Chapter 12
Ethical Considerations in Development of Future Therapies for Women and Children

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Abstract Translational toxicology has the potential to equip healthcare providers with new strategies to address health effects from exposure to toxic agents, especially for women. Yet in many cases, the existence of developmental milestones is coextensive with vulnerability, such that these populations merit special protections when it comes to their participation in the very research that would yield these strategies. This chapter reviews the ethical considerations and regulatory limitations that obtain to these groups of research participants and then applies these considerations to the fundamental concepts in translational toxicology. The focus of this chapter is the development of future therapies. First, the chapter reviews the criteria for what makes research ethical, and then describes the ethical and regulatory considerations that attach to the kinds of projects necessary for the development of future therapies in translational toxicology. Following this, the chapter details considerations unique to each experimental strategy (prevention, mitigation, and reversal), and finally includes several general ethical considerations for the discipline as a whole.

Keywords Ethics • Regulation • Vulnerable populations • Toxicology and pregnancy • Research ethics

Translational toxicology has the potential to equip healthcare providers with new strategies to address health effects from exposure to toxic agents. Rather than simply advising patients to avoid exposures – advice often difficult to follow when the exposures are outside of the patient's control – this new field may provide strategies for protecting, mitigating, or reversing adverse effects of environmental exposures. Such strategies are particularly desirable in populations where developmental milestones may provide opportune windows for intervention, and therefore (pregnant) women, fetuses, and children are the targets for therapy. Yet in many cases, the

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existence of developmental milestones is coextensive with vulnerability, such that these populations merit special protections when it comes to their participation in the very research that would yield these strategies.

In this chapter, I will review the ethical considerations and regulatory limitations that obtain to these groups of research participants and then apply these considerations to the fundamental concepts in translational toxicology. While there are certainly a host of clinical ethics issues that will be related to the initiation of any proposed therapy, the focus of this chapter is the *development* of future therapies. Therefore, I will restrict my comments to those related to the research participation of these groups. And as a side note: while animal studies are necessarily prior to trials with humans, the ethics of animal experimentation is also beyond the scope of this work.

I will begin the discussion of research by reviewing the criteria for what makes research ethical, and then describe the ethical and regulatory considerations that attach to the kinds of projects necessary for the development of future therapies in translational toxicology. Following this, I will describe considerations unique to each experimental strategy (prevention, mitigation, and reversal), and finally identify several general ethical considerations for the discipline as a whole. This work will set out the framework for those considering the development of one of the proposed strategies to develop therapies for women or children in a way that is accessible, thought-provoking, and practically applicable to study design.

12.1 What Makes Clinical Research Ethical?

In an influential article in the *Journal of the American Medical Association*, Emanuel and colleagues identified seven features that constitute ethical biomedical research (Emanuel et al. 2000). Ten years later, Emanuel and colleagues updated their thinking to reflect the contemporary nature of clinical research (Emanuel et al. 2011). They argue that none of the regulatory guidelines are sufficiently broad or specific enough to include both the ethical considerations for the context of research, nor are they sufficiently action-guiding for researchers who endeavor to involve humans as participants in their studies. As a response, their (now) eight-faceted approach to clinical research creates a framework which, when considered in its entirety during both the planning and implementation stages of the research, will enable researchers to have a solid ethical foundation for their research project.

While the standard approach to biomedical research is the randomized clinical trial (RCT), Emanuel et al.'s framework is geared toward any research that aims "to improve health and healthcare" (Emanuel et al. 2011, p. 125). Trials of chemopreventive agents or other pharmaceuticals (even those "generally-recognized-as-safe") often take the same form as an RCT, and therefore this framework is directly applicable. But even for those observational studies or social and/or behavioral modification efforts that differ in format from an RCT, to the extent that the goal is to improve health (either of the participants directly or of future patients), the framework will still serve as an important foundational reference point.

In what follows, I discuss each of the eight constitutive elements in turn, applying examples from translational toxicology to demonstrate how the ethical considerations would influence study design and conduct.

12.1.1 Collaborative Partnership

Fundamental to the ethical considerations in research is the notion that research is done *with* people, not to them (Weijer and Emanuel 2000). As a result, it is helpful to think of research participants as partners in the enterprise (and why some have moved away from the terminology of "subjects," which may suggest a lower position in the research hierarchy than investigators). Partnering with participants not only helps to guard against exploitation by having participants help design fair and just study practices, but it also helps to ensure that the proposed research meets the needs of the community (Emanuel et al. 2011). Consider a study that attempts to reduce nicotine exposure to women and fetuses by getting pregnant women to quit smoking. Without partnering with the targeted audience, it will be impossible to know the context in which the pregnant women are making the choice to smoke and therefore know whether or not the study design is optimized. For example, for pregnant women in high stress environments, smoking may provide the only "escape" or the only feature of their lives over which they have control. Mitigating exposure in these contexts, then, must address the underlying rationale for the smoking, rather than merely the smoking behavior itself in order to be successful. Partnering with members of this community demonstrates an attitude of mutual respect and helps to ensure a fair sharing of the benefits and burdens of research participation (Emanuel et al. 2011).

