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Minimal Risk in Research Involving Pregnant Women and Fetuses

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Introduction

How should the definition of “minimal risk” in the federal research regulations be interpreted in regard to pregnant women and fetuses? Surprisingly, there has been little discussion of this question. There is, after all, a substantial amount of published work addressing the question of how “minimal risk” should be interpreted. Similarly, there is a large body of literature on the ethics of research involving pregnant women and fetuses, particularly maternal-fetal surgery. However, in neither of these bodies of work can one find an analysis of minimal risk in regard to fetuses or pregnant women.

The concept of minimal risk is defined in the regulations as follows:

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.¹

What would it mean to speak of risks ordinarily encountered in daily life by a fetus? And how is the concept of risks during the performance of routine physical or psychological examinations or tests to be applied to fetuses and pregnant women? These questions suggest that it is not clear how the concept of minimal risk should be translated into specific levels of risk for this category of research subjects.

Clarifying “minimal risk” for pregnant women and fetuses is important for current and future research because the concept serves several important purposes in the regulations. Subpart A, which states general rules for human subjects research, requires that risks be minimal or less for (1) expedited review of research protocols,² (2) alteration or waiver of informed consent in some cases,³ and (3) waiver of documentation of informed consent in some cases.⁴ Subpart B, which sets forth additional requirements for research involving pregnant women and fetuses, states that fetal risks being minimal or less is a requirement for (4) approval of research holding out no prospect of benefit for the pregnant woman or fetus⁵ and (5) the adequacy of maternal consent alone, without paternal consent, in research holding out no prospect of benefit for the pregnant woman or fetus.⁶ Thus, the rules cited in Subpart A require minimal risk for both the pregnant woman and fetus, and the rules in Subpart B require minimal risk for the fetus.

These rules can be applicable in various types of research involving pregnant women and fetuses. Expedited review can be carried out for various types of studies, including research on medical devices used during pregnancy that already are approved for marketing, studies

of amniotic fluid obtained at the time of rupture of membranes prior to or during labor, and research involving the collection of data through noninvasive procedures such as ultrasound, doppler umbilical artery blood flow measurements, and fetal echocardiography.⁷ Alteration of informed consent could occur in research that cannot practicably be conducted if subjects know the purpose of the study. Examples might include research involving sensitive topics such as detection of drug or alcohol use during pregnancy. Research in which there is no prospect of direct benefit to the pregnant woman or fetus could include epidemiological or pharmacokinetic studies. There is growing interest in research involving administration of medications during pregnancy to treat diseases of either the pregnant woman or fetus. Some Phase I studies of medications during pregnancy likely will not offer direct benefit. This is because the primary purpose of a Phase I study is to characterize the toxicities of the investigational agent and establish the maximal-tolerated dose, in preparation for Phase II evaluations of efficacy. Also worth mentioning is a type of research that is likely to be carried out in the future; namely, prenatal gene transfer that will aim to learn how to correct certain genetic diseases *in utero*. There is growing interest in prenatal gene therapy, for several reasons.⁸ First, some genetic diseases begin to have pathological effects even before birth; examples include alpha-thalassemia and severe combined immunodeficiency. For some diseases, like alpha-thalassemia, postnatal gene therapy would be too late to reverse these harmful effects. Second, during early gestation the fetal immune system is undeveloped, and it is hoped that there is a window during which vectors carrying normal genes can be introduced without being rejected by an immune response. Given these potential advantages, various diseases are being considered for prenatal gene therapy, including hemophilia, cystic fibrosis, muscular dystrophy, and sickle cell anemia, among others.⁹ Animal research currently is under way, aiming at future clinical trials. As with Phase I drug trials, it is likely that some Phase I *in utero* gene transfer studies will reasonably be regarded as not holding out a prospect of direct benefit for the fetus or pregnant woman.

The extensive literature on minimal risk arose in response to a need to clarify the regulatory definition. A serious shortcoming of the definition is that it leaves unanswered the question of *whose* daily life IRBs are to consider in comparing the risks of daily life to the risks in a research protocol. A number of views about this have been put forward, in discussions focusing primarily on research involving children. To answer the question of how the definition should be interpreted in regard to pregnant women and fetuses, it will be helpful to examine the views on minimal risk in that literature.

