autonomy and reliance on proxies (parents and guardians) to consent for research participation. Unlike autonomous adults who can assume the risks of research following their own altruistic values, children cannot. The 2 main mitigating strategies for limited autonomy are the requirement for direct benefit and documentation of assent; both discussed later in this article. Additional protections include pediatric expertise in institutional review boards (IRBs), minimization of risks in study protocols, and training requirements for those conducting the study. These and other principles governing pediatric research are included in the guideline to industry E11 produced by the International Conference on Harmonization in 2000 and amended in 2014. The original signatories to the International Conference on Harmonization were the United States, the European Union, and Japan, and it aimed at providing a framework in which human research is to be conducted. E11 specifically deals with pediatric research.[3]

Subpart D is the backbone of pediatric research legislation in the United States and is included in both Title 45, Part 46 (Common Rule) and Title 21, Part 50 (FDA). It consists of 9 sections, 4 of which are devoted to classifying pediatric research into 4 approvable categories based on the interplay of risk and benefit (Table 1). The notion of the minimal-risk threshold is at the center of this classification. Title 21 provides such threshold in section 50.3k as "the probability and magnitude of harm or discomfort

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TABLE 1 Categories of Research According to Subpart D (Title 45 Part 46 and Title 21 Part 50)

Section	Risk	Anticipated Direct Benefit	Additional Requirement	Signature Requirement	Approvable by
404	Minimal	Not required	None	Either parent	IRB
405	More than minimal	Commensurate to involved risk	None	Either parent	IRB
406	Minor increase over minimal	Not required	Population involved affected by condition under study	Both parents	IRB
407	More than minor increase over minimal risk	Not specified	The condition under study is a serious health issue addressable by the study	Not specified	Secretary of DHHS assisted by panel of experts ("407 committee")

TABLE 2 Examples of Well-Child Procedures According to the Pediatric Subcommittee of the Secretary Advisory Committee on Human Research Protection (Modified)

The procedures listed below are acceptable under the minimal-risk threshold. More invasive or risky intervention require a commensurate level of direct benefit to be approvable.

- Physical examinations
- Procedures consistent with routine dental examinations and prophylaxis (eg, plaque removal and collection)
- Measurements of height, weight, head circumference, or temperature
- Assessment of obesity with skin-fold calipers
- Collection of blood or voided urine,[a] saliva, feces, hair or nail clippings
- Measurement of heart rate and blood pressure
- Hearing and vision tests
- Modest changes in diet or schedule
- Testing of fine and gross motor development
- Noninvasive physiologic monitoring (ECG, EEG, surface EMG),[b] pulse oximetry, FEV-1
- Medical and social history
- Psychological examinations or tests
- Guidance and education interventions (for child and/or parents)

Index routine psychological tests to standardized screening or assessment measures such as the following: child and adolescent intelligence tests, infant mental and motor scales, educational tests, reading and math ability tests, neurologic or motor disorder screening, social development assessment, family and peer relationship assessments, emotional regulation scales, and scales to detect feelings of sadness or hopelessness.

ECG, electrocardiogram; EMG, electromyogram; FEV-1, forced expiratory volume in 1 second.

[a] The volume of blood considered to be at the minimal standard is 3 mL/kg with 50 mL maximum within an 8-week period (DHHS).

[b] Acceptable imaging may include dual-energy radiograph absorptiometry scans, noncontrast plain films, nonsedation ultrasound, or MRI. Sinus computed tomography may be acceptable. Institutional policy varies. A radiation committee for research approval is usually required.

anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[2] Another commonly invoked definition was provided by the National Commission for the Protection of Human Subjects[4] and it states that minimal risk is (the) "risk encountered in the daily life or routine examination of healthy children." Attempts to move away from the "healthy children" threshold and accept the standard of "children suffering from the condition under study" or the "daily life" circumstances in which the research was performed was strongly resisted by the ethical guidelines published by the Secretary Advisory Committee on Human Research Protection, the Institute of Medicine, and the National Human Research Protections Advisory Committee.[5] The notion is known as the Uniform Standard. In summary, "healthy children living in a safe environment" is now solidly established as our minimal-risk threshold. Why is this definition so important? For starters, it allows IRBs to classify a research study in one of the approvable categories. Research approvable under Subpart D 404 will be at or below minimal risk and can be reviewed by using an expedited procedure rather than full committee (convened IRB meeting). In this category, we have all retrospective research based on medical record review or existing clinical samples, interventional research involving blood sampling, other noninvasive testing, and survey- or questionnaire-based research, among many others. When research involves existing samples, the portion removed for research should not render the remaining sample/tissue unusable for clinical purposes. As Table 1 shows, this research does not require direct benefit to the participating child. Table 2 lists some of the interventions falling at or below this threshold and thus approvable under Subpart D 404.

Pediatric studies entailing risk higher than minimal can be approvable

by the IRB only if those risks are balanced by a commensurate direct benefit. Randomized clinical trials with or without placebo arms, device trials, or research involving randomization of any intervention fall into this category and are approvable under Subpart D 405. The idea of direct benefit is crucial, because the remote benefit of a new drug approval that could help the participating child or the social benefit of advancing science in general cannot be invoked as a risk balancing benefit. Be reminded that financial incentives or other payments related to participation are never to be considered a benefit in the context of balancing risk. Payments should be included in the consent or assent documents but NOT in the benefit section.

In this category of research, IRBs will look at the components of the research, an exercise known as component analysis, with the purpose of separating aspects of the protocol that are research-related from those that constitute the regular clinical care of the patient. The quantification of risk to be matched by commensurate direct benefit is limited to research-related procedures. IRBs will stipulate revisions that allow for research data to be obtained as part of the routine clinical care to minimize risk. Minimizing risk is a required in research for all ages and is specifically included in the Common Rule Part 46.111 (1) (i). For example, IRBs will be questioning the permissibility of a liver biopsy performed only to assess the effects of an experimental treatment but not a clinically indicated one, even if information from that biopsy is used for the experiment. This can translate into a range of stipulations from using routine phlebotomies to procure an extra "research tube," an extra small sample of tissue during elective surgery, or allowing an extra biopsy during a clinically indicated colonoscopy. Minimizing risk also can involve stipulations requiring additional tests to ameliorate risks or monitor toxicity.

IRBs can approve research with no direct benefit (nonbeneficial research) when the entailed risk is slightly above the minimal-risk threshold. This is known as minor increase over minimal risk. The law expects the IRB to decide what constitutes "minor increase" in a given protocol. This type of research requires that participants suffer from the condition under study and stipulates that the 2 parents sign the consent. It is regulated under Subpart D 406. Pharmacokinetic studies requiring an approved medication for a short period (too short to produce benefit) or a sinus computed tomography scan in a cystic fibrosis cohort study are examples of this subpart. IRBs may have to consult experts or require the investigators to provide rationale in support of a minor increased level of risk. Minor increase over minimal risk may not be permitted in healthy control randomization arms, because those participants will not have the condition under study.

If the IRB determines that a research study involves risk higher than minor increase over minimal and finds either none or insufficient benefit, its jurisdiction is surpassed and a referral to the Department of Health and Human Services (DHHS) is required. This research is regulated under Subpart 407 and is extremely rare.

ASSENT

Subpart D 408 regulates the consent process for pediatric research and establishes the requirement of assent. Most IRBs require that the assent process be formalized by a written document signed by the child or adolescent after the parent has provided parental permission. Pediatric human research protection programs usually provide templates for developmentally appropriate assents, including a child assent for participants 7-11 years of age and an adolescent assent for participants 12-17 years of age. In drafting assents for a given protocol, investigators and IRBs should consider 2 important issues: (1) the intellectual capacity of participants, and (2) the magnitude of prospect of direct benefit. The IRB could provide a waiver to the requirement of assent if the expected population under study is not capable of comprehending and signing assent documents. The waiver can be extended to the entire study population or to a subset of participants. In the latter case, the investigator has to determine such capacity for a given candidate participant and document the basis for the decision in the research record. The IRB can grant waiver of assent if the anticipated benefit of the intervention is such that honoring dissent may jeopardize the life or health of the child. In all other circumstances, assent is required. Investigators preparing an IRB submission should carefully draft these documents, so they can be understood by the child, not only by adjusting reading level, but also considering the ability of the child to grasp certain concepts, risks, and benefits. A matter of debate is, for example, the inclusion of pregnancy language in child assents.

