

Recommendation 3: Pre-conditions to National-Level Review of Pre-event Pediatric Medical Countermeasure Research

Pre-event pediatric medical countermeasure research may proceed to national-level review under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54 only when researchers have demonstrated and reviewers concur that a minimal risk study is impossible and the proposed study poses no more than a minor increase over minimal risk to research participants. In part because of the inherent uncertainty of a bioterrorism attack, pre-event pediatric medical countermeasure research posing greater than a minor increase over minimal risk should not be approved under 45 C.F.R. § 46.407 or 21 C.F.R. § 50.54.

When research meets these two threshold conditions—minimal risk research is impossible and the proposed research presents no more than a minor increase over minimal risk—the framework specified below provides the considerations necessary to approve a pediatric MCM research protocol under section 407. While this framework might provide useful guidance for other types of 407 review, the Bioethics Commission developed it specifically for pre-event pediatric MCM research. The term “407 review” here refers to review under both HHS provision 45 C.F.R. § 46.407 and FDA regulation 21 C.F.R. § 50.54.

Specifying a Framework

Under section 407, the Secretary of HHS, in consultation with an independent panel of experts, can review and approve pediatric research, including investigations with healthy children that involve greater than minimal risk and offer no prospect of direct benefit to participants.¹⁴⁶ Before approving this type of research, however, by regulation, the Secretary must determine that the protocol under review meets *all* of the following conditions required under section 407:

1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
2. The research will be conducted in accordance with sound ethical principles; and

3. Adequate provisions are made for soliciting the permission of parents or guardians and the meaningful assent of children.¹⁴⁷

The Bioethics Commission's recommended framework, structured around the three conditions for national-level review, clarifies the circumstances in which proposed research presents a "reasonable opportunity" to address a "serious problem," specifies a rigorous set of conditions necessary to determine whether the research would be conducted in accordance with "sound ethical principles," and reiterates the importance of informed parental permission and meaningful and developmentally appropriate child assent. Decision makers should assess proposed pre-event pediatric MCM research that poses more than minimal risk using this framework in order to ensure that all the necessary aspects of a study have been evaluated and found ethically permissible before moving forward.

Importantly, only after the Secretary of HHS, with the advice of an independent panel, has found it ethically permissible to proceed would parents be asked to decide whether to enroll their children in research.

1. Does the Research Present a Reasonable Opportunity to Further the Understanding, Prevention, or Alleviation of a Serious Problem that Could Affect the Health or Welfare of Children?

In order to satisfy the first condition for approval under 407 review, proposed research must present "a *reasonable opportunity* to further the understanding, prevention, or alleviation of a *serious problem* affecting the health or welfare of children."¹⁴⁸ To provide more granular guidance, the Bioethics Commission specified the type of problem that qualifies as a sufficiently "serious problem" and reiterated the importance of identifying a "reasonable opportunity."

A. Serious Problem

At the outset of 407 review for pre-event pediatric MCM research that poses more than minimal risk, decision makers must confirm that the proposed research addresses "a serious problem affecting the health or welfare of children."¹⁴⁹ Evaluation of the seriousness of the problem is the first step of a 407 review because if there is no serious problem or threat of a serious problem to address, then enrolling healthy children in greater than minimal risk research is clearly unwarranted. This evaluation is conducted independently of

the merits of any particular protocol. As a matter of beneficence and respect for persons, it would be unethical to expose child research participants who cannot consent to unnecessary research risks or to any risk if a problem is not sufficiently serious. And, when a problem is serious, beneficence calls for investments (e.g., through research) to protect children from potential threats.

In the context of MCMs, a serious problem can be specified along at least two dimensions: (1) the consequences of exposure and (2) the likelihood of exposure. The panel reviewing a protocol must determine and advise the Secretary whether proposed research satisfies both of these criteria.

i. Seriousness Due to Consequences of Exposure

To determine the seriousness of the consequences of exposure, one must consider not only the magnitude of harm should an exposure occur, but also the vulnerability of children to exposure and the relative adequacy of any available therapeutic options or research alternatives.¹⁵⁰ In this assessment, reviewers should consider the anticipated public health and security responses at the federal, state, and local levels and their ability to mitigate the consequences of any exposure, as well as the existence and availability of other suitable alternative MCMs. Reviewers should also consider the possibility and sufficiency of post-event pediatric research to mitigate both the short- and long-term consequences of exposure.