Critical Review of the Literature on Minimal Risk

Absolute vs. Relative Standards

Views on how to interpret the definition can be separated into those advocating an “absolute” and those favoring a “relative” standard. What has come to be called an absolute standard was first suggested by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (hereafter National Commission). In its report *Research Involving Children*, the National Commission stated that minimal risk should be understood as “the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of *healthy* children”.¹⁰ In other words, the ordinary risks of healthy children would serve as the uniform standard for all research involving children.

By contrast, Benjamin Freedman and coauthors advocated a standard that is based, not on the risks confronting healthy children, but the risks of daily life encountered by the research participants.¹¹ Freedman’s argument for this relative standard is based on the view that minimal risk should not be interpreted in a strictly quantitative way. His argument uses the

concept of “a minor increase over minimal risk”, found in Subpart D, which states additional requirements for research involving children. Freedman maintains that this concept should be interpreted using an analogy with parents deciding whether to let their child engage in a new activity—for example, an overnight camping trip with friends. Parents do not arrive at these judgments by making a quantitative assessment but rather compare the risks of the new activity to those of the child’s current daily life. These judgments about what is an acceptable increase over current risks are based on the child’s actual situation, which can vary between children. In other words, a relative standard is a feature of how parents typically make judgments about risks for their children.

By analogy, according to Freedman, in the research context judgments about what is minimal risk and whether a risk is a minor increase over minimal should be based on the child’s actual situation. Freedman refers to these judgments that are not strictly quantitative as “categorical” judgments. Freedman also claims that the concept of risks of daily life is not simply descriptive but also normative. When we compare research risks to the risks parents permit their children to experience in daily life, the latter risks should be bounded by a notion of what are *socially acceptable* risks. This also is relative, varying with time, place, and culture.

In considering this controversy, the National Bioethics Advisory Commission (NBAC) advocated an absolute standard on grounds of justice.¹² It argued that a relative standard would permit ill subjects to be exposed to greater risks than healthy subjects. Presumably this is because some ill subjects encounter in their daily lives the risks associated with their diseases, medical treatments, and institutional environments. A related argument is that a relative standard would permit children living in unsafe neighborhoods to be exposed to higher research risks than children living in safe locations. Because of these justice-based concerns, several other professional commissions that have interpreted “minimal risk” have endorsed an absolute standard, including the National Human Research Protections Advisory Committee (NHRPAC),¹³ the Institute of Medicine (IOM) Committee on Clinical Research Involving Children,¹⁴ and the Department of Health and Human Services (DHHS) Secretary’s Advisory Committee for Human Research Protections (SACHRP).¹⁵

The principle that the ill should not bear heavier burdens of research risk is supported by consideration of cases in which it has been violated. One well-known example is the Willowbrook experiments in which institutionalized children with developmental disabilities were inoculated with hepatitis. The researchers defended these inoculations by claiming that the subjects already had an elevated risk of developing hepatitis in virtue of being in Willowbrook. If an absolute standard had been followed, the Willowbrook experiment would not have occurred.¹⁶ For reasons such as these, an absolute standard seems preferable, and it clearly is supported by a consensus in the literature. Although Freedman seems correct in pointing out that judgments about risk typically are not quantitative, his view overlooks the argument based on justice.

Loretta Kopelman points out that the routine examinations standard, as well, can be understood as either an absolute or a relative standard. As an absolute standard, it refers to the routine examinations of healthy individuals, based on the idea that those are the only ones “we might all encounter”.¹⁷ A relative standard would refer to the routine tests that someone with a particular illness might regularly undergo. Most commentators agree that the justice-based considerations that support an absolute interpretation of the daily life standard also support an absolute interpretation for the routine examinations standard. SACHRP provides examples of tests and procedures conducted during routine medical and psychological examinations of healthy children.¹⁸

Interpreting the Absolute Standard

In discussing the risks “ordinarily encountered in daily life” as an absolute standard, Kopelman points out that some healthy people encounter greater risks in daily life than others.¹⁹ This gives rise to several ways to interpret the standard. On one interpretation, the standard includes the risks ordinarily encountered by the most risk-prone healthy people. Kopelman correctly notes that this standard, which includes the risks of fire fighting and hang gliding, for example, would permit research risks that are unacceptably high.²⁰ Two alternative interpretations have been put forward. In the context of research involving children, these are (1) the socially acceptable risks healthy children encounter²¹ and (2) the risks that all healthy children have in common.²² Good reasons can be given for rejecting the “socially acceptable” standard. As Kopelman notes, some children’s activities, such as playing football, are socially permitted but are too risky to serve as a minimal risk standard in research.²³ Similarly, the IOM report gives the example of corporal punishment in schools being socially condoned but involving harms that are too great to be the standard in research.²⁴ By comparison, the standard invoking the risks all healthy children have in common avoids this problem.