Assent expires as an acceptable consenting form when the child turns 18. At that point, the investigator must obtain informed consent from the now adult participant. This process, commonly known as re-consenting, is important in long-term longitudinal observational studies.

CONSENT WAIVERS AND OTHER CONSENT ALTERATIONS

The default procedure preceding any activity in a human research study

TABLE 3 Requirements for Consent Waiver (45CFR46.116)

1. The research involves no more than minimal risk to the participants.
2. The waiver or alteration will not adversely affect the rights and welfare of the participants.
3. The research could not practicably be carried out without the waiver or alteration.
4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

involves an informed consent process in person that culminates with the signature of a document that attests such process. In pediatrics, it involves a parental permission followed by an assent process. The emphasis on process has to do with the high value attributed to the ethical principle of self-determination that emanated from both the Nuremberg code and the Belmont report. There are, however, permissible alterations that are considered both legal and ethical and are known as consent waivers. These waivers are restricted and approvable only if they fulfill all the specific requirements. When an IRB grants a waiver, it is virtually acting on the behalf of the future participant; in other words, consenting in his or her name. In pediatric research, the IRB in this case is acting as a "second in keen" after the parent/guardian.

There are 2 types of waiver; namely, waiver of consent process and waiver of documentation of consent. They are defined in 2 sections of the Common Rule 45.46.116 and 45.46.117, respectively.[1] The FDA regulations do not include waiver of consent, one of the few differences between the 2 laws. We already discussed the principles of assent waiver. For the consent process to receive a waiver, 4 conditions need to be met (Table 3). The criteria that elicits most interpretative discussions between investigators and their IRB is number 3: the research cannot be practicably carried out without the waiver or alteration. The criterion of practicability should be the participant's, not the investigator's, convenience. Prototypical examples include retrospective research on existing records or clinically acquired stored samples. Contacting a participant years after the patient was seen in clinic or had undergone the targeted surgical procedure is clearly impractical, and can be at best annoying to the family.

A waiver of documentation of consent under section 117 is very different. It was included in the regulations as an extra protection when the consent document would be the only link to the participant's identity. It applies mainly to anonymous survey research and is particularly relevant when sensitive information is collected. The IRB usually stipulates that the surveys are to be accompanied by an "information sheet" containing the elements of consent without the signature line.

Other alterations of the consent process include community consent for emergency research, short-form consent for non-English readers, witnessed consent for people who cannot read or who have an impediment, assumed consent for adult-based survey research, and telephone or video consent. A full description of those alterations is beyond the scope of this review. The best source to consult is the policy manual or your IRB Web site.

AMENDMENTS

Any change in protocol, consent, or recruitment material must be submitted to the IRB in the form of an amendment request. Amendments need to be approved by the IRB before they can be implemented. IRBs produce amendment application forms that need to be completed by the investigator or research team member. They should not be a "page reference" of the amended document but should contain the rationale and nature of the changes. Your IRB needs your expertise to make determinations, and remember that time spent at the front end saves time at the tail end. Amendment requests can be reviewed by expedited procedure or by the full committee, depending on their nature. In general, changes that increase risk (increased number of research participants, dose changes, additional invasive procedures, additions or changes in study arms) require review by full committee. On the contrary, routine personnel changes and reassignments, minor editing of the consent forms, and new versions of the protocol not involving study procedures may be reviewed by expedited procedure. Be sure that new members of the research team have their credentials and training up to date. Addition of outside collaborators usually requires a more involved process, including proof of IRB approval at the new investigator's site, material transfer agreements, data-sharing agreement, and other interinstitutional contracts and agreements. Some IRBs may allow for a parallel process with approval contingent on the filing of the additional documents. When grants are involved, the office of sponsored research will be involved.