12.1.2 Social Value

In order for research to be beneficial, it must have social value: it must lead to improvements in health or healthcare or sufficiently advance knowledge so that such improvements are possible in the future (Emanuel et al. 2011). Without this value, there is no ethical justification for enrolling participants in a protocol because there will be no possibility for benefit to offset the risks of participation. Note that this is true even for observational research: asking participants questions or having them participate in a focus group may, at least, waste their time and, depending on the questions, expose them to psychological or social harm, for no benefit. This does not mean that every research project must confer direct benefit on the participants; rather, the possibility of generalizable knowledge on a societal scale can also justify the conduct of research involving human participants. With respect to research attempting to mitigate or reverse exposure, investigators should be cautious to ensure that their studies have sufficient statistical power for the results to be meaningful to a wider audience and that the strategy proposed can be practically

implemented by others in the community (Emanuel et al. 2011). For example, a strategy that involves physically moving participants away from the environment where the exposure is occurring (e.g. to a new school or a new house) is likely to be impractical to be implemented on a large scale. Instead, consider approaches to research that are adaptable to communities who may not have the same resources as the research team.

12.1.3 Scientific Validity

Every research project should begin with a clear hypothesis (or null hypothesis), an approach that is designed to answer the scientific question, and a data analysis plan that is appropriate to the methods selected (Emanuel et al. 2011). As with social value, research projects that lack scientific validity will yield no generalizable results and therefore will result in the exploitation of participants (because there is no possibility of benefit to offset the risks of participation). As translational toxicology begins to mature, there are at least two significant challenges that researchers will face when they move into the health arena. The first is ensuring that participants retain access to whatever healthcare services they are routinely entitled, regardless of whether or not accessing those healthcare services cohere with the goals of the study (Emanuel et al. 2011). So, for example, investigators may study over-the-counter or prescription drugs used by pregnant women in an observational study design, but may not restrict a woman's access to pharmaceuticals generally available or prescribed by her healthcare provider. Secondly, estimating sufficient statistical power for studies that aim to improve health often require different considerations from the types of studies that environmental scientists conduct. Those engaging in these new strategies to develop therapeutics to exposure must consider these alternative approaches to study design and participant recruitment.

12.1.4 Fair Participant Selection

Science should dictate which individuals are targeted for participation, not convenience to the investigator or predictions about which kinds of people a recruitment scheme will be easier to attract. Rather, in order to minimize the possibility of exploitation, participants should be chosen because they meet scientific goals and therefore enhance the social utility of the research. For researchers who are developing new therapeutic strategies, it is also important to remember the responsibility to minimize risk in both designing the study and selecting the participants. Because the target for much translational toxicology research will be individuals at or near developmental milestones, many of them will fall into the "vulnerable" category (see next section). This means that extra research protections will need to be in place in order to ensure risks are minimized for participants from these groups. In some cases, their vulnerability is precisely what makes them appropriate

participants for the research, which can cause extra complications (Schonfeld 2013). Regardless, choosing participants fairly is essential to the ethical conduct of research.

12.1.5 Favorable Risk-Benefit Ratio

All research carries risk, even if the risk is simply time or inconvenience spent on activities the participant would not otherwise choose. Yet for research to be ethical, on balance the research must favor benefits over risks (Emanuel et al. 2011). One way to do this is to ensure that risks are minimized to the greatest extent possible consistent with sound scientific design. Capitalizing on procedures already happening as part of clinical care (e.g. a routine blood draw where an extra vial can be drawn) minimizes risks. But enhancing the benefits to the participants and the community in which they reside is another way to ensure a favorable risk-benefit ratio (Emanuel et al. 2011). Suppose you are concerned about the effect of maternal diet on the development of Autism Spectrum Disorder (ASD) in children, but you have reason to believe that folic acid intake at the appropriate stage of development may be protective against ASD (Lyall et al. 2014). Providing folic acid to all participants in the study, free of charge, is one way to maximize benefits to participants since we know that folic acid is beneficial for many other aspects of development (Kim et al. 2014).

Risks and benefits can be categorized by type, magnitude, and frequency, and it is important to carefully articulate these in the research design phase (Emanuel et al. 2011). Otherwise, a comparison of risks and benefits may fail to accurately capture the trade-offs involved in research participation. Regardless, benefits and risks conferred on research participants are limited to the risks of the research interventions only. So if, as suggested earlier, investigators are going to capitalize on a routine blood draw and simply take an extra vial of blood, then the risks of the blood draw itself are not risks of the research. Rather, the risks conferred on the participant are the risks of taking the *extra* blood. Finally, when there are no direct benefits to participants in the study, it is important to consider the societal benefits carefully in comparison to the individual risks to participants (Emanuel et al. 2011). This is a common situation for early Phase drug trials, where the safety of the pharmaceutical is part of what investigators are trying to establish. Any study, however, that does not offer individual-level benefits must be extra careful to minimize risks to the greatest extent possible.