Another choice among alternatives for the absolute standard is discussed in the NBAC report, where a distinction is made between “healthy individuals” and “the general population”. According to NBAC, the standard should refer “to common risks—for example, driving to work, crossing the street, getting a blood test, or answering questions over the telephone”.²⁵ NBAC claims that the general population standard is less restrictive than the healthy individual standard, presumably because nonhealthy people encounter greater risks. NBAC states that the general population standard is preferable because it “more accurately captures the risks that are familiar to most persons”.²⁶ However, this view can be rebutted, assuming we accept the idea that the standard should be based on the risks that people have in common. Given that “healthy individuals” is a subset of “the general population”, the risks that are *in common* among the general population will just be those that are in common among healthy individuals. So, the NBAC comments give no reason to reject the “healthy individual” standard.

NHRPAC has suggested a further refinement of the standard based on the risks “ordinarily encountered in the daily lives of healthy children”; namely, that the application of the standard should take into account the age of the child.²⁷ The idea is that the risks of daily life of teenagers, for example, are greater than those of two-year-olds, who rarely are left unattended. The IOM and SACHRP agree that the daily life standard should be indexed to the age and developmental status of the child.²⁸

SACHRP further suggests that the definition should refer to healthy children *living in safe environments*.²⁹ This qualification is intended to avoid the injustice of subjecting children who live in unsafe neighborhoods to higher research risks than those to which other children would be exposed. However, if we understand the standard as involving risks in common, then it seems unnecessary to specify that the environment must be safe. The risks that healthy individuals have in common do not include those that are specific to unsafe neighborhoods.

Equivalent Risks

Freedman and coauthors suggest that satisfaction of the minimal risk standard can be shown in two ways—by showing that a procedure falls within the definition or by showing that it is relevantly similar to interventions known to fall within the definition.³⁰ Building on this idea, Kopelman points out that one way to apply the regulatory definition is to identify agreed-upon paradigm examples of minimal risk. As she puts it, “If we had clear and openly

adopted examples of minimal risk, minor increase over minimal risk, and so on, such examples could serve as paradigms to make other decisions”.³¹

Kopelman later argues against this approach on the grounds that several studies show wide disagreement over what medical procedures involve no more than minimal risk.³² In reply, although there is disagreement about some medical procedures, as the cited studies illustrate, there is a set of examples concerning which we can reasonably say there is little or no disagreement. I suggest that these include some examples given in the National Commission report, including routine immunizations, modest changes in diet or schedule, physical examination, obtaining blood and urine specimens, and developmental assessments.³³ Other examples can be found in the list of well-child examination procedures given by SACHRP, including hearing and vision tests, assessment of obesity with skin-fold calipers, noninvasive physiological monitoring, and guidance and education interventions.³⁴

Other commentators have discussed what it means for risks to be relevantly similar, or equivalent, to paradigm risks or risks known to fall within the definition. The IOM states that judgments about equivalence should take into account the duration, probability, and magnitude of the potential harms or discomforts.³⁵ SACHRP added that equivalence should take into consideration the cumulative risk posed by all of the research procedures to which a subject would be exposed, as well as the reversibility of harms.³⁶ Taking all of these factors into consideration, it is possible to make judgments about equivalency of risks.