DEVIATIONS, VIOLATIONS, AND UNANTICIPATED PROBLEMS

During the course of a prospective study, unexpected events will occur. From involuntary confidentiality breach (eg, lost/stolen laptop) to fatalities or severe morbidity associated with an experimental drug or device. All unanticipated problems are to be reported to the IRB. Minor problems may not require immediate reporting and can be summarized at the time of annual continued review, but others require prompt communication to

TABLE 4 Most Common Mishaps During the Planning and Conduction of Multicenter Trials

	Problem	How to Prevent
Preparatory phase	1. Unrealistic estimation of available patients	Review carefully your patient's records, including place of residence and transportation means, before you estimate your recruitment capability
	2. Underestimation of time commitment by investigator/staff	Review the budget and talk to your future coordinators
	3. Under resourced study	Read the protocol carefully, make notes ask questions
	4. Insufficient familiarity with protocol and procedures	
Recruitment and screening	1. Inclusion of patients who do not meet inclusion criteria	Know your protocol and read the investigator brochure
	2. Logistics: patient lives too far, working schedule	Involve yourself in the drafting of recruitment material
	3. Coercion/undue influence in recruitment procedures	Be strategic in how to make the study known to your patients, but be aware of excessive enthusiasm
	4. Unrealistic expectations from sponsor	
Conduction	1. Delay in reviewing IRB stipulations and revising documents	Know your team and the sponsors
	2. Missing adverse event and Data and Safety Monitoring Board reports from sponsor	MAKE A GOOD RESEARCH BINDER
	3. Misplaced research documents (consents, in particular)	Take your time when your coordinator calls; fast or under-pressure decisions are at the root of regrettable mistakes
	4. Recurring deviations	
	5. Violations	
Conclusion	1. Publication authorship	Read the contract and the confidentiality agreement before you sign it; ask questions
	2. Limited freedom to report negative results	

the IRB, and all need communication to the sponsor who in turn has reporting responsibilities with the FDA. Guidelines by the FDA for ethical conduction of clinical trials are particularly useful.[6] In 2009, as a result of proliferation of clinical trials, the FDA provided a new guidance that limited the scope of reportable unanticipated problems and alleviated the work load of local IRBs by giving the sponsor a more active role in managing, assessing, and determining course of action for reporting of unanticipated problems in multicenter trials (Table 4).[7]

During the conduction of clinical trials, adverse events that are serious, unexpected, and related to the research intervention need to be reported to the sponsor and the IRB. The rules for reporting are complex and beyond the scope of this review. They also vary by institution. The IRB is particularly interested in events that either occurred to local participants or that by their nature could affect local participants. It is important to take those reports seriously. Transcribing and forwarding to your IRB reports that come to your attention have little value. Your IRB wants your input, particularly your opinion on applicability of the adverse event to the study patients of the institution. So, review them before sending them to the IRB! Seriousness of an event is clearly defined by the FDA guidelines and usually refers to those events that are life or limb threatening, or require hospitalization or prolongation of inpatient care. Death is always serious, regardless of its relatedness to the research intervention.

The issue of assignation of relatedness (unrelated, possibly or likely related, or related) to the experimental drug is convoluted, and each event is to be considered on its own merits. Sources that inform IRB reviewers at the time of attribution are preexisting similar cases and biologic plausibility. Here the input of the local investigator who is an expert in the field of study is the most useful. Unexpected is self-explanatory, simply if it is not in the protocol and/or consent it is unexpected. Sometimes an adverse event is expected but its severity or frequency is not. Severity is different from seriousness. Severity is graded from I to V for each type of event and used to describe and collect data on adverse events at the time of reporting, publishing, or drafting the drug label. An event could be severe but not meet the seriousness threshold, as an episode of mild thrombocytopenia requiring no hospital admission.

Deviations are instances in which the study procedures are at variance from what is in the protocol. Some deviations are made purposely in the best interest of the participant and are usually authorized in advance by the sponsor and the IRB, unless they are urgent. Many deviations are minor and involve a missed or delayed visit. If they are frequent, an amendment may be necessary.