12.1.6 Independent Review

In order to ensure regulatory compliance with the Common Rule (see below), all[1] research studies that involve human subjects must be reviewed by an independent body (known as an Institutional Review Board in the US and a Research Ethics

[1] Some studies are in fact exempt from IRB review; see 45 CFR 46.101 (b).

Board or Research Review Board in other parts of the world). But there are important ethical reasons for this, too. Third-party review of proposed research guards against conflict of interest among the investigators. In addition, by submitting the protocol to an independent, diversely-constituted body, broader considerations about the research can be brought to bear. Sometimes it is easier for a third party to identify and address issues with study design, subject recruitment, and informed consent precisely because it has fresh eyes to devote to the issue. The diverse expertise on something like an IRB can be very useful in helping to refine a study design to ensure compliance with the previously-mentioned concepts. Consider a research proposal that suggests a rigorous exercise regimen for a particular group of postmenopausal women as a strategy to reverse the toxic effects of a series of environmental exposures. It might be that a geriatrician on a review board knows of data that would help to bolster the study's hypothesis, or she might have information about a particular risk that could be conferred by this strategy that needs to be addressed before the research can go forward. In either case, the review board serves to facilitate the conduct of ethical research by helping to ensure that the risks to subjects are minimized. In this way, independent review of research protects research subjects, investigators, and the institution/organization that sponsors the research.

12.1.7 Informed Consent

Obtaining informed consent from research participants respects the autonomy of participants by ensuring that they can make a decision about whether or not the research activity coheres well with their values, goals, and priorities. To accomplish this, investigators must (1) provide information about the study in a cognitively-appropriate, non-jargoned fashion; (2) ensure that potential subjects understand the risks and benefits of participating in the trial; and (3) describe to participants any alternatives to participation, including the right not to participate, to ensure that individuals are freely choosing participation (Emanuel et al. 2011). Designing a consent process that respects subjects and their context, capacities, and community is not easy; investigators must be sensitive to the cognitive capacity, social and economic status, and specific contexts of their participants in order to ensure that consent will be truly voluntary (Emanuel et al. 2011). There are a whole host of vulnerabilities that may influence one's ability to give truly informed consent (Kipnis 2003), and investigators must consider these features ahead of time and plan accordingly. For example, suppose a researcher is interested in mitigating the role of endocrine disruptors in pre-teens. Adolescents are particularly sensitive to confidentiality concerns in healthcare, and have reported instances in which they either withheld information or failed to seek help in the first place because of concerns about their confidentiality not being respected (Sankar et al. 2003). Researchers who want to involve pre-teens in a study, then, should consider carefully what added

protections they can reasonably offer to this group who is particularly sensitive to information sharing.[2]

12.1.8 Respect for Participants

Informed consent does not end when the research participant signs the informed consent document. Rather, informed consent is a process that continues throughout the duration of the study. As new information becomes available to the research team, it is essential that team members communicate with active participants in a way that is appropriate to the individuals. Similarly, investigators have the responsibility to monitor the well-being of their subjects and to act accordingly (e.g. remove participants from the trial if they are experience significant adverse events from the study agent). As part of the voluntary nature of consent, participants must always be free to withdraw from the study without penalty; however it is the research team's responsibility to inform the participant if he or she needs to take certain precautions when leaving a study for safety reasons (e.g. titrate down a pharmaceutical rather than stop "cold turkey"). Finally, part of respecting participants as equal partners in the research process includes returning research results to them after the research has concluded and the data have been analyzed. This demonstrates to participants the value of their time in the study, even if the null hypothesis has not been disproven.

12.2 Ethical and Regulatory Considerations with Research involving Women and Children as Participants

Because of the focus on developmental milestones as an ideal opportunity for intervention regarding exposure, the majority of research that will be conducted in translational toxicology involves pregnant women or children as the primary participants. In many respects, this is quite laudable since these two groups have historically been excluded from participation in potentially beneficial research (Shields and Lyerly 2013; Diekema 2006), giving rise to the term "therapeutic orphans". There are several reasons for these exclusions, most of them having to do with risk aversion. Researchers and sponsors have been loathe to do anything that exposes children or fetuses to risk, for both legal and moral reasons: no one wants the legal liability of a birth defect, nor do they want to be responsible for harming children. Yet the consequence of this reluctance is a clinical situation where the vast majority of treatments for childhood illnesses are still "off label" – that is, lacking the appropriate scientific

[2] This is true even though permission to participate must be obtained from an adolescent's parents since they are not at the legal age of consent. Regardless, getting teens to assent to research participation is essential, and just as context-specific as consent in other populations.

data to demonstrate efficacy (and, relatedly, treatment toxicities) and where "reducing adult dosing" simply will not work (Palmaro et al. 2014; Frattarelli et al. 2014).