Proposals to Modify the Definition

Several authors have maintained that the regulatory definition of minimal risk should be modified. One view is that the part referring to “routine physical or psychological examinations or tests” should be dropped. This is recommended in the NBAC report, but no argument in support of this change is given.³⁷ Kopelman states that NBAC’s reason was to “make it easier to conduct research”.³⁸ Presumably, the idea is that the routine examinations standard is more restrictive than the daily life standard. Kopelman refutes this argument by pointing out that the “daily life” and “routine examinations” standards are stated as disjuncts in the definition. Because only one disjunct need be satisfied, dropping the “routine examinations” standard does not make it easier to do research.³⁹

Another view is that the part referring to risks “ordinarily encountered in daily life” should be deleted. A report by the Council for International Organizations of Medical Sciences (CIOMS) advocates this view, but no supporting argument is given by CIOMS.⁴⁰ Kopelman also supports this view based on the following arguments: (1) we are unable to identify the risks of daily life;⁴¹ and (2) even if we knew what these risks are, we would not be able to quantify them.⁴² Resnik agrees with Kopelman that it is difficult to identify and describe the risks of daily life of a healthy individual.⁴³ However, Freedman gives a convincing reply to (1), pointing out that indeed we can identify the common risks:

While there will always be exceptions, within any given society daily life will present the bulk of its citizens with ordinary hazards at home, at work, at play, and in transit, crossing the street or taking a bath. It is not hard to identify this set of common social risks. We are, by definition, each acquainted with them; and, almost by definition, if we are unsure whether they belong within the set of common risks then they don’t.⁴⁴

In reply to (2), at least some of the commonly encountered risks of daily life can be quantified. For example, Wendler and coauthors provide quantitative estimates of the risks of car trips, bathing, and playing various sports.⁴⁵ Moreover, the need to quantify all the risks of daily life is called into question by Freedman’s point that our assessments of risk are not always quantitative.

Another argument by Kopelman against the daily life standard is that it is unclear why daily risk is a morally justifiable threshold to set for research risks.⁴⁶ Concerning this argument, it is noteworthy that nowhere in the literature is an attempt made to justify the daily life standard. However, I suggest that a justification can be given. When a child is *not* participating in a research study, she is being exposed to the risks ordinarily encountered in daily life. If the child enters a research study that holds out no prospect of benefit to the child, the risk of daily life is a suitable limit to the risks the child should encounter in the study because the risk to which she will be exposed is not greater than what she would otherwise encounter. Her risks are not increased—they are the same as the background risks of daily life.

Fisher and colleagues also argue against the daily life standard.⁴⁷ They point out that the risks children encounter in daily life can be considered acceptable because the activities in which these risks arise have benefits for the children. For example, athletic activities can offer children opportunities for personal growth and development. In research that does not hold out the prospect of direct benefit to the child subject, there is no offsetting benefit to the child and therefore the risks are not as acceptable, compared to the risks of daily life.⁴⁸ Wendler also makes this argument against the daily life standard.⁴⁹ In reply, although the risks of daily life sometimes are associated with activities that offer benefits to the child, often this is not the case. For example, parents may take their children across the street or riding in a car for reasons that do not benefit the child. Therefore, the contrast in question is not as sharp as Fisher and Wendler make it out to be. Moreover, there can be indirect benefits and growth and development for a child from participating in research, such as learning about, and feeling good about, being altruistic. For these reasons, this argument by Fisher and colleagues and Wendler is not persuasive.

Another view, advocated by Wendler and coauthors, is that the entire definition should be rejected.⁵⁰ First, they would reject the daily life standard based on their quantitative estimates of the risks of daily life of healthy individuals. They maintain that their estimates show that these risks are higher than what IRB's typically permit, implying that the daily life standard is not restrictive enough. In reply, it is reasonable to hold that if the actual risks of daily life are too high to serve as the minimal risk standard, then they should not be used and another definition of minimal risk should be sought. However, the risk estimate by Wendler and colleagues is based on a selection of particularly risky activities; namely, playing football and high-risk car trips—specifically involving teenaged drivers on wet rural roads. This estimate overlooks the arguments supporting the view that the daily life standard should reflect the age-indexed risks that virtually all healthy children have in common. Playing on a school football team is not an activity that is common to virtually all children, and younger children tend to be less frequently exposed to the risks of teen driving than teen drivers themselves. Wendler's argument is unsuccessful because the numbers are based on particularly risky activities rather than risks in common.

Wendler's rejection of the routine examinations standard is also based on estimates of the risks involved in the routine physical and psychological examinations and tests of healthy children. Because these risks are very low, Wendler maintains that the routine exam standard is too restrictive and should be rejected. We have already considered the flaw in this argument—it overlooks that the two parts of the definition are disjuncts, and the daily life part prevents the definition from being too restrictive.

After rejecting the current definition, Wendler and colleagues discuss several alternative risk standards.⁵¹ One is called the "*de minimus*" standard, which refers to the risks in daily life that we typically ignore because they are low. This differs from the daily life standard, according to Wendler, because parents may ignore the risks of traveling in a car but not

ignore the risks in their children playing, say, football. In reply, it is not clear that parents generally ignore the risks that children have in common. Many parents, for example, do not ignore the risks in crossing the street but urge their children to be careful. Similarly many parents do not ignore the risks involved in driving a car.

Another alternative suggested by Wendler and coauthors is called the “community risk” standard, which refers to the risks considered acceptable by society that children are allowed to undergo to benefit others as part of family life, such as riding in a car to take a sibling to an event. Yet another alternative is the “charitable participation” standard, which refers to risks children undergo in doing charitable acts such as mowing an infirm neighbor’s lawn or shoveling a neighbor’s sidewalk. However, it is not obvious that the level of risk involved in the community standard is different from the level involved in the charitable participation standard. Shoveling snow, for example, would seem to be an activity children are allowed to undergo for the benefit of family members.

Wendler defends the charitable participation standard as being analogous to children participating in research for the benefit of others.⁵² He reasons that the risks permitted in research that does not hold out the prospect of benefit to a child should be no greater than the risks children encounter in daily life to benefit others. In reply, if the “risks in common” standard is adopted, it is not clear that the level of risk involved in the charitable participation standard differs from that of the daily life standard. Wendler’s examples of mowing the lawn and shoveling snow would seem to be equivalent to the risks healthy children have in common, for the relevant age-indexed groups. More importantly, Wendler’s argument that an alternative standard is needed is based on the point that some children’s activities of daily living involve risks that are too high. But this supposed problem can be eliminated by adopting the “risks in common” interpretation. All children do not participate in risky sports, for example. Thus, the argument for turning to an alternative standard is flawed.

In summary, all of the arguments given to date for revising the regulatory definition of minimal risk are unsuccessful.

Implications for Research Involving Pregnant Women and Fetuses

Our examination of the pros and cons of alternative interpretations of “minimal risk” supports the following conclusions:

1. The concept of minimal risk should be understood as putting forth an *absolute* standard, on grounds of justice.
2. The concept of minimal risk should be referenced to *healthy* individuals.
3. The daily life standard should be referenced to the risks that healthy individuals have *in common*.
4. The daily life standard in regard to children should be *age indexed*.
5. Risks can satisfy the minimal risk standard by either falling within the definition or being equivalent to risks that fall within the definition.

Let us consider whether these conclusions should be applied to research involving pregnant women and fetuses. First, in regard to the absolute standard, the justice-based considerations that support it are applicable. It would be unjust, for example, to expose pregnant women living in unsafe neighborhoods to higher research risks than pregnant women living in safer locales. The same can be said for fetuses carried by women living in unsafe versus safe areas. One might object that fetuses lack rights or interests and that considerations of justice

toward fetuses therefore do not apply. In reply, a main reason that justice is relevant is concern for the children into which the fetuses will, in some cases at least, develop. Research-related risks to fetuses that materialize can be harmful to the children they become. Justice toward those children who develop from researched-upon fetuses requires that the same standard of risk be used for all fetuses. Therefore, an absolute standard should be used in prenatal research.

Second, given that an absolute standard should be used, it would be consistent with the standards used for children and adults to reference it to the risks that *healthy* individuals encounter. Third, it would similarly be consistent to take as a reference risks *in common*, as opposed, say, to the risks encountered by the most risk-prone pregnant women. Fourth, the argument for indexing risks by pediatric age seems to have implications for fetuses. If it would be unjust to allow minimal risk to be the same for infants and teenagers, then on what basis could one allow minimal risk for fetuses to be the same as that for teens? One natural way to extend the concept of age-indexing to fetuses is to regard all fetuses to be members of a group that is distinct from newborns and other young children. Fifth, it is reasonable to accept the idea that, in the context of prenatal research, risks can meet the minimal risk standard by either falling within the definition or being equivalent to risks that fall within the definition. Thus, the conclusions appear to be applicable to research involving pregnant women and fetuses.

Application to Pregnant Women

Having analyzed “minimal risk”, we are in a better position to describe the risks associated with each disjunct that apply to pregnant women and fetuses. Given an absolute standard with the features stated above, the relevant risks of daily life for pregnant women are the ones they have in common with other healthy adults. In particular, this entails that the risks peculiar to pregnancy are not to be considered. These include medical risks associated with pregnancy, such as hyperemesis gravidarum, preeclampsia, and placental abruption. They also include risks in daily life activities that arise or are elevated because of pregnancy, such as an association between hot tubs and miscarriage, or an elevated risk of listeria infection from eating soft cheeses. Given that pregnancy involves risks to the woman over and above those that healthy adults have in common, it would be unjust to make the minimal risk standard relative to pregnancy. For purposes of expedited review, waiver or modification of informed consent, and waiver of documentation of consent, the standard for pregnant women is the same as that for all adults. In regard to the risks encountered during routine physical or psychological examinations or tests, again the concept of minimal risk is the same for all adults. These considerations suggest the following principle:

- In regard to pregnant women, “minimal risk” should be understood as risk that is not greater than the risks healthy adults have in common in daily life or encounter in common during the performance of routine physical or psychological examinations or tests.

On the assumption that the risks in routine prenatal examinations for healthy women are no greater than those of routine medical examinations of other healthy adults, the former can be regarded as meeting the minimal risk standard, based on the concept of equivalence.

Application to Fetuses

Assuming that the concept of minimal risk for fetuses should be referenced to healthy fetuses as a group, the relevant “routine physical or psychological examinations or tests” should be the routine prenatal examinations and tests that are carried out for healthy fetuses. Moreover, it can be argued that the relevant examinations and tests are the routine prenatal ones that are undergone by healthy women who have healthy fetuses. The requirement of

healthy women prevents the potential injustice of fetuses of nonhealthy women being exposed to greater research risks, in the event nonhealthy women were to undergo tests that are riskier for fetuses. The routine prenatal examinations and tests for healthy women with healthy fetuses include maternal blood and urine tests, Pap smears to check for cancer and certain sexually transmitted infections, vaginal and anal swabs to check for group B streptococcus, and ultrasound examinations.⁵³ These procedures involve very low risks to the fetus. There are no known harmful effects to the fetus from routine diagnostic ultrasound.⁵⁴

It is necessary to consider how the concept of risks ordinarily encountered in daily life should be interpreted in regard to fetuses. The absolute standard we have been considering implies that the relevant risks of daily life for fetuses are the ones all healthy fetuses have in common, on the assumption that risks are to be age-indexed to fetuses as a group. What are the risks of daily life that all healthy fetuses have in common? I suggest that these risks fall into two main categories. We need to consider whether each of these categories of risks provides an appropriate standard for research.

First, there are fetal risks associated with the risks that pregnant women have in common with other healthy adults. These include fetal risks associated with the woman traveling in cars, crossing the street, bathing, and so on. For example, when a pregnant woman is injured in a motor vehicle accident, there can be fetal injury or even miscarriage. It seems appropriate to regard the daily life standard as including these risks.

Second, there are obstetrical complications that can occur in virtually any pregnancy. The relevant risks are those that occur during the fetal stage of development. By convention, the embryonic stage ends, and the fetal stage begins, at eight weeks following fertilization. Discussion of these fetal risks should address both mortality and morbidity. Quantitative estimates of these risks are relevant to our discussion, keeping in mind that appropriate judgments about minimal risk need not be purely quantitative, as pointed out by Freedman and coauthors. Concerning mortality, the incidence of spontaneous abortion during the first trimester, defined as the first twelve weeks of pregnancy, is approximately 10 to 12 percent.⁵⁵ However, most of these losses occur during the embryonic stage, and throughout the first trimester they are attributable predominantly to genetic anomalies including aneuploidies and chromosomal rearrangements.⁵⁶ Thus, the first trimester spontaneous abortion rate is not germane because, for the most part, these losses do not occur to healthy fetuses. The post-first-trimester pregnancy loss rate is relevant, however. Common causes of these losses include uterine anatomic problems such as fibroids and uterine septum, maternal endocrine and immunologic problems, infections, and placental problems such as abruption.⁵⁷ In a review of the literature, I have identified two studies that provide data on this loss rate. Philip R. Wyatt and colleagues used a database of the Canadian Institute of Health Information to review the obstetrical records of 250,011 women whose fetuses did not have chromosomal or structural (such as neural tube) abnormalities. They reported that the rate of pregnancy losses, defined as spontaneous miscarriage or intrauterine fetal demise, from 15 weeks of gestation onward was 0.60 percent.⁵⁸ Lorraine Dugoff and coauthors reviewed the pregnancy outcomes in a multicenter study involving 35,253 women enrolled between 10 and 13 weeks gestational age whose fetuses did not have chromosomal or structural anomalies, and they reported a pregnancy loss rate of 1.19 percent.⁵⁹ Consideration of these two studies together suggests a post-first-trimester fetal mortality rate of approximately one percent.

There also are obstetrical complications causing morbidity that potentially can occur in any pregnancy. One common example is nuchal cord, which occurs in 20 to 34 percent of pregnancies.⁶⁰ Although nuchal cord can cause serious problems such as cerebral palsy and

stillbirth, these adverse outcomes are rare.⁶¹ Another main example is amniotic band syndrome, which causes limb amputations and craniofacial deformities and is estimated to occur in one in 1200 live births (.08 percent).⁶² Preterm delivery, which occurs in approximately 12.5 percent of births,⁶³ can also result in various types of morbidity. Other harms to the fetus can occur as a result of maternal behavior such as alcohol consumption and smoking. However, because not all women drink or smoke, these risks probably should not be classified as risks that all fetuses have in common. Concerning *overall* morbidity risks, one possible way to estimate this is to use as a proxy the percentage of newborns who are admitted to neonatal intensive care units, excluding those with pathologies present throughout gestation, which would prevent them from being classified as having ever been healthy. Using this approach, one can draw upon data from the Centers for Disease Control and Prevention (CDC). A recent CDC report compiled birth data from all 19 states that use the most recent version of the U. S. Standard Certificate of Live Birth. The report gives the total number of live births, NICU admissions, and congenital anomalies for 2006 in the reporting states. Based on this data, one can estimate that previously healthy fetuses have a morbidity risk of 5.66 percent.⁶⁴

If these estimates are correct, they indicate that the risks associated with obstetrical complications arising for previously healthy fetuses include a mortality rate of approximately 1 percent and a morbidity rate of about 6 percent. We need to ask whether a standard involving this degree of risk is appropriate for research that does not hold out a prospect of direct benefit to the pregnant woman or fetus. I suggest that these risks are too high to serve as an appropriate standard. A chance of dying of 1 out of 100 is far above what should be regarded as minimal risk. Here one can appeal to the idea of Wendler and coauthors that if the actual risks are too high to serve as a minimal risk standard for research, then they should not be used. If this view is reasonable, then we need to reconsider how the daily life standard should be interpreted in regard to fetuses. One resolution would be to regard the standard as consisting only of those fetal risks associated with the risks referred to above that healthy pregnant women ordinarily encounter in daily life and have in common with other healthy adults. By restricting the standard to these risks, we avoid having a standard that is unacceptably risky. Although this approach excludes pregnancy complications that can be harmful to the fetus, it remains closely aligned to the justifiable standards of minimal risk for categories of research subjects other than fetuses--in particular, children and adults, including pregnant women. In all of these categories, the daily life standard involves risks associated with day-to-day activities and not medical conditions.

Taking into account these various considerations, we are led to the following principle:

- In regard to fetuses, “minimal risk” should be understood as risk that is not greater than the fetal risks associated with the risks that healthy pregnant women ordinarily encounter in daily life and have in common with other healthy adults or the risks fetuses encounter during routine prenatal examinations or tests of healthy women with healthy fetuses.

In summary, judgments about whether minimal risk is exceeded are important for various types of research involving pregnant women and fetuses. These judgments are relevant to expedited review, alteration of informed consent, waiver of documentation of consent, the adequacy of maternal consent alone, and the permissibility of research not holding out a prospect of direct benefit to the pregnant woman or fetus. I have argued that the considerations discussed in this essay are the sort that should guide investigators and IRBs in making judgments about whether research risks meet the minimal risk standard for pregnant women and fetuses.

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