



## Review

## Biomedical ethics and clinical oversight in multisite observational neuroimaging studies with children and adolescents: The ABCD experience



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## ABSTRACT

Observational neuroimaging studies with children and adolescents may identify neurological anomalies and other clinically relevant findings. Planning for the management of this information involves ethical considerations that may influence informed consent, confidentiality, and communication with participants about assessment results. Biomedical ethics principles include respect for autonomy, beneficence, non-maleficence, and justice. Each project presents unique challenges. The Adolescent Brain and Cognitive Development study (ABCD) collaborators have systematically developed recommendations with written guidelines for identifying and responding to potential risks that adhere to biomedical ethics principles. To illustrate, we will review the ABCD approach to three areas: (1) hazardous substance use; (2) neurological anomalies; and (3) imminent potential for self-harm or harm to others. Each ABCD site is responsible for implementing procedures consistent with these guidelines in accordance with their Institutional Review Board approved protocols, state regulations, and local resources. To assure that each site has related plans and resources in place, site emergency procedures manuals have been developed, documented and reviewed for adherence to ABCD guidelines. This article will describe the principles and process used to develop these ABCD bioethics and medical oversight guidelines, the concerns and options considered, and the resulting approaches advised to sites.

## 1. Introduction

Observational studies (i.e., non-intervention human research) provide critical knowledge on factors accelerating (i.e., risks) or preventing (i.e., resiliencies) risky behaviors and related disorders in the adolescent developmental period. Observational studies using magnetic resonance imaging (MRI) to measure adolescent brain development provide information vital to improve health and prevent disorders. These studies have relatively low physical risk, since MRI methods used

for assessment do not typically pose significant hazards, and the health care or other services received by the participant are generally unchanged. Along with the MRI assessment, observational studies on adolescent brain and cognitive development typically include cognitive testing, measures of mental disorders, substance use indicators, and assessments of environmental influences. In the study of child and adolescent health, both a child or adolescent (“minor”) and a parent or guardian [“parent”] are typically participants, as subjects of the study and as members of a family unit with distinct interests. Adherence to

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biomedical ethical principles and implementation of related oversight procedures assure that the rights and interests of the participants are respected in the context of conducting scientifically valid observational research.

Conducting observational research presents many ethical challenges. Most notably, when assessments may result in the adolescent disclosing at-risk characteristics, the researcher must determine whether such reports will be considered fully confidential, with no further responses, or will initiate responses that may include disclosure to the parent (see Fisher, 2013 for review). Ideally, ethically challenging situations that may arise in a particular study may be anticipated and approaches for responses are developed by consensus prior to the initiation of the project. Considerations include the best interests of the participants as well as the investigators' obligation to conduct scientifically valid research (Fisher and Goodman, 2009).

As a result of or incidental to the assessments conducted in an observational MRI study, potentially clinically relevant findings are frequently encountered. The term "clinically relevant" is broadly defined here to include signs, symptoms or circumstances that may indicate or predictably result in harm to the participants, including risks for medical or psychiatric disorders. The consideration of bioethical principles in the context of observational research with children and adolescents involves many aspects of the study, including study design, informed consent procedures, measures, study procedures, and oversight. While many relevant studies have been conducted, the published literature on related ethical issues and clinical oversight is limited. Formal ethics guidelines often do not definitively address adolescent confidentiality issues (Fisher, 1999, 2002; Hiriscau et al., 2014). Consultation with experienced investigators may be helpful.

This discussion focuses on the processes, deliberations and decisions made by the Adolescent Brain and Cognitive Development study [ABCD: [abcdstudy.org](http://abcdstudy.org)]. The challenges presented while initiating this large, multisite study have provided an opportunity to systematically explore the issues presented and develop consensus among a team of diverse experts. The ABCD study is a large multisite study supported by the National Institutes of Health and conducted at 21 sites. The primary goals of ABCD are to study healthy brain development in childhood and adolescence, with a particular emphasis on the risks and consequences of substance use, in over 10,000 subjects recruited and assessed at 9 or 10 years old and followed for 10 years.

## 2. Principles of biomedical ethics

The principles of medical ethics are applicable as an ethical framework for developing confidentiality limitations, plans for additional assessments or referrals, and oversight procedures to address assessment results and incidental findings. To provide a conceptual framework, we consider the four principles of medical ethics that are consensually held to be critical for studies involving humans: (1) respect for autonomy; (2) beneficence; (3) non-maleficence; and (4) justice (Beauchamp and Childress, 1989; Gillon, 1994).

*Respect for autonomy* identifies the individual right to self-determination. This principle, embodied in federal regulatory requirements for informed consent, promotes "deliberated self rule" by providing individuals with sufficient information to enable them to make an informed, rational, and voluntary participation decisions. In the context of an observational study with a child or adolescent and parent as participants, adherence to this value requires that both the minor and the parent be given relevant information about the study procedures and their implications. Informed consent procedures must provide the information in a manner suitable to the minors' and parents' ability to understand this information and make study participation decisions without perceived coercion. The parent provides consent for their own participation, and has the primary responsibility for providing permission or consent for their minor child. The minor is typically also required to provide his or her assent.

*Truthfulness and honesty* are values essential to implementing *respect for autonomy*. An important aspect of informed consent in this context is providing the minor and parent with information about the handling of sensitive information. Minors, for example, may have concerns about responding to questions about substance use if they believe the information will be shared with the parent. As another example, parents may have concerns about responding to questions about disciplinary practices, with willingness to provide information dependent on whether that information may be interpreted as "child abuse" and lead to mandatory reporting to governmental authorities. To be consistent with *respect for autonomy*, the informed consent process must describe information that will be kept confidential [e.g., substance use reports from the minor that will not be communicated to the parent] and confidentiality limitations [i.e., parental behaviors considered to be potentially child abuse that will be reported to designated authorities]. Explicit and thorough information to the minor and parent about confidentiality limitations prior to initiating the assessment is essential for implementing *respect for autonomy*. Investigators should not assume that families are familiar with mandatory reporting requirements and thus should include relevant explanations (Fisher et al., 2002).

To be truthful, confidentiality promises must be kept over the course of study participation. Thorough and explicit communication to the minor and parent on the confidentiality conditions may help address issues that arise. For example, even after agreeing to a procedure where the parent is told he or she will not be informed of the assessment results, a parent may request findings. A parent may be concerned about the minor's substance use, and view the assessment as a means for obtaining helpful information. Typically, the minor has been promised that the results would not be provided to the parent without the minor's consent and their consent may not be forthcoming. The investigator needs to anticipate this and other similar circumstances. Since there may be some information that cannot be kept confidential, such confidentiality limitations must be considered in developing the study design, assessment, operating procedures and, importantly, informed consent language. A coherent approach consistent with the principle of *respect for autonomy* includes the identification of aspects of the assessment protocol that may raise confidentiality issues, careful review of information to be provided to the parent and minor about confidentiality and limitations, and plans for keeping the promises made to participants. Investigators should also develop plans for preparing the minor for circumstances that require disclosure (Fisher, 2017).