All need to be reported to the IRB. Policies vary with respect to deadlines for such reporting

Violations are those found after the fact either by an audit, routine review of research records by coordinators or investigators (highly recommended!), or (hopefully not) when an adverse event occurred. Violations are not necessarily part of the study intervention. Examples include enrolled participants who did not meet inclusion or who had exclusion criteria, or consents that are incomplete, outdated, or unsigned, among others. Keeping the consent documents organized and easily retrievable is crucial. In pediatrics, parental permissions signed by individuals without parental rights do occur. Coordinators and investigators have the responsibility to verify parental rights or the status of a legally authorized representative before accepting the signature in a parental permission form. Monitors from the sponsor periodically review documentation from the site. Almost always there are findings. The IRBs must determine if those findings are serious enough to question the safety of the study. Serious and recurrent noncompliance lead to study closures or holds until a corrective plan is in place. IRBs have the obligation to report continued or serious noncompliance to the sponsor, the Office of Human Research Protection, and in certain cases the FDA.

RECRUITMENT ISSUES

The longer a trial takes, the more expensive it is. Sponsors and contract research organizations with budgetary restrictions have an interest in promoting fast recruitment and investigators almost always overestimate their recruitment capacity. Sponsors can use competitive recruitment and de-incentivize centers with lower recruitment rates, or draft flashy recruitment material or payment incentives to participants and/or investigators. They publish newsletters ranking centers by recruitment success or send letters to investigators trying to improve recruitment numbers. All those strategies put pressure on the local investigator that can lead to excesses and sometimes infringement of ethical principles or federal law. An example is the recruitment of patients who do not meet inclusion criteria or, in rare instances, phony participants.

Recruitment materials (flyers, podcasts, webcasts, and radio and TV ads) must be approved by the IRB. Scripts, recordings, and hyperlinks to Web sites are to be included with the recruitment material at submission. The IRB will assess those materials to ensure that individuals are not subjected to undue influence. The more risk the research entails, the more scrutiny will be applied. Fair payment for time spent and reimbursement for travel and lodging are usually acceptable. IRBs produce written policy on the type of permissible reimbursement to participants and require transparency on the payments to local investigators.

RESEARCH ON SAMPLES, BIOBANKS, AND DATA BANKS

In this section, we depart briefly from the world of clinical trials and highlight some of the ethical and legal issues surrounding an increasingly popular type of research that emerged in the 1990s with the revolution in genetic testing. As genetic discovery became technically possible, DNA samples from the clinic or from research became highly valued. Research laboratories eager to get their hands on DNA from patients and their families with "interesting phenotypes" led to massive demand for samples, leaving pediatricians in a difficult position. The main risk associated with genetic research on stored samples is loss of privacy, and the ethical principle mostly invoked autonomy.

If there is a specific research project involving sampling with opportunity for full consent, the procedure is simple. The project will be reviewed by the IRB as a minimal-risk study, and there will be a signed consent document in which the parent will have the opportunity to direct the researcher on what could and could not be done with the sample.

Protections to participants whose genetic material is being studied and for whom gene discovery could have future consequences for employability or insurability are, since 2008, protected by law, namely the Genetic Information Nondiscrimination Act,[8] as well as state and local laws. Genetic Information Nondiscrimination Act language is included in consents involving sample collection. The consent will provide opportunity to the parent to determine what to do with the sample after the testing is completed. A series of "opt outs" are usually included on the signature page. Choices include sample destruction, or storing with a linking code (de-identified) or stripped of identifiers (anonymous). Secondary use of those samples for research will depend on the choice by the parent who can also limit the type of research to be performed with the sample. Complete de-identification provides protection to privacy but sacrifices the chance of giving back useful clinical information to family or to honor a decision to destroy a sample. Consideration to all these factors is important at the time of drafting protocols and consents. Ways of de-identification by allowing a trustee to hold the key to re-identification are currently available to sample and tissue banks (biobanks). Biobank-based research is a growing industry and its regulatory framework is

evolving. There are multiple sources of information for the interested reader.[9]

Another evolving field is practice-based research, which could be multicenter (consortia), in which data mining into massively stored clinical information can provide unique opportunity to address questions. In some cases, the level of identifier encryption is so sophisticated as to render the activity as "nonhuman" research. Information technology and genetic testing are pushing the boundaries and creating unprecedented challenges for IRBs, investigators, institutions, and legislators.