Similarly, pregnant women – and, in fact, those "potentially pregnant" (Merton 1993) – have been excluded from clinical research because of the risks to a fetus from investigational interventions. Ironically, both of these situations have led to the same consequence: a dearth of information about how to care for pregnant women (and, by extension, their fetuses) in the context of illness, disease, and discomfort: a situation that may, in fact, place both pregnant women and children at GREATER harm than if data were collected. Consider the historical example of Thalidomide, where babies were born with severe birth defects as a result of a medication commonly provided to pregnant women as an anti-emetic. No one wants to create or be responsible for the effects of the next Thalidomide. Yet the irony is that the widespread harm to fetuses resulted from *excluding* women from clinical trials; in fact, had rigorous studies been done of this and similar drugs, the magnitude of the harm to children could likely have been attenuated (Lyerly et al. 2009; Friedman 2012). Instead, the response has been to exclude pregnant women – and most women of childbearing potential (Schonfeld 2013) – from clinical trials. As Ruth Macklin argues, "the most compelling reason [for including pregnant women in a greater number of clinical trials] is the need for scientific evidence gathered under rigorous scientific conditions, in which fewer women and their fetuses would be placed at risk than the much larger number who are exposed to medications once they come to market" (Macklin 2010, p. 632).

Some argue that it is restrictive regulations that prohibit the advancement of research involving these populations, while others claim that these regulations offer fundamental protections for those who want to involve these groups to participate in research. Regardless, it is important to understand the regulatory context prior to designing studies involving pregnant women or children as participants.

12.2.1 International Research Regulations

There are several international guidelines that offer assistance to investigators when designing trials, although to be maximally applicable for research they include only general statements about "vulnerability" when referring to pregnant women and children. For example, the Declaration of Helsinki (Appendix I) includes a section on "Vulnerable Groups and Individuals," but there simply states that "[s]ome groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or incurring additional harm," and as a result deserve "specifically considered protection" (World Medical Association 2013). An example of such protections specifically listed in the Declaration is the investigator's assurance that the proposed research could not be conducted adequately with a non-vulnerable population.

The International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) from the Council for International Organizations of Medical

Sciences (CIOMS) also incorporates general language about vulnerability and consent, but has additional language specific to children and pregnant women. Guideline 14, "Research Involving Children," includes considerations such as first conducting the research with adults, when possible, and obtaining both consent from parents and assent from children to participate in the study (CIOMS 2002). Guideline 17, "Pregnant Women as Research Subjects," describes the default status for pregnant women as able to be included in research, which differs greatly from the US regulations (see below). The guideline reminds investigators about their responsibility to clearly and accurately describe the risks and benefits of research participation but makes no specific reference to the level of risk to the woman or her fetus that is acceptable; rather, there is a recognition in these guidelines that the well-being of one is inextricably linked to the well-being of the other. Still, the general principles hold that the research should be important to be carried out in this population, and the evidence of pre-clinical and clinical studies should be provided whenever possible (CIOMS 2002).

Additionally, many nations have their own national research ethics committees and associated guidance, and some of those organizations have joined international consortia or offer conferences to share best practices and establish common processes and approaches (e.g. the European Network of Research Ethics Committees [EURECNET]; Asia-Pacific Research Ethics Conference [APREC]; the National Health and Medical Research Council of Australia, etc.). Researchers planning translational toxicological research in those areas should consult the relevant guidance documents.

12.2.2 Research Regulations in the USA

The U.S. regulatory context for conducting research with pregnant women and children as participants is somewhat complicated. The regulations from the Department of Health and Human Services (DHHS) can be found at Part 46 of title 45 of the Code of Federal Regulations (CFR). The primary set of protections for human subjects, Subpart A, is known as the "Common Rule" on account of the fact that 18 federal agencies in addition to DHHS have agreed to adopt those provisions for federally-funded research that involves human participants. Included in this subpart are the requirements for informed consent and for independent review of the research, conducted by Institutional Review Boards (IRBs). Moreover, the Common Rule also includes guidance for conducting research with groups identified as requiring "additional protections." The regulations refer to these groups as "vulnerable populations": "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects" (45 CFR 46.111b). Note that both pregnant women and children are included in the list of those likely to be vulnerable to coercion and undue

influence. As a way of specifying additional safeguards, both groups have special regulatory sections dedicated to their "protections;" Subpart B for "Pregnant Women, Human Fetuses, and Neonates involved in Research" and Subpart D for children (see Appendix II).[3]

There are several features of each of the subparts that deserve special mention, and so we will pay particular attention to them here. Note that these are not the only considerations; for the full text of the regulations, please see Appendix II. Here I simply highlight some of the key features that should be considered by researchers in the design phase of studies.

12.2.2.1 Special Considerations involving Pregnant Women as Research Participants

First, Subpart B makes clear that agents should not be tried in pregnant women prior to having been studied in pregnant animals and non-pregnant human participants. Even if this is an intervention that is specifically designed for pregnant women and/or their fetuses, the regulations require that information on reproductive and general toxicities be available before designing studies with pregnant participants. This is true even though (a) animal studies do not always translate well to human studies (Rhrissorrakrai et al. 2014), and (b) pharmacokinetics are different in pregnancy, and as a result agents may operate very differently in pregnant women than in other participants (Lyerly et al. 2008).

Secondly, note that the regulations require separate risk and benefit considerations for the pregnant woman and the fetus. Essentially, the regulations ask investigators to consider to whom the possibility of direct benefit obtains. If there is no possibility of direct benefit to the woman or to the fetus, then the research is not approvable if the risk posed by the interaction is greater than minimal to the fetus.[4]

The third consideration relates to the risk/benefit calculus described above. The regulations tie consent requirements directly to fetal risk: if the risk of the intervention is not greater than minimal to the fetus, then the pregnant woman's consent is sufficient for the research to proceed. This is true even if there is no prospect of

[3] Note that while the DHHS regulations apply to research funded by DHHS (NIH, etc.), the subparts may not apply to projects funded by other federal agencies if they have not adopted those parts of the regulation. For example, the EPA has not adopted Subpart C (regulations involving prisoners), so researchers using EPA funds exclusively are not bound by those requirements. In addition, some institutions apply the subparts to all research, regardless of funding – known in common parlance as "checking the box." For those institutions that do not check the box, then research that does not receive funding from DHHS is not subject to those regulatory requirements.

[4] DHHS does reserve the right to approve research that does not meet these requirements if they agree there is "an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates" and the requisite approval criteria are met [45 CFR 46.207].

direct benefit for the woman or the fetus, as mentioned above. However, in situations where there is the possibility for the intervention to provide direct benefit to the fetus alone, consent of both the father and the pregnant woman are required. This "two-parent consent" holds regardless of the fact that some interventions that hold out the prospect of direct benefit to the fetus may create significant risk for the pregnant woman herself (e.g. surgical correction of fetal myelomeningocele (Adzick 2010; Cohen et al. 2014)). It is the one place in the federal regulations where someone with decisional capacity is unable to give her own consent (alone) for a procedure that will happen to her body (Schonfeld 2013).

12.2.2.2 Special Considerations involving Children as Research Participants

For children, there are two risk classifications listed (but not defined) within the regulations: minimal risk and a minor increase over minimal risk. These categories are important for determining (a) what kind of research is approvable, and (b) whether consent from one parent or two parents is necessary in order for the research to proceed. Additionally, investigators must identify whether or not there is the possibility of direct benefit to the children participating in the study. It is these considerations (the possibility of direct benefit as compensatory for risks incurred on study) that make some research approvable that otherwise would not be.

Finally, researchers must get assent from the children who are participating in the study in addition to consent from the parents (often termed "permission" in this context since the parents are authorizing the participation of others). Certainly, assent will not be possible for the very young or for those who are unable to understand the intricacies of a research protocol. However, explaining in a very general way what the research is and why the child is being asked to participate in it (e.g. "we are trying to understand what you breathe into your lungs during recess", what the procedures may entail (e.g., "we will ask you to blow into a tube before and after recess"), and what alternatives there are (e.g. "you can still play with your friends at recess if you do not want to be part of this research") gives the child an opportunity to have some control over what happens to her body. Many institutions go by the rule of "7 s": up to age 7, no assent is required. From age 7-14, assent should be obtained by describing the basic study design and procedures in an age-appropriate way and assessing the child's willingness to participate. From age 14 forward, children have meaningful veto power so that researchers will not enroll them in a study to which they do not assent, regardless of whether or not their parents provided permission for them to participate. The idea here is that children at this stage are capable of enough understanding and self-determination to weigh the benefits and burdens of participation and have a deciding hand in determining the course of their own future.

12.3 Experimental Strategies in Translational Toxicology

Translational toxicology aims at three experimental strategies for addressing environmental exposures that produce adverse health outcomes: preventing the exposure (or preventing the exposure from having negative health effects), mitigating the adverse health effects of the exposure, or reversing the effects of the exposure. While laudable in their innovative approaches to address clinical outcomes of environmental exposures, each of these strategies must be coupled with careful sensitivity to the ethical issues that obtain to the proposed research projects. In each of these cases, I will identify examples of possible research projects and highlight the ethical and regulatory challenges related to each one. This is not to say that this research cannot be conducted; quite the contrary, my purpose here is to facilitate the design of ethical research by proactively identifying the issues investigators must consider.

12.3.1 Prevention Research

Consider an experimental strategy that attempts to restrict the caloric intake of pregnant women in order to prevent the development of negative metabolic outcomes (like obesity) in the fetus (Hughes et al. 2013a). As part of this study, women of normal weight are asked to eat no more than 35 kcal/kg each day, divided roughly into roughly 40–50 % complex carbohydrates, 20 % lean protein, and 30–40 % good fats.

To the extent that the goal is to prevent the negative health outcomes associated with pediatric and adolescent obesity, ascertaining the effect of restriction of maternal caloric intake is intriguing. But investigators must be careful to design the trial so that it takes into account the risks and benefits conferred not just on the fetus, but also on the pregnant women whose calories are restricted. As with any trial, risks should be described in relationship to likelihood and severity in a way that a woman can assess the risk-benefit relationship for herself and determine whether or not participation coheres with her goals, values, and priorities. For example, suppose that a woman is interested in participating in the research precisely because her two other children are obese. However, the requirements of the protocol may be such that, as a busy mother of two with two part-time jobs, she lacks the time necessary to prepare the healthy meals that are the central feature of the research. She usually just runs through the drive-through at a local restaurant, or else makes easy things that please her kids (like spaghetti) because she knows she always has the ingredients in the house – she has little time to shop for fresh fruits and vegetables. In such a case, while she is committed to the outcomes of the research and values its goals, the study design simply does not work with her life. She wants the best for her baby, but isn't willing or able to sacrifice the time she spends with her kids to do the shopping and cooking that the protocol requires. However, an alternative research design, where subjects are given the pre-prepared meals (e.g. weekly deliveries cataloged by meal and date) that she simply has to put in a bowl or heat in the microwave

might, in fact, work for her. This is a way that partnering with the research community during the study design phase could create a research context that is sensitive to the needs of the target population.

As a second example, consider an experimental strategy where women with no known underlying disease conditions (and who therefore take no prescription medications) planning to become pregnant enroll in a trial where they agree to refrain from taking any over the counter (OTC) medications, including herbal supplements. Given the number of potential influences intrauterine chemical exposures can have on fetuses, elimination of one source of chemical exposures could be postulated as a preventive strategy. However, it is difficult to adequately communicate the risks of this participation, as every pregnancy, and every woman, is different. She might develop symptoms that cause her significant discomfort, which could otherwise be relieved with OTC medications. And since it is difficult to predict how one will feel in that situation, some would call into question her ability to give truly informed consent here. Certainly, there would need to be provisions for attrition on such a study, both for women who change their minds about refraining from OTC use, or for those who develop a condition that requires prescription treatment – both situations that would likely result in the participant's withdrawal from the study. And if the attrition rate is too great, then the research may be in danger of not being completed in a timely fashion or in a way that facilitates the statistical analysis described in the research plan. In that case, then, the risk/benefit ratio of the study has changed negatively for all participants as the potential for societal benefit has significantly decreased. This outcome may happen even if the investigators try to recruit those who are least likely to withdraw (say, women with a history of previous pregnancies during which they took no or few OTC medications); in addition, that recruitment strategy would call into question the generalizability of their results given that two-thirds of pregnant women are prescribed a drug during their pregnancy (Andrade et al. 2004; Daw et al. 2012; Yang et al. 2008). Ironically, this protocol might also fail to get through some IRBs, since the "no medication" rule while on study may in fact put women and fetuses at risk if they, for example, delay necessary medical care because of a desire to stay on the study, or if they refuse to take a standard antiemetic that would enable them to consume the nutrition required for successful fetal development because of study restrictions.

12.3.2 Mitigation Research

For those environmental exposures that are unavoidable or inevitable, mitigating the negative effects of those exposures may lead to better overall health outcomes. One strategy proposed for this is to use "Generally-Recognized-as-Safe" (GRAS) agents that can be tested rigorously in a population exposed to a particular hazard (Hughes et al. 2013b). In theory, using GRAS agents lessens the risk of the study, which is particularly important to already vulnerable populations like pregnant women and children. However, it is not entirely clear that this strategy is substantially safer than

other investigational agents that do not carry the GRAS label or that regulatory bodies would see them in this way. Consider, for example, the use of green tea, long hailed as, among other things, an antioxidant stemming from the polyphenols and catechins in the tea (Hughes et al. 2013a). It is conceivable that researchers might design a trial of concentrated green tea catechins as a food additive for peri- and post-menopausal women as an anti-aging strategy to preserve structure and function despite a long history of exposure to environmental toxins. Yet preliminary data are not conclusive about the benefits of green tea extracts, and in fact suggest that adverse effects disproportionately affect women (Abdel-Rahman et al. 2011). Given the regulatory requirements described earlier, it is plausible to think that in the face of these data, IRBs would insist that these risks be calculated in the risk/benefit relationship and described in the consent process. That is to say, IRBs may view this through the same lens as any other investigational agent.

This brings up the question about GRAS agents in general: what do we mean, exactly, when we say an agent is "safe" or term it an "ethical pharmaceutical"? GRAS agents are not tested through the same phased drug trial system that applies to drugs that are looking to be approved by the U.S. Food and Drug Administration (FDA) (21 CFR 170.20). Rather, manufacturers themselves make the determination that their substance is safe, with safe being defined as "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use" (21 CFR 170.3(i)). But careful analyses of the agents often produce complicated results. Many agents are safe in one preparation but may be toxic in another or with a different population (Abdel-Rahman et al. 2011). Plus, there is no standard mechanism for evaluating safety; rather, each substance is evaluated individually. Given that researchers would be proposing *novel* uses for these GRAS agents in the kind of research proposed here, one wonders whether or not the assurances of safety would persuade IRBs that the agent in question is appropriate for testing. Given the pharmacokinetic challenges to pediatric (Sage et al. 2014) and obstetric (Lyerly et al. 2008) drug development, one wonders about the challenges posed by even something like a GRAS agent.

There are occasions when manufacturers submit their information to the FDA regarding their GRAS substance. These notifications are reviewed by a panel convened by the FDA, who then responds to manufacturers only if they do not agree with the determination – no news is good news in this case (Neltner et al. 2013). However, a recent study calls into question the objectivity of these panels by pointing out that "between 1997 and 2012…financial conflicts of interest were ubiquitous in determination that an additive food was GRAS"(Neltner et al. 2013); p. E4). Additionally, at least 1 of 10 individuals served on more than 75 % of all panels convened for these food additive GRAS determinations. It is possible that this speaks to the need for expertise in these areas, but it may also speak to problems with objectivity and integrity. Regardless, to the extent that the IRB is charged with guarding against conflicts of interest, these are issues to which they would likely attend.

The upshot of all of this is that it is not at all clear that even GRAS agents would gain special privileges in research involving children and pregnant women as participants. This is partly because of the risk-averse nature of society, but also is because of the current regulatory structure. Regardless, researchers should not assume that their studies will receive "easier" handling because they involve GRAS agents rather than standard pharmaceuticals.

12.3.3 Reversal Research

The final strategy possible in translational toxicology is to attempt to undo the harm caused by toxins after the exposure has occurred. An example of this kind of research is the introduction of N-acetylcysteine (NAC) to reverse the negative effects of smoking by changing some biomarkers that may reduce the cancer-causing effects of the toxins (Hughes et al. 2013b, p. 3). The idea, then, is that NAC could be introduced into pregnant women to both reverse the damage to themselves done by smoking (or by passively being exposed to secondhand smoke) and to simultaneously mitigate the risks of smoking to the fetus by mitigating the DNA damage done by the toxins (Hughes et al. 2013b).

Such interventions look like they have the potential to promote direct benefit to both the pregnant woman and the fetus. The question then becomes what the level of risk is to both the woman and her fetus of the NAC. It is certainly true that smoking is a risky activity – but smoking is not part of the research. Rather, that is a background condition that sets the stage for the intervention, and therefore the risks of smoking do not factor into the risk/benefit calculus of the research. Instead, investigators must consider the risks and benefits of the intervention on its own merits in order for it to be approvable under the regulations – including, in this case, any differences that obtain to the dangers of first-hand compared with second-hand smoke (Kalkbrenner et al. 2014). Certainly, investigators would have to provide data about pregnant animal studies as well as additional information about clinical studies involving non-pregnant adults for the research to move forward. But the challenge really comes with the risk assessment. Assuring IRBs and other oversight groups that the intervention is "safe enough" to use in pregnancy will be an uphill battle for investigators. Consider that as of 2007, there were only 12 drugs approved for use in pregnant women, and 10 of them involved how to get the baby out (Lyerly et al. 2008)! The current risk-averse research climate rests the burden of proof on the investigators regarding safety, and the burden comes to a suspicious public. Most research involving pregnant women currently is observational in nature, with very few intervention studies being approved. And while there are both good scientific and ethical reasons to change this (Lyerly et al. 2008, 2009), there would have to be a sea change in the way that pregnant women and fetuses are viewed before this kind of research is likely to be able to move forward.

12.4 General Ethical Issues Related to the Development of Future Therapies

There are a few remaining ethical issues to discuss related to the development of future therapies. These are points for investigators to consider as they begin designing their trials.

12.4.1 Clinical vs. Biological Significance of Results

Many times in toxicological research, end points rest on biologically significant markers. Yet it is the case that not all biologically significant results will also be clinically significant. To the extent that biological significance must be established prior to clinical significance, then this makes sense. But it does create a particular challenge related to informed consent of participants. Suppose that an endpoint of a particular intervention is reduction of airway inflammation. Airway inflammation may not translate into anything that participants would notice (depending on the severity, etc.). Investigators, then, must be very careful to explain this distinction to participants in a way that they understand it. Otherwise, the risk of therapeutic misconception is great: participants may expect to receive clinical benefit from participation in the trial. One way to address this is to add surrogate endpoints like biomarkers onto other studies that are looking at clinical significance. This will give researchers access to data they may not otherwise have, while at the same time minimizing additional risk and burden to participants.

12.4.2 Social/Behavioral Interventions vs. Pharmaceutical/ Chemical Interventions

Some argue that social and behavioral interventions are preferable over chemical interventions because the "risk" is lower, as is the possibility for adverse effects. This is not always the case. Questionnaires are one thing; behavioral modification is a different beast entirely. Consider the woman who is asked to curtail or change her activities in a fundamental way during her pregnancy in order to reduce exposures to her fetus (see, for example, (Lyall et al. 2014)). Such behavioral changes can have significant costs financially, socially, and emotionally. Given that we as a society have not been particularly successful at getting the population to modify behavior to reduce the most common killer of Americans – cardiovascular disease – there is reason to suspect that there are burdens to behavior change not broadly considered by those groups who recommend such behavioral changes. Even for those populations who are particularly motivated to make a change, desire does not always equate to success.

12.4.3 Developmental Milestones in Context

There is good scientific reason to intervene at important development milestones to optimize the ability to address adverse health effects caused by toxins. However, it is important to remember that all prenatal fetal exposures entail that the pregnant woman is also exposed to an agent. In some cases, as with NAC for reversing the effects of smoking exposure, there may be benefit to both parties. But in cases where the benefit is solely or largely conferred on the fetus, investigators must consider the context in which this research will occur: through the woman's body. Her welfare is just as important as that of the fetus and must be treated as such. Therefore, "development milestone opportunities" must be considered as part of the overall strategy of research.

12.5 Conclusion

Translational toxicology holds promise for addressing the adverse health effects of environmental exposures. Indeed, investigating options directly with the groups of participants who stand to gain the most from interventions is both scientifically sound and morally laudable. Yet there are ethical and regulatory considerations that attach to research involving participants at several important developmental milestones. Attending to these issues in the early design stages of a research project can help to ensure that the research proceeds according to best practices in ethics and passes regulatory muster.

Appendix I: WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other

health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This

intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix II: Code of Federal Regulations

Subpart B	Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
	Source:66 FR 56778, Nov. 13, 2001, unless otherwise noted.

§46.201 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates conducted or supported by the Department of Health and Human Services (DHHS). This includes all research conducted in DHHS facilities by any person and all research conducted in any facility by DHHS employees.
(b) The exemptions at §46.101(b)(1) through (6) are applicable to this subpart.
(c) The provisions of §46.101(c) through (i) are applicable to this subpart. Reference to State or local laws in this subpart and in §46.101(f) is intended to include the laws of federally recognized American Indian and Alaska Native Tribal Governments.
(d) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§46.202 Definitions

The definitions in §46.102 shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) Dead fetus means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.
(b) Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means.
(c) Fetus means the product of conception from implantation until delivery.
(d) Neonate means a newborn.
(e) Nonviable neonate means a neonate after delivery that, although living, is not viable.
(f) Pregnancy encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

(g) Secretary means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.
(h) Viable, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

§46.203 Duties of IRBs in connection with research involving pregnant women, fetuses, and neonates.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart and the other subparts of this part.

§46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
(c) Any risk is the least possible for achieving the objectives of the research;
(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;
(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

§46.205 Research involving neonates.

(a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

a. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
b. Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
c. Individuals engaged in the research will have no part in determining the viability of a neonate.
d. The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

a. The IRB determines that:

i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or
ii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
iii. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

a. Vital functions of the neonate will not be artificially maintained;
b. The research will not terminate the heartbeat or respiration of the neonate;
c. There will be no added risk to the neonate resulting from the research;
d. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and
e. The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(c) and (d) do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.
(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

(a) The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §46.204 or §46.205 only if:
(b) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

(c) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

a. That the research in fact satisfies the conditions of §46.204, as applicable; or
b. The following:

i. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
ii. The research will be conducted in accord with sound ethical principles; and
iii. Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

Subpart D	**Additional Protections for Children Involved as Subjects in Research**
	Source:48 FR 9818, March 8, 1983, unless otherwise noted.

§46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

a. This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.
b. It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of §46.101 of subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at §46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at §46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at §46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of §46.101of subpart A are applicable to this subpart.

[48 FR 9818, Mar.8, 1983; 56 FR 28032, June 18, 1991; 56 FR 29757, June 28, 1991.]

§46.402 Definitions.

The definitions in §46.102 of subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) *Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.
(b) *Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
(c) *Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in research.
(d) *Parent* means a child's biological or adoptive parent.
(e) *Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;
(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;
(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

(a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
(b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

    a. that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:

        i. the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
        ii. the research will be conducted in accordance with sound ethical principles;
        iii. adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

§46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health

or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by §46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §46.404 or §46.405. Where research is covered by §§46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in §46.116 of subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by §46.117 of subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if such research is:

a. Related to their status as wards; or
b. Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco

parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

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