*Beneficence and non-maleficence* refer to promoting the well being of others and "first, do no harm" (Latin: *primum non nocere*). The purely observational study is generally not designed to provide clinical screening, preventive interventions, systematic referral or treatment. Nevertheless, the assessment may reveal information that would be potentially helpful to the participant. Several circumstances may be anticipated. The minor may provide information covered by a confidentiality agreement and, where the investigator judges the information may be helpful to provide to the parent, the investigator may obtain permission from the minor to share that information. If the minor freely consents for that the information to be shared with the parent, adherence to the principles of *respect for autonomy* and *beneficence* is retained. If the minor declines to consent, *respect for autonomy* demands that the confidential information not be communicated to the parent. Circumstances where providing information to parents over the objection of the minor is considered necessary, holding *beneficence* over *respect for autonomy* in particular cases, should be anticipated and communicated prior to the assessment as confidentiality limitations. Disclosure of information provided by the minor, particularly if the assent procedures led to a misunderstanding that the communication would be fully confidential, may lead to problematic and potentially harmful consequences (Fisher, 2013).

*Non-maleficence*, in the observational study context, primarily involves preventing harm that may occur as a result of the assessment procedures and related disclosures. For example, exposure to the MRI

magnet may be hazardous for some participants, such as those with implanted medical devices. Therefore, screening subjects for such conditions is imperative and has become routine in MRI study procedures and at MRI facilities (Kumra et al., 2006).

*Justice* is synonymous with fairness. In a research study on humans, the principle of justice primarily requires that the burden of such research that would benefit all people not fall in any one group of persons in society. Justice, after all, became one of the guiding principles of American bioethics after revelations that poor African American men, prisoners and orphans were being used for experimentation due to their less privileged place in society. In research such as the ABCD study, justice requires that we not seek out particular populations of youth who lack the social standing to say “no.”

There is no broadly accepted mechanical way to weigh and balance these principles. The application of biomedical ethics in the research context involves the consideration and reconciliation of conflicts among principles and among the many stakeholder interests. In a multisite observational study, investigators, administrators, parents and minors may have competing concerns. Furthermore, within each of these groups, variations in the interpretation of principles and their implementation raise controversies that need to be addressed for the study to proceed in a systematic and ethically sound fashion. The operational application of these principles primarily involves planning how information provided by participants will be utilized in decisions about whether disclosures and referrals will occur (Fisher, 2013). The differing perspectives of adolescent participants, parents and researchers, the conflicting goals of protecting participants and conducting observational research without interfering with the natural course of events, and the unique circumstances that each critical situation presents, results in challenges to developing comprehensive algorithmic methods and the necessity for thoughtful decision making. In the following sections, we describe and discuss the approaches ABCD has taken to address these dilemmas.

### 3. Operationalization of biomedical ethics: oversight guidelines and procedures

The general application of biomedical ethics principles to clinical issues in observational research with children and adolescents involves some areas where implementation is relatively uncontroversial. However, many issues are subject to conflicts among the principles, as well as variations in their interpretation, multiple perspectives, and conflicting goals. Since unique issues are presented in each research protocol, investigators need to follow a process for developing guidelines and procedures applicable to their study. We will next describe the process that was undertaken in identifying potential ethical issues in the ABCD study, review some of the issues that have arisen, and present the approaches that were decided upon for this study. We will then present the considerations and approaches taken in addressing three types of clinical findings that may require disclosure or referral.

Research procedures are governed by federal regulations, state laws and guidelines, and involve local and/or centralized oversight by human subjects institutional review boards (IRB). In developing ABCD guidelines, our recommendations needed to be sufficiently flexible to allow adherence to variations in state regulations and other institutional oversight authorities, and yet sufficiently coherent to provide a framework for the ethical conduct of the overall project. State reporting requirements and other laws may vary in their dictates to licensed health professionals and non-licensed researchers. While our goal was for the guidelines to provide a framework for IRB application materials, such as informed consent procedures and documents, these guidelines were developed independent of the institutional IRB committees and their review and approval procedures. The settings for ABCD sites include institutions with imbedded licensed clinical faculty, such as academic medical centers, but also other sites where clinical faculty may not typically be present, such as neuroscience departments or

research institutes. We advised that each site enlist a clinician to provide suitable expertise when needed.

The age of the participants has important implications for clinical approaches and oversight. Studies involving only competent adults may confront some of the issues described here. However, such studies are simplified by having only one individual as a participant who provides consent, who is inherently aware of their own communications, and who is responsible for receiving information or advice. While the ABCD study is anticipated to follow minor participants from age 9 or 10 through age 19 or 20, we essentially focused on issues pertinent to the earlier developmental period under study with a plan to address older age periods with subsequent revisions or additions. We undertook the development of these guidelines as an iterative consensus building process and provided these written guidelines to the investigators, scientific partners at the National Institutes of Health, and other oversight and advisory committees prior to study initiation.

This next section describes the process undertaken for developing guidelines, some of the general issues that were discussed, and an overview of the guidelines and procedures. The resulting ABCD Bioethical and Medical Oversight (BMO) Guidelines are presented in the Appendix A. In the subsequent section, we will describe in additional detail three clinical issues we anticipated, the points that were considered, and the recommendations made on related procedures.

#### 3.1. General issues

##### 3.1.1. Informed consent

Truthful, honest, and thorough informed consent is an essential basis for implementing *respect for autonomy* in research. Confidentiality parameters need to be anticipated and communicated, particularly the conditions under which sensitive information will be collected. Prior to study initiation, information collected or prompted by study measures needs to be anticipated, and information that cannot be considered confidential identified. Typical examples include child abuse or neglect, suicidal or homicidal ideation, and other information that would indicate an immediate hazard to a participant or others. Confidentiality limitations that can be anticipated need to be thoroughly considered, age and educationally appropriate language for communicating these limitations developed for the informed consent procedures, and plans for evaluating and responding to problematic situations need to be organized. In developing the informed consent procedures, investigators need to anticipate clinically relevant information likely to be revealed during assessments, the potential perspectives of the participants, investigators and regulators [e.g., Human Subjects Institutional Review Boards], the developmental status of child and adolescent participants, the concerns of parents and minors, and the study design requirements. These plans need to be supported by local resources, consistent with local, state and federal regulations, and vetted by IRBs.

##### 3.1.2. Developmental status

Respect for the child's developing autonomy requires assent procedures tailored to the child or adolescent cognitive level to effectively communicate their research rights, including the voluntary nature of participation (Fisher, 2017). These procedures must also encourage participant engagement in ongoing decision making with regard to whether or not to participate in specific aspects of the study, and whether or not to provide specific information. Adolescents are generally more willing to provide sensitive information, such as reports of substance use or suicidal thoughts, under conditions of full confidentiality (Ford et al., 1997; Lothen-Kline et al., 2003); they also favor referrals and assistance for suicidal ideation (Fisher, 2003; Fisher et al., 1996; O'Sullivan and Fisher, 1997). Minor participants may find disclosure of a particular risky behavior, such as substance use, irrelevant if able to respond that they have not engaged in the behavior. However, in longitudinal studies, their views may change as a result of engaging

in or anticipating initiating the behavior. Recruitment of at-risk subjects and the validity of assessments may be influenced by developmentally specific confidentiality concerns. Adolescents have been noted to consider forgoing health care due to confidentiality concerns (Lehrer et al., 2007), and some adolescents may decline research participation for similar reasons.