One important notion regarding collaborative sample-based research is the concept of engagement. When a clinician's only involvement in a research project is the procurement of a de-identified patient sample, the research laboratory makes a written commitment to not seek the patient's identity, such identity is not readily available to the researcher, and the clinician is not interested in authoring the publication, he or she may be considered not engaged in human research.[10] If, on the other hand, the clinician is hoping to be part of the publication, then he or she must join the research laboratory in a study and become a collaborative site. When research samples are shipped to other institutions, additional approval from the biosafety committee and a material transfer agreement must be in place. Glory demands effort! Similarly, if all you are doing is posting a flyer in your office about a research study performed at another institution, you are not engaged (be sure that study was approved by their IRB!).

COMMERCIAL AND CENTRAL IRBS

To decrease variability in timing and outcome of local IRB reviews, some research networks have opted for a central IRB (CIRB), administered by the network itself. Recently, the Children Oncology Group (COG) moved all their sponsored protocols to the CIRB and reliance agreements between local institutions and COG were executed, with the local IRB assuming limited administrative jurisdiction on COG protocols but keeping the authority to disapprove institutional participation. The jury is still out in terms of assessing the balance between the cost saving and achieved efficiency[11] and the possible sacrifice to ethical diversity provided by multiple reviewing boards.[12]

Commercial IRBs constitute a subtype of a CIRB. They are, in general, for-profit groups that provide review to research studies under the same rules and procedures as institution-based IRBs. Sponsors commonly choose commercial IRBs based on a cost-saving, efficiency-seeking logic. Local institutions may or may not allow their employed physicians to participate in multicenter studies involving commercial IRB review. This type of IRB may fill a gap for those participating private practices not affiliated with academic institutions.

RESEARCH IN THE SCHOOL SETTING

Pediatricians may be invited to participate in studies involving students. When research is performed in the school setting, it is usually minimal risk and involves mostly population-based projects in healthy children. Schools provide an excellent opportunity for large clinical or epidemiologic studies. It is important to know that research studies in public schools are subjected to review by IRB and regulated by the Common Rule, although the Health Insurance Portability and Accountability Act of 1996 does not usually apply because schools are not covered institutions. Investigators should be aware that there are 2 additional pieces of legislation that apply to research in public schools: (1) the Protection of Pupil Rights Amendment, which applies to students in K–12 and any research funded by the Department of Education,[13] and mainly deals with the need for parental consent; and (2) the Family Educational Rights and Privacy Act pertains to the privacy of student records.[14]

When considering research studies performed on students at any level, including students in graduate programs, IRBs consider them a vulnerable population. Incentives for participation as recruitment tools may become coercive and students may assume risks (mainly psychological) to obtain rewards. Participation as "part of the student curriculum" is usually frowned on by IRBs.

CONCLUDING REMARKS

This 2-part article was aimed at providing general pediatricians with a bird's eye view account of the process and regulatory framework on human research. The choice of topics is based on 15 years of experience at the leadership of an IRB at an academic pediatric institution and as a member of an international human research protection organization. This article cannot cover the myriad of issues and ethical views involving this rather complex activity, but the most crucial and frequent ones. Those who wish to further their knowledge can consult some of the provided references. Your local IRB and the Internet have vast resources at your disposal, and if the interest is that great, then join your IRB. It is a wonderful committee in which ethical discussions can motivate your intellect and continue to help you define your values. In addition, it provides an opportunity to learn research methodology and to keep you informed of what goes on in research fields other than your own. From time to time you will come

across neat ideas that you could apply to your own practice as well.

ABBREVIATIONS

CIRB: central IRB
COG: Children Oncology Group
DHHS: Department of Health and Human Services
FDA: Food and Drug Administration
IRB: institutional review board

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