Taking all of these factors into account, a serious problem is one in which the consequences of exposure are life threatening, permanently disabling, debilitating, or similarly grave. It is not enough that consequences are simply detrimental to the well-being of children; the detriment must be a crucial obstacle to the growth and development of children in order to support the conduct of research offering no prospect of direct benefit that poses a minor increase over minimal risk. Beneficence requires that, if the consequences are serious enough, we take measures to ameliorate the welfare of children as a class, including those who participate in research and future generations of children.

ii. Seriousness Due to Likelihood (or Threat) of Exposure

A second dimension of the seriousness of a problem is the likelihood of exposure. This dimension adds compelling urgency to the governmental obligation to take steps to reduce or prevent future harms to the public welfare,

and to the welfare of children more specifically. Fear of exposure, however, is not an appropriate measure of its likelihood.

Calculating the precise probability of an attack is impossible (unless an attack is known to be imminent, in which case the circumstances are essentially similar to those of post-event rather than pre-event research).¹⁵¹ Rather, in the face of inevitable uncertainty, those considering the potential for harm to children as a class should use the best quantitative and qualitative evidence available to inform firmly grounded beliefs that estimate the likelihood of future events. This analysis should take into account determinations of the threat based on established methods for assessing risk, such as the U.S. Department of Homeland Security Material Threat Determination or other assessments that inform it. Assessments should also incorporate, to the extent possible, considerations of imminence, the physical properties of the agent, the plausibility of accessing and producing a chemical or biological agent, the ease with which the agent could be deployed, or the possibility that a change in formulation or virulence might affect the severity and incidence of exposure.¹⁵² Evidence that an attack is relatively likely, as opposed to remote, supports the idea that the proposed research addresses a sufficiently serious problem.

The Bioethics Commission concluded that, as part of 407 review, the Secretary should provide reasons that the likelihood of exposure renders the problem a serious one. The Secretary's rationale should be made publicly known, even if the determination is based on classified information. For example, the Secretary could make an unclassified rationale publicly available or provide a classified rationale to authorized representatives of the public (e.g., members of Congress). Articulating an explicit rationale helps to ensure a rigorous deliberative process and holds decision makers accountable to the public. Accountability is particularly important in cases where the threat level is classified because this information is often held by small groups of people with specific credentials and role-related priorities.

EXAMPLES OF CIRCUMSTANCES THAT MIGHT PRESENT A SERIOUS PROBLEM

Concrete examples can inform what constitutes a “serious problem.” Current regulations were developed in the wake of polio outbreaks, and the National Commission pointed to examples such as an impending epidemic in which considerable dangers to children or to the community at large might be avoided or prevented by enrolling children in greater than minimal risk research. Additional hypothetical examples might include:

1. Large quantities of weaponized sarin gas have gone missing under suspicious circumstances. Sarin is estimated to be five hundred times more toxic than cyanide, and even non-lethal exposure is likely to have unknown long-term effects on a child’s neurological development. A new MCM offers a promising potential intervention, but has not yet been tested with children.
2. Smallpox, a disease that no longer occurs naturally, is stolen from a research facility. The possibility of exposure poses a threat to the community at large due to its infectiousness and high mortality rate; pediatric populations are especially vulnerable. Historically, physicians have only been able to treat the symptoms rather than combat the virus itself. Scientists have found one new antiviral agent that is effective in combating the disease. This new treatment has just been approved for use by adults.
3. Security sources reveal that while certain terrorist cells in unknown locations cannot currently deliver a “dirty” bomb—which would entail significant radiological exposure—they have both the intent and will to develop delivery capability within five years. A new form of therapy has been developed, and it has been tested and found safe in adults and older children. No testing on young children has yet been undertaken.

iii. Seriousness Due to “Vital Importance”

The Bioethics Commission drew insight in specifying what constitutes a serious problem from sections 404 through 406 and, in so doing, adopted language from section 406—a section that also regulates research offering no prospect of direct benefit to participants and involving more than minimal risk. Section 406 allows for research to be approved if the research is likely to generate knowledge of “vital importance for the understanding or amelioration of the subjects’ disorder or condition.”¹⁵³ Although in section 406 the knowledge sought can relate to any condition of a research participant, section 407 limits research to only that which is likely to yield knowledge about a serious problem. In specifying what constitutes a serious problem,

the Bioethics Commission recognized that the ethical standard for the information to be gained from a protocol approved under section 407 must also, at the very least, be as rigorous as the ethical standard established in section 406, and therefore the information to be gained must be of *vital importance* to addressing that serious problem as well.

“[T]he criterion for judging the potential contribution of research must, ethically, be as stringent for reviews conducted under Section 407 as for those conducted under Section 406.”

IOM. (2004). *Ethical Conduct of Research Involving Children*. Washington, DC: The National Academies Press, p. 134.

B. Reasonable Opportunity

In addition to being of vital importance to addressing a serious problem, the proposed MCM research must present a “reasonable opportunity” to further the understanding, prevention, or alleviation of that serious problem.¹⁵⁴ Although various natural and manufactured threats can present a serious problem, the gravity of the problem alone is not enough to justify the research if the research itself does not present a reasonable opportunity to learn something significant to developing or deploying an MCM.

To constitute a reasonable opportunity, the proposed protocol must be based on the current state of the science and must present an opportunity to learn about a specific MCM candidate that might be useful in protecting or treating children exposed to a serious threat. Research that can be expected to yield knowledge that improves the safety, availability, or feasibility of MCM delivery could meet this requirement. If research does not constitute a logical step toward ameliorating a serious problem, principles of ethical research—including beneficence and respect for persons—require that additional risks not be imposed on others, particularly those who cannot consent.

2. Will the Research be Conducted in Accordance with Sound Ethical Principles?

Drawing on the principles of respect for persons, beneficence, justice, and democratic deliberation, the Bioethics Commission proposed a rigorous set of ethical conditions that must be employed when assessing whether pre-event pediatric MCM research reviewed under section 407 will be conducted in

accordance with “sound ethical principles.”¹⁵⁵ These conditions fall into five general categories: 1) ethical threshold of acceptable risk and adequate protection from harm; 2) ethical research design; 3) post-trial requirements to ensure ethical treatment of children and their families; 4) community engagement in pre-event research; and 5) transparency and accountability.

A. Ethical Threshold of Acceptable Risk and Adequate Protection from Harm

Because children themselves cannot legally or ethically consent to research and its attendant risks, the level of research risk to which children can be exposed when there is no prospect of direct benefit is strictly limited—typically to the level of “minimal risk.”¹⁵⁶ Thus, consistent with the principles of beneficence and respect for persons, the level of risk to which the government—and researchers—can ask parents to expose their children is limited and small. Although parents may reasonably permit their children to engage in certain higher-risk activities (e.g., contact sports), the government lacks comparable latitude. When children are at serious threat of future exposure, however, there might be reason to reluctantly accept testing with a small amount more risk if minimal risk research is impossible. As argued above, pre-event pediatric MCM research risk should always be limited to no greater than a minor increase over minimal risk.

“[T]he question is to what extent we, as a society, think it’s appropriate to put that decision in front of a parent... .”

Nelson, S., Senior Pediatric Ethicist and Lead Medical Officer, Office of Pediatric Therapeutics, Office of the Commissioner, FDA. (2012). Presentation to the Presidential Commission for the Study of Bioethical Issues, May 17. Retrieved from <http://bioethics.gov/cms/node/708>.

Although the level of risk permitted under section 407 is not specified or limited by regulation, the distinct characteristics of pre-event pediatric MCM research warrant strict risk limits. In particular, because this research offers no prospect of direct benefit and the likelihood of an exposure in which the research results would be required is unknown and unknowable, children involved in pre-event MCM research must be protected by keeping research risks both limited and small.

It is generally accepted that children should be protected from harm, and, in the context of pediatric research, limiting the research risk to which children may be exposed is one means of ensuring such protection. Under the current regulatory

framework, research protections can be summarized as adequately protecting children from harm in light of the expected results of the research—that is, whether the research is of possible direct benefit to individual participants, of potential benefit to an identifiable class of children with a disorder or condition, or of potential benefit to all children as a class.

In the case of pre-event pediatric MCM research, there is no prospect of direct benefit to individual participants or benefit to an identifiable class of children because the likelihood of an attack is speculative. Rarely does a bioterrorism agent exist naturally in a weaponized form or in the quantity or virulence necessary to cause the breadth of harm expected during an attack. Given the particularly remote possibility that results of pre-event pediatric MCM research will be put to use—more so than in other types of research approved under section 407—and the legal and ethical incapacity of children to consent, when it is impossible to design a minimal risk pre-event pediatric MCM research trial, the only ethically tolerable level of risk is a minor increase over minimal risk.

This “minor increase over minimal risk” threshold has been described by the National Commission as a narrow expansion over minimal risk, entailing “no significant threat to