### 3.1.3. Disclosure of assessment results

In observational studies involving children or adolescents, most assessment results are not routinely provided to parents or others. Nevertheless, individually identifiable findings from the child's assessment are provided to the parent or others in some instances that do not require the child's assent, including reports of child abuse and neglect, imminent potential harm to self or others, specified incidental findings, or life threatening circumstances. There may be instances where parents request information, the child assents to the disclosure and the investigator is able to provide the information requested. Confidentiality policies are not intended to prohibit such disclosures. For example, the ABCD guidelines provide a suggestion for the parent consent statement that reads: "This is a research assessment that is not intended as a clinical evaluation. With the exception of concerns specifically described here, the results of the research assessment will typically not be provided to you."

### 3.2. ABCD BMO guidelines & procedures development

Following the Notice of Grant Award (NGA: 9/30/15), the process for establishing an approach for providing biomedical ethics advice and oversight guidelines to the ABCD investigators began with ABCD leadership communicating plans for the development of the ABCD Bioethics and Medical Oversight Advisory Group (ABCD BMO) and the invitation and appointment of BMO members. As described in the BMO Charter (Appendix A), the BMO members included ABCD investigators, NIH officials, and outside consultants. The expertise represented includes clinical psychology, psychiatry, developmental neuroscience, science administration, federal regulations, and ethics. Other ad hoc participants have included members of the ABCD Observational Study Monitoring Board and External Advisory Board, NIH officials with specific expertise, and investigators consulting with BMO or inquiring on particular issues.

The first meeting (via telephone conference) for this group occurred about one month after receipt of the NGA. In collaboration with ABCD leadership, the BMO goals were to develop the BMO Charter, provide guidance to the investigators on bioethical issues and medical oversight, and review site-specific procedures for responding to clinical issues. The draft BMO Charter and Guidelines were widely circulated and edited in response to comments over several months, a provisional version was utilized to support site IRB applications and assessment staff training, and a final version was completed and circulated in June 2016. (ABCD BMO Charter & Guidelines: see Appendix A). In addition, as part of the annual ABCD investigators meeting, an in-person ABCD BMO meeting was held (11/17/16). A plan was established to engage in on-going discussions on these guidelines and their interpretation, and to annually revise the guidelines to consider anticipated developmental issues and respond to additional suggestions.

The BMO Charter specifies that this committee is responsible for proposing guidelines for identifying and responding to potential significant threats to participant well-being. The current guidelines (Appendix A) were reviewed and approved by the ABCD Steering Committee, with consultation by the ABCD Observational Study Monitoring Board (OSMB) and External Advisory Board (EAB). The BMO Charter specifies that the BMO provides advice and consultation to the ABCD Coordinating Center and sites. The ABCD Coordinating Center implements site monitoring, reporting and response procedures, and provides reports to BMO, OSMB and EAB.

Consistent with BMO Guidelines and IRB requirements, each site

was advised to develop and provide to the BMO a written emergency procedures plan. The document describes responsible investigators, including a site clinician, their contact information, and procedures to be followed in the event of reports of child abuse, responses indicating the possibility of harm to self or others, neurological anomalies, and other incidental findings. The ABCD Site Emergency Procedures documents and subsequent revisions are reviewed by the ABCD BMO, and the ABCD Coordinating Center required approval of this document by BMO prior to the initiation of study subject assessments.

For any concern that arises, each Site PI is responsible for assuring that inquiries and communications with participants are conducted by appropriate personnel. The ABCD Coordinating Center implements site monitoring, reporting and response procedures. The ABCD Coordinating Center has conducted emergency procedures training sessions for ABCD site project coordinators, provides opportunities for discussions among the investigators and NIH partners on biweekly conference calls, and receives and reviews reports from sites on actions taken in response to problematic incidents. The ABCD Coordinating Center will provide a semiannual report on reported incidents to oversight groups (see Appendix A).

## 4. Implementation of biomedical ethics: three illustrations

For each research protocol, investigators need to follow a process for identifying areas of concern, developing guidelines, and establishing procedures. In consultation with the ABCD investigators, OSMB and EAB members, and NIH partners, ABCD BMO identified several areas of concern prior to the initiation of the project, including imminently life threatening substance use, neurological anomalies, imminent self-harm or harm to others, child abuse and neglect, and other incidental findings, including medical or mental disorders. Some decisions were rather straightforward. With regard to child abuse for example, we elected to advise each site to inform participants that information indicating child abuse would not be considered confidential, to systematically collect information when such concerns were prompted, and to follow state regulations for reporting. Other areas were somewhat more controversial, generating discussions and proposals for their confidentiality conditions and response procedures. These considerations and decisions will be reviewed in this section for three areas: (A) substance use; (B) neurological anomalies; and (C) self-harm and harm to others.

### 4.1. Substance use

Studies examining the risks for and effects of influences on adolescent brain development, such as ABCD, typically involve assessment of substance use in minor participants. The willingness of the minor participant to provide valid substance use reports depends, in part, on assurances and perceptions of confidentiality (Delaney-Black et al., 2010). From the perspective of the minor participant, respect for autonomy might be optimally implemented through assuring unconditional confidentiality for any substance use reports. However, while the majority of teens prefer that no action be taken in response to research reporting of alcohol, cigarette or drug use, a substantial proportion report that they favor reporting their substance use to a concerned parent (Fisher, 2002, 2003; Fisher et al., 1996). Parents are often unaware that their teen has been using substances (Berge et al., 2015). Parents often hold conflicting views, on the one hand appreciating the benefits of and supporting confidentiality provided to their teen while, on the other hand, expressing the preference for being provided with this information (Duncan et al., 2011; Dempsey et al., 2009; Fisher, 2003; O'Sullivan and Fisher, 1997).

When informing the minor participant and parent about the confidentiality conditions during informed consent, truthfulness and honesty dictate providing information to parents and minor participants describing confidentiality conditions pertaining to substance use reports. While the minor participant may, in some instances, be willing to

provide valid reports about substance use under conditions where the information is conveyed to the parent, the viability of conducting the substance use assessment in a research setting is generally considered to require confidentiality (Clark and Winters, 2002; Del Boca and Darkes, 2003). Many longitudinal observational research studies provide global confidentiality for substance use reports without exception (e.g., Clark et al., 1997). In general, global confidentiality is preferred by teens and ambivalently accepted by parents.

For situations where an imminently life threatening substance use pattern is identified, the best interest of the minor participant, as well as the inclinations of youths and parents, support disclosure. Generally, in circumstances where the adolescent's welfare is in jeopardy, confidentiality limitations may be required. In a series of studies, Fisher and colleagues (Fisher, 2013) determined that teens and parents thought that researchers had an ethical obligation to disclose information if the participant was in danger. In such instances, *non-maleficence* focused on the best interest of the minor participant, particularly from the perspective of the parent or investigator, may involve communicating affirmative substance use reports to the parent. The goal of the communication is so that further evaluation or interventions may be initiated to reduce the likelihood of substance use related hazards. In such instances, *respect for autonomy* may conflict with *beneficence*. Several steps may be taken to minimize or manage this conflict. The confidentiality conditions of substance use reports need to be determined and communicated to the participants prior to the assessment. Collecting a minor participant's substance use reports under a promise of complete, unconditional confidentiality and subsequently communicating the information over the objection of the minor participant would violate the assent agreement. If the minor participant communicates the information to the parent, or agrees to such communication without perceived coercion, both *respect for autonomy* and *non-maleficence* principles are upheld. Confidentiality limitations may also be communicated in the informed consent process. For example, prior to the assessment, the minor participant could be informed that a report of an imminently life threatening substance use pattern will not be considered confidential. By taking this position, the investigator is adhering to *truthfulness and honesty* while prioritizing *non-maleficence* in extreme circumstances.

#### 4.1.1. ABCD approach

While absolute confidentiality on minor participants' substance use reports was considered, stakeholder discussions revealed concerns that failing to provide parents with information on their child's hazardous substance use may be ethically problematic. Consequently, the approach recommended by BMO provides confidentiality to the substance use reports of the minor subject except when the report indicates an "imminently life threatening substance use pattern." The proposal generated discussion about whether an algorithm could be devised to define such patterns, in terms of substance class, frequencies, and/or quantities. BMO decided to recommend that each site clinician be authorized to determine whether an "imminently life threatening substance use pattern" was present in a particular case utilizing the totality of circumstances and information available.

#### 4.1.2. Neurological anomalies

Over the course of MRI studies, some subjects without known or suspected neurological disorders will be observed to have brain anomalies (e.g., Sullivan et al., 2016). Neurological anomalies as an unanticipated finding raises issues pertaining to the clinical monitoring of MRI findings in observational research, determinations about whether particular findings have clinical significance, and the circumstances under which findings need to be communicated to minor subjects and parents (Cole et al., 2015; Cramer et al., 2011; Kumra et al., 2006; Shoemaker et al., 2016).

In MRI research with children, adolescents and young adults, the incidence of neurological anomalies has been reported to be 10–13%

(Gur et al., 2013: 10.6%; Seki et al., 2010: 11%; Sullivan et al., 2016: 11.8%; Kumra et al., 2006: 13%). Among 1400 subjects ages 8 through 23 years old, Gur et al. (2013) identified 148 (10.6%) with anomalies. MRI findings were classified into three groups: (1) normal: no incidental findings (n = 1252: 89%); (2) coincidental: incidental findings noted and reviewed by a pediatric neuroradiologist, and judged to be of no clinical significance (n = 136; 10%); (3) incidental finding with potential clinical significance and referral recommended (n = 12; 1%). In the National Consortium on Alcohol and Neurodevelopment in Adolescents (NCANDA), 831 subjects (ages 12 through 21 years) participated in structural MRI data collection (see Brown et al., 2015 for study details). A board certified neuroradiologist examined all T1-weighted MRI sessions (Sullivan et al., 2016). Brain structure anomalies were observed in 11.8% (98 of 831) of these readings. The most common anomalies were mega cistern magna (n = 26, 3.1% of sample), cysts (n = 27, 3.2%), and white matter dysmorphologies (n = 12, 1.4%). At baseline, two additional cases were considered to clearly require further clinical evaluation (i.e., right parietal cortical mass; bilateral tonsillar herniation with Chiari I malformation), and these cases were excluded from subsequent analyses. The NCANDA study compared 98 cases with neurological anomalies and 619 cases without anomalies, and observed no significant differences on cognitive test accuracy scores in all seven functional, including abstraction, attention, emotion, episodic memory, working memory, balance, and general ability. While those with anomalies, compared with others, were on average significantly slower on attention and motor functioning tests, their attention speed and motor speed scores were within the same range as subjects without anomalies. Thus, NCANDA subjects with anomalies did not show evidence of cognitive abnormalities.

Prior to initiating an observational MRI study, researchers need to decide whether MRI data will be routinely examined by a neuroradiologist, determine the procedures for reporting to investigators, and determine the approach to deciding whether to inform parents and recommend referral for additional assessment. A consensus in the field is developing that supports routine radiologist review in MRI research, especially for studies with minor participants, to ensure detection of neurological anomalies (Illes et al., 2002, 2006), along with a call to develop greater standardization and guidance (Borgelt et al., 2013; Cramer et al., 2011). Screening for neurological anomalies and disease in research contexts may have potential problems. Some research groups or facilities may not have access to a neuroradiologist, and adding this function may at best add to the study expense and at worst impact study feasibility. When a neuropathological finding indicating the possibility of disease is detected, additional clinical assessments and neuroimaging are needed.

There is currently no consensus or accepted standard guiding investigators in providing research participants with information on neuroradiologist readings of MRI results (Nelson, 2008; Phillips et al., 2015; Royal and Peterson, 2008). Research scans are typically not ideal for neurological diagnosis, and clinical follow-up may be expensive for the participant. In some instances, future medical insurability may be jeopardized (Illes et al., 2006). While incidents where neurological disease discovered as a result of participating in MRI research leading to loss of health insurance coverage have been reported (Milstein, 2008), the frequency of this and other adverse consequences consequent to providing participants with MRI results has not been systematically studied. Most MRI research subjects expect that, if present, a clinically significant abnormality will be detected and that they will be informed, and many also report a preference for receiving reports of benign findings (Cole et al., 2015; Kirschen et al., 2006). However, concerns have been raised that communicating findings with no clinical importance may generate unwarranted concern and lead to unnecessary medical visits and testing, along with associated expenses for the participant (Royal and Peterson, 2008). In cases where results indicate that an anomaly is not suggestive of disease, decisions about whether to inform the participant may be difficult because participants seeking

treatment for what may not be of clinical significance can itself be harmful.

In a study on the disclosure of incidental findings in MRI research, Phillips et al. (2015) describe the views of 196 research participants, 150 investigators and 50 IRB members. The participants were adults (mean age 38, range 18–88 years), with 91% having at least some college education. Among the participants, all of whom had received a MRI report, 78% responded that they wanted “all scan findings to be communicated,” a considerably higher proportion than among investigators and IRB members (27%). The authors report that 36 participants received an MRI report with a recommendation that they follow-up with their primary care physician, but only 10 of these participants followed this recommendation. Seven participants obtained clinical follow-up after receiving a report specifically stating that no clinical follow-up was necessary. The article reporting the study lacks details in some pertinent areas. Information about the studies from which these participants were sampled and the number of research participants contacted compared to the number participating are not reported. The extent to which the views of these participants may be representative of those participating in these studies or the generalizability to other study participants cannot be determined. The rates and types of MRI results provided to the 196 participants were not provided, and the relationships between their results and their views were not described. For example, participants who received a report indicating no findings would presumably report they understood the information and that they would recommend that findings be communicated. Their views of the process may systematically differ from others who were provided with findings with unclear implications. In the qualitative component of the study, participants describe their expectation to be informed about “a serious medical problem” with the goal to “begin whatever medical process I would need.” In the survey, most participants reported an understanding of the MRI report. However, a few responded in the survey that their understanding was 0 on a scale of 0–100, and a respondent in the qualitative study indicated “I didn’t understand what the MRI results were...” While this study is informative, these results do not provide definitive results for addressing these issues. With regard to the implications of such research for ABCD procedures, the needs, concerns and responses of parents receiving information about MRI incidental findings pertaining to their own children need to be studied.

#### 4.1.3. ABCD approach

Consistent with several prior studies (Gur et al., 2013; Sullivan et al., 2016), an experienced neuroradiologist will review all ABCD MRI scans to determine whether an anomaly is present, and to provide a recommendation on whether further clinical evaluation is recommended. The neuroradiologist will communicate with the site clinician when the MRI indicates minor anomalous findings, where asymptomatic cases may or may not require communication about the finding with the participant, notable findings where clinical follow-up is recommended, and major clinical findings with clinical evaluation strongly recommended. The neuroradiologist will be available to discuss the finding and to collaborate on decisions about communications with the participant and referral. The site PI and site clinician are responsible for determining the clinically appropriate response, and for providing reports on the actions taken to the ABCD Coordinating Center.

#### 4.2. Self-harm and harm to others

The minor participant may report prior self-harm or intent to harm self as a response to an assessment item or as an incidental communication. Self-harm communications may involve reports of prior suicide attempts, current or past suicidal ideas, and non-suicidal self-injury. For suicidal ideation, limiting confidentiality and responding to affirmative reports with additional assessment and, if warranted,

referral may seem clearly indicated. However, this limit to confidentiality may have unintended consequences.

Adolescents may be less likely to disclose suicidal ideas when these communications are not considered confidential. In a study of adolescents assessed in association with a primary care visit (Lothen-Kline et al., 2003), 263 adolescents responded to a “suicidal thoughts” item [i.e., “for the last two weeks, have you had thoughts that you would be better off dead or of hurting yourself in some way nearly every day?”] under full confidentiality, and 181 responded under conditional confidentiality. Under full confidentiality, there were no exceptions and disclosures about suicidal ideas were not communicated to parents or providers. Under conditional confidentiality, affirmative answers were followed by an additional assessment and the parent and provider were informed. Compared to the rate of endorsement of suicidal ideas under full confidentiality (8%), a significantly lower rate of endorsement (1%) was observed under conditional confidentiality. The authors speculate that, under conditional confidentiality, adolescents may have more thoroughly considered whether their suicidal thoughts were sufficiently serious to endorse an affirmative response, or may have elected to invalidly respond to avoid disclosure to the parent and/or provider. The study did not report subsequent outcomes. Research that would further inform the interpretation of such results, including data on long-term clinical outcomes, is needed. The Lothen-Kline study item may be interpreted as asking about non-suicidal self-injury as well as suicidal thoughts. Reports of past non-suicidal self-injury or related thoughts also prompt consideration of confidentiality limitations. In addition to the potential injury directly reported, adolescents who report self-injury are at higher risk for suicidal thoughts and behaviors (see Lloyd-Richardson et al., 2015 for review). Adolescents sometimes forgo health care due to confidentiality concerns (Lehrer et al., 2007). While confidentiality limitations may be ethically sound, research assessments results may be less valid.

In general, researchers have typically been considered to have an obligation to intervene when the subject reports imminent life-threatening risk to self or others. In the case of responses to questions on self-injury and suicidal thoughts, additional assessment may be needed to determine whether imminent risk is present. Similarly, threats to others also typically need further evaluation prior to action. When a threat is identified, “duty-to-protect” laws generally dictate informing the potential victim (Fisher, 2013).

#### 4.2.1. ABCD approach

An affirmative answer to select mental disorder assessment items, by the parent or minor subject, indicating current suicidal or homicidal ideation triggers an email alert to the ABCD site clinician. The site clinician is required to acknowledge the alert. If the recipient does not respond to a sequence of three messages over a period of fifteen minutes, a second site contact is notified. [If these attempts to contact fail, other methods are then used, including telephone calls.] The following is an assessment item example from the parent assessment: “In the past two weeks, did your child actually do something to kill himself or herself and make a suicide attempt?” In addition, site assessors are instructed to review other items indicating self-harm or harm to others in the assessment protocol. (e.g., parent and minor subject responses to questionnaire items: “I deliberately try to hurt or kill myself.” or “I think about killing myself.”) Affirmative answers are to be immediately reported to the site clinician for further evaluation.

### 5. Conclusion

Biomedical ethics principles provide a conceptual framework for considering ethical issues. In several arenas, standard, accepted approaches have been established through federal and state regulations (e.g., child abuse), judicial precedents (e.g., homicidal threats), standard practices at MRI facilities (e.g., screening for magnetic metallic objects), and expert panels leading to best practices (e.g., MRI screening

for neurological anomalies). Nevertheless, multisite neuroimaging research projects studying the childhood and adolescent developmental periods present ethical challenges.

The ABCD experience indicates that plans for addressing ethical issues in clinical oversight need to begin several months prior to the initiation of subject recruitment and assessment. The assessment protocol is ideally developed with consideration and identification of responses that may require clinical oversight, resources for responding to possible hazards, and plans for communication to participants described in informed consent material. The necessary review and consensus development may be facilitated by a written document, providing an opportunity to hold discussions among investigators, engage oversight committees, and enlist consultants in considering issues and plans. In multisite research projects, written guidelines may then be disseminated to provide a framework for developing tailored local plans.

There are some anticipated issues where the available literature may be consulted, the experiences of investigators reviewed, and experts engaged to thoroughly develop and vet plans. The clinical issues discussed in detail in this article – substance use, neurological anomalies, and self-harm and harm to others – predictably arise in observational MRI studies with children and adolescents. Prior experiences can be utilized to identify and plan for problematic circumstances. For substance use and other sensitive information involving risky behaviors, confidentiality conditions have implications for study design, assessment validity, and participant recruitment and retention. Adolescent participants may view confidentiality as necessary for providing valid affirmative responses. If the study design and assessment procedures result in circumstances where confidentiality cannot be provided, the anticipation of participant concerns about confidentiality limitations may necessitate study design changes to assure participant engagement and valid data collection. Investigators need to consider that parents may understandably expect assessment results indicating clinical concerns will be communicated to them and therefore, to the extent that this is not planned, parents need to be informed prior to assessment initiation.

Unanticipated problems will occur. Furthermore, the discrimination between hazardous and benign situations typically requires thoughtful judgment and consideration of the totality of circumstances involved, rather than a formulaic approach. To the extent that broadly defined confidentiality limitations are described – such as imminently life threatening situations regardless of their origin – plans need to be in place for involving a responsible site clinician or investigator to direct additional evaluation and appropriate actions that assure, as far as possible, participant safety. For ABCD, the site clinicians play this important role.

This article is not intended to discuss a comprehensive range of ethical issues pertinent for observational MRI studies with children and adolescents (see Hoop et al., 2008; Kennedy, 2004; Sternberg and Fiske, 2015). Although clinical standards have not yet reached a consensus stage, an emerging issue is the potential for functional MRI results to identify anomalies (Scott et al., 2012). There has been considerable discussion and debate as to the extent to which researchers have ethical obligations to communicate incidental findings to participants and to provide related referrals or interventions (e.g., Richardson, 2008). Wolf (2008) concludes ‘The truth is no one knows how to handle these difficult situations. There is no consensus as yet on how to handle incidental findings in human subjects research.’ Regarding findings that do not indicate imminent potential for harm, the advantages and disadvantages of systematically providing psychological testing findings to parents has been considered (Lefavre et al., 2007). To the extent that the research assessment instruments and procedures provide clinically interpretable information, and clinically experienced investigators are available to provide feedback, systematic information may arguably be appropriately provided to participants. Systematic feedback with clinical recommendations, however, changes the design of the study from

observational to one having some elements of screening, brief intervention, and referral to treatment (SBIRT). For ABCD, aside from indicators of potential hazards, we have elected not to provide systematic feedback, but ABCD policies also do not prohibit site investigators from conveying information in response to parents’ and minor participants’ requests. While the developmental period including ages 9 and 10 years may be too early to engage minor participants in these deliberations, the possibility that adolescents, as well as parents, may have a greater role in considering these oversight issues (Di Pietro and Illes, 2013; Houghton, 2015) will be addressed in future discussions.

In summary, observational research collecting information on brain development, substance use and psychological characteristics may identify neurological anomalies and other clinically relevant findings that raise ethical challenges. For large multisite studies involving children and adolescents such as ABCD, the process of identifying pertinent assessments, consideration of potential approaches, and the development of guidelines and procedures should be initiated several months prior to participant recruitment and consent. Pertinent clinical issues include child abuse, imminent potential harm to self or others, substance use, neurological anomalies, and other clinically pertinent incidental findings. While discussions on approaches to findings indicating imminent hazards may readily reach consensus, discussions on approaches for findings with more ambiguous implications may generate debate and disagreement. In selected arenas, this article discusses some of the issues presented and approaches developed for the ABCD study. In addition, the literature cited provides discussions of other areas and the deliberations of others. We do not intend for this review of biomedical ethical principles and the ABCD study approaches for identifying and addressing clinical oversight issues to necessarily be directly applicable to other such projects. In fact, we expect that further deliberations will result in alterations or additions to the ABCD study approaches. We hope that this discussion contributes to a growing literature on ethical issues in observational neuroimaging studies with children and adolescents by clarifying the framework needed for developing ethical clinical oversight procedures.

#### Conflict of Interest

None.

#### Acknowledgements

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#### Appendix A

##### ABCD Bioethics and Medical Oversight Advisory Group Charter

The ABCD Bioethics and Medical Oversight Advisory Group, comprised of experienced clinicians and ethicists, will propose guidelines for identifying and responding to information obtained during the course of the study that may indicate significant threats to the participants’ well-being. Anticipated examples of such information include evidence or reports of child abuse and neglect, imminent potential for self-harm or harm to others, serious medical and psychiatric disorders, substance use and related problems, incidental findings, and confidentiality limitations. The guidelines will protect the rights of parents and participants to privacy and confidentiality, address the critical need to obtain unbiased information in order to achieve the study aims; and define responsible protective actions to be taken to address the needs of vulnerable participants. This group will propose guidelines and procedures for the ABCD Research Sites to monitor and respond to parent and child assessment results that have clinical significance and incidental findings on bioassays (including neuroimaging). The group will propose (for approval and implementation) guidelines and procedures pertaining to

bioethics and medical oversight for approval by the ABCD Steering Committee, with consultation from the ABCD Observational Study Monitoring Board [OSMB] and External Advisory Board [EAB]. The Advisory Group will oversee the review and revision process, resulting in the ABCD Bioethics and Medical Oversight Guidelines and Procedures Manual. The ABCD Bioethics and Medical Oversight Advisory Group will provide advice and consultation to the ABCD Coordinating Center and Research Sites regarding the implementation of these guidelines and procedures. Each ABCD Research Site will develop site specific standard operating procedures for the implementation of these guidelines and procedures. The ABCD Bioethics and Medical Oversight Advisory Board and the ABCD Coordinating Center will review these ABCD Research Site standard operating procedures to ensure the implementation plans are consistent with these guidelines. Over the course of the study, the Advisory Group will provide clarification regarding the interpretation of guidelines and, when necessary, will propose amendments to the guidelines and procedures to the ABCD Steering Committee. The ABCD Coordinating Center will develop and implement site monitoring, reporting and response procedures in accordance with these guidelines, and provide reports of any adverse events and a semiannual report of monitored indices to the ABCD Bioethics and Medical Oversight Advisory Group, as well as the ABCD OSMB and the ABCD EAB, for review. The ABCD Bioethics and Medical Oversight Advisory Group will also conduct an annual review of these guidelines and will provide recommendations for any changes or additions to the ABCD Steering Committee, including those in anticipation of subjects' reaching the legal age of consent.

ABCD Bioethics and Medical Oversight Guidelines (05/10/16 version)

**Introduction:** These recommendations are intended to focus on clinically pertinent issues, including the topics outlined below. ABCD Research Sites will be responsible for developing and documenting local plans. Examples will be provided to facilitate the development and documentation of individual site plans. Prior to the initiation of the project, this proposal will be reviewed and a final version approved by the ABCD Steering Committee, in consultation with the ABCD OSMB and EAB.

**Monitored indices:** The ABCD Coordinating Center and the ABCD Bioethics and Medical Oversight Advisory Group will collaborate on the identification and documentation of assessment items that may prompt concerns and lead to additional assessment [i.e., "monitored indices"].

**Disclosure of assessment results:** Individually identifiable findings from the child's assessment will be provided to the parent in some instances that do not require the child's assent, including reports of child abuse and neglect, imminent potential harm to self or others, specified incidental findings, life threatening substance use patterns, or as specified by the Certificate of Confidentiality. The results of the research assessment will typically not be provided to parents or others. However, there may be instances where parents request information, the child assents to the disclosure and the investigator is able to provide the information requested. These policies are not intended to prohibit such disclosures. **Example:** Parent consent: "This is a research assessment that is not intended as a clinical evaluation. With the exception of concerns specifically described here, the results of the research assessment will typically not be provided to you."

## Child Abuse and Neglect

### Guidelines

Although the ABCD study has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services, the investigators will voluntarily inform appropriate individuals or agencies if they determine that there is risk of harm to the participant or others, including child abuse or neglect.

Prior to initiating the assessment, the subject [i.e., child participant]

and parents will be informed that confidentiality is limited and does not extend to reports of child abuse or neglect. When the assessment or other contacts with participants raise concerns that an individual under age 18 is being subjected to ongoing abuse or neglect, the investigator or staff member will collect as much information as possible about the identification of the victim [name, current location, age when abuse occurred, current age, contact information], perpetrator [name, relationship to victim, description, current location, contact information; adult or child], description of abuse or neglect, time period of occurrence, any current serious hazard to the individuals [if yes, call 911 immediately], and whether the abuse has been previously reported and/or investigated. [If the instance of abuse or neglect has been previously reported, and the prior report is verified, duplicate reporting may not be required.] The site Principal Investigator and, if appropriate, other investigators or staff, should be informed and become involved in the assessment and decision making process as soon as possible. The instance will be documented and reported to the ABCD Coordinating Center for review.

### Procedures

**Informed consent:** The consent [parent] and assent [child under 18 years old] procedures will clearly indicate that confidentiality does not extend to reports of child abuse and neglect.

**Example:** "Exceptions to confidentiality include any information about possible child abuse or neglect... If the researchers learn that your child or someone else may be seriously harmed, they will need to inform the appropriate agencies. The investigator will report such information to the appropriate local (e.g., Children and Youth Services) or state agency..."

**Child Protective Services reporting:** The site staff or investigator will report the incident to local Child Protective Services consistent with state regulations. If the child is removed from the family, regulatory requirements for research with children who are wards of the State or any other agency, institution or entity [45 CFR part 46, subpart D § 46.409] will be followed.

**Site Documentation:** A local report with identifying information will describe the information collected, the information source [i.e., child subject and/or parent], a copy of the submitted report, whether the participant and parent were informed that the report was being filed and their response to this, and any follow-up actions taken. This report will be filed and secured with documents containing identifying information.

**ABCD Coordinating Center report:** This report will not include identifying information. The instance will be documented and reported to the ABCD Coordinating Center for review. The documentation should include a summary of the information included in the site documentation.

### Site responsibilities:

- [1] written instructions to assessors and other staff
- [2] documentation of state regulations
- [3] site reporting procedures [e.g., phone numbers, online forms]
- [4] report plan

## Imminent potential for self-harm or harm to others

### Guidelines

The immediate safety of the child subject, parents or others takes priority over research participation. When imminent potential for self-harm or harm to others is identified, ABCD Research Site investigators and staff will take action to prevent harm to self or others. Prior to initiating the assessment, the subject [i.e., child participant] and parents will be informed that confidentiality is limited and does not extend to reports of imminent self-harm or harm to others. When the assessment or other contacts with participants raise concerns that a child



subject or parent poses an imminent potential for self-harm or harm to others, a licensed clinical professional will be contacted and will conduct an assessment to determine clinical actions that are needed. If an appropriate licensed clinical professional is not immediately available, emergency medical, security, and/or police services will be contacted, as indicated by the specific situation, and further assessment and/or intervention thereby initiated. The site Principal Investigator and, if appropriate, other investigators or staff, should be informed and become involved in the assessment and decision making process as soon as possible. The instance will be documented and reported to the ABCD Coordinating Center for review.

#### Procedures

**Informed consent:** The consent [parent] and assent [child under 18 years old] procedures will clearly indicate that confidentiality does not extend to information indicating imminent potential for self-harm or harm to others.

**Example:** “Exceptions to confidentiality include any information about possible ... intent to physically injure oneself or another person. If the researchers learn that your child or someone else is in serious danger of harm, they will need to inform the appropriate agencies... If current suicidal or homicidal thoughts, plans or attempts are identified, a study investigator or staff member will discuss the findings with you and your child and, if needed, will ask that your child undergo a psychiatric evaluation in the emergency room at the most appropriate hospital setting immediately after discussion of the results.”

**Site Documentation:** A local report with identifying information will describe the information collected, the information source [i.e., child subject and/or parent], and any actions taken. This report will be filed and secured with documents containing identifying information.

**ABCD Coordinating Center report:** This report will not include identifying information. The instance will be documented and reported to the ABCD Coordinating Center for review. The documentation should include a summary of the information included in the site documentation.

#### Site responsibilities:

- [1] written instructions to assessors and other staff
- [2] identification of local licensed clinical professionals
- [3] report plans

#### Incidental findings, including medical and mental disorders

##### Guidelines

“Incidental findings” are defined here to include life threatening medical or mental disorders, pregnancy, and aberrant neuro-radiological findings. When the assessment determines that the child subject may have a potentially life threatening medical or mental disorder, or an aberrant neuro-radiological finding [i.e., incidental finding], ABCD Research Site investigators or staff will inform the parent. Prior to initiating the assessment, the subject [i.e., child participant] and parent will be informed that such “incidental findings” will be disclosed to the child and parent.

If the child has a primary health care provider, the parent will be provided with information about the incidental finding and advised to follow-up with the child’s health care provider. If requested by the parent, and written release of information is provided, the ABCD site investigator or staff will provide a description of the incidental finding to the health care provider. If the child does not have a primary health care provider, the parent will be provided with information on local resources that may be able to provide assistance. The incidental finding will be documented and reported to the ABCD Coordinating Center.

**Pregnancy:** Subjects known to be or suspected of being pregnant will not participate in MRI procedures. Each site will develop pregnancy assessment and/or testing approaches, confidentiality policies,

and communication procedures. The procedures will include assurance of confidentiality for pregnancy and related information for all female subjects. These procedures will be described in the IRB materials and Site Procedures Manual.

Findings of the ABCD research assessment are not intended to be a comprehensive clinical evaluation. The assessment is not designed to be a substitute for an annual medical check-up, and does not include a comprehensive screen for all possible life threatening conditions. The results will typically not be provided to the parent or subject.

#### Procedures

**Informed consent:** The consent [parent] and assent [child under 18 years old] procedures will clearly indicate that the parent will be informed when potentially life threatening medical or mental disorders, or an aberrant neuro-radiological finding, are detected.

The methods for determination and communication of known or suspected pregnancy will vary by site. The informed consent procedures will indicate that individuals known or suspected to be pregnant individuals will not be allowed to participate in imaging procedures.

**Example:** Parent consent: “If your child is found to have a life threatening medical or mental disorder, or an unusual brain characteristic detected by the brain scan, you will be informed. We will recommend that the child receive a clinical evaluation, and you will be provided with sources for obtaining information on local medical facilities or coordination services.”

**Site Documentation:** A local report with identifying information will describe the information collected, the information source [i.e., child subject and/or parent], and any actions taken. This report will be filed and secured with documents containing identifying information.

**ABCD Coordinating Center report:** This report will not include identifying information. The incidental finding and actions taken will be documented and reported to the ABCD Coordinating Center.

#### Site responsibilities:

- [1] written instructions to assessors and other staff
- [2] local resources for health care assistance
- [3] report plans

#### Substance Use

##### Guidelines

The validity of substance use reports by the child depends, in part, on confidentiality. However, the immediate safety of the child subject takes priority over research concerns. Prior to initiating the assessment, the subject [i.e., child participant] and parents will be informed that confidentiality is limited and does not extend to imminently life threatening substance use patterns. Therefore, when the child reports imminently life threatening substance use patterns, the parent will be informed, will be advised to obtain a clinical assessment for the child, and will be provided with information on local options for obtaining an immediate assessment. The site Principal Investigator and, if appropriate, other investigators or staff, should be informed and become involved as soon as possible. The instance will be documented and reported to the ABCD Coordinating Center.

#### Procedures

**Informed consent:** The consent [parent] and assent [child under 18 years old] procedures will indicate that the results of the substance use assessment and substance use screening will not be provided in most instances. The consent procedures will state that imminently life threatening substance use patterns will be reported to the parent and recommendations for obtaining a clinical assessment for the child will be provided.

**Example:** Parent consent form: “Your child will be asked to provide

a urine sample to test for recent drug use and he/she will be asked to undergo a breathalyzer test for recent alcohol use before the assessments begin. If your child tests positive and is currently under the influence of drugs and/or alcohol, we will ask you and your child to reschedule their appointment. An investigator will discuss the positive findings with your child, recommend further assessment and treatment, and provide information on assessment and treatment options. We will ask your child's permission to discuss these matters with you. If your child does not give us permission to discuss these matters with you, we will not be able to tell you."

"Your child will be asked about his or her alcohol, nicotine and other drug use. In general, you will not be informed about the results of this substance use assessment. However, if the child reports a substance use pattern that may be deadly in the immediate future, you will be informed and provided with information about local resources for obtaining a clinical evaluation for your child."

**Site Documentation:** For instances when the child reports an imminently life threatening substance use pattern, a local report with identifying information will describe the information collected, the information source [i.e., child subject and/or parent], and any actions taken. This report will be filed and secured with documents containing identifying information.

**ABCD Coordinating Center report:** This report will not include identifying information. The instance will be documented and reported to the ABCD Coordinating Center.

**Site responsibilities:**

- [1] written instructions to assessors and other staff
- [2] identification of local licensed clinical professional
- [3] identification of local clinical resources
- [4] report plans

## Incarceration

### Guidelines

Subjects will not be eligible to participate in assessments during periods during which they are a "prisoner." A "prisoner" is defined as "any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing (45 CFR 46.303(c))."

### Procedures

Periods during which the subject meets the definition of being a "prisoner" will be documented. The subject will not undergo study assessments or other procedures during such periods. At such time that the subject no longer meets the definition of a "prisoner," their participation in the study may resume.

**Informed consent:** The consent [parent] and assent [child under 18 years old] procedures will indicate that if the subject becomes a prisoner, the study assessments and procedures will stop during the period that he/she is a prisoner and will resume after the subject is not a prisoner anymore.

**Example:** Parent consent form: "if your child becomes involuntarily confined or detained in a penal institution, the investigators will not do any study procedures until your child is released from prison."

**Site Documentation:** A local report with identifying information will describe the information collected, the information source [i.e., child subject and/or parent], and any actions taken including the period of time that data cannot be collected. This report will be filed and secured with documents containing identifying information.

**ABCD Coordinating Center report:** This report will not include

identifying information. The instance will be documented and reported to the ABCD Coordinating Center.

**Site responsibilities:**

- [1] written instructions to assessors and other staff
- [2] report plans

## Study Withdrawal and Discontinuation

### Guidelines

The child and/or parent may decline participation in the research, in part or whole, at any time and for any reason. For parents and children who have voluntarily provided research assessments and who decline future participation, the data collected during the consented period will be retained and utilized. If the investigators decide to terminate a subject's participation in part of the research procedures without regard to the subject's consent because the procedure is exposing the subject to an unacceptable level of risk [e.g., a metal medical device resulting in exclusion from MRI], the investigators will offer the subject participation in other research procedures. If the investigators terminate a subject's participation, the investigators will explain to the subject and parent or guardian the reasons for this action.

### Procedures

**Informed consent:** The consent [parent] and assent [child under 18 years old] procedures will indicate that the child and/or parent may decline participation in the research, in part or whole, at any time and for any reason.

**Example:** "You may withdraw, at any time, your consent for your child's participation in this research study, to include the use of your child's identifiable information. (Note, however, that if you withdraw your consent for the use and disclosure of your child's identifiable information for the purposes described above, your child will also be withdrawn, in general, from further participation in this research study.) Any identifiable research information recorded for, or resulting from, your child's participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for your child's participation in this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for your child's participation in this research study will have no affect on your current or future relationship with [institution]. Your decision to withdraw your consent for child's participation in this research study will have no affect on your or your child's current or future medical care at [institution] or affiliated health care provider or your or your child's current or future relationship with a health care insurance provider.

**Example:** 'If the investigators decide that a research procedure is exposing your child to an unacceptable risk [e.g., a implanted metal medical device resulting in the MRI being hazardous], the investigators will stop your child's participation in that part of the research procedures. The investigators will offer your child continued participation in other research procedures. In the unlikely circumstance that the investigators need to stop your child's participation in the research, the investigators will explain to you and your child the reasons for this action.'

**Site Documentation:** For instances when the child is withdrawn or discontinued from study participation, a local report with identifying information will describe the information collected, the information source [i.e., child subject and/or parent], and any actions taken. This report will be filed and secured with documents containing identifying information.

**ABCD Coordinating Center report:** This report will not include

identifying information. The instance will be documented and reported to the ABCD Coordinating Center.

#### Site responsibilities:

- [1] written instructions to assessors and other staff
- [2] subject withdrawal or discontinuation will be reported to the IRB as required
- [3] report plans

#### • Certificate of Confidentiality

#### • Guidelines

The ABCD consortium will apply for a Certificate of Confidentiality. The following section assumes application approval.

Identifying information protected by a Certificate may be disclosed under the following circumstances:

- Voluntary disclosure of information by study participants themselves or any disclosure that the study participant has consented to in writing, such as to insurers, employers, or other third parties;
- Voluntary disclosure by the researcher of information on such things as child abuse, reportable communicable diseases, possible threat to self or others, or other voluntary disclosures provided that such disclosures are spelled out in the informed consent form;
- Voluntary compliance by the researcher with reporting requirements of state laws, such as knowledge of communicable disease, provided such intention to report is specified in the informed consent form (see Attachment D, which sets forth PHS policy on reporting of communicable diseases); or
- Release of information by researchers to DHHS as required for program evaluation or audits of research records or to the FDA as required under the federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.)

#### Procedures

**Informed consent:** The consent [parent] and assent [child under 18 years old] procedures will indicate that the ABCD study has obtained a Certificate of Confidentiality [when issued] and will provide a description of the related implications.

Example: “We will keep the study information private to the extent possible by law. We have a Certificate of Confidentiality from the Department of Health and Human Services (DHHS). This certificate will protect us from being forced to release any research data in which you or your child are identified, even under a court order or subpoena.

However, we will report certain contagious diseases, information about child abuse, and threats to self or others. Information needed for your child’s care during a medical emergency may be given to the medical people who are treating your child. In addition, under certain conditions, people responsible for making sure that the research is done properly may review your study records, such as people from the National Institutes of Health. All of these people are also required to keep your identity confidential. Otherwise, the information that identifies you will not be given out to people who are not working on the study, unless you give permission.”

**Overall site monitoring and reporting procedures:** To assure procedures are consistent with these guidelines, the ABCD Coordinating Center will develop and implement site monitoring, reporting and response procedures in accordance with these guidelines. In addition to clinical issues, pertinent issues include unanticipated problems, adverse events, protocol deviations, lapsed IRB approval/other non-compliance issues, data breach, confidentially breach, and inappropriate PHI access. The ABCD Coordinating Center will provide reports of these events and a semiannual report of monitored indices to the ABCD Bioethics and Medical Oversight Advisory Group, as well as the ABCD OSMB and the ABCD EAB, for review.

#### Summary: policy reviews

These guidelines will be subject to on-going review and any changes approved by the ABCD Steering Committee will be implemented. In addition, the ABCD Bioethics and Medical Oversight Advisory Group will undertake an annual review and a report with recommendations for any changes will be submitted to the ABCD Steering Committee. In the year prior to the subjects’ reaching the legal age of consent, the ABCD Bioethics and Medical Oversight Advisory group will propose changes and additions for obtaining subject consent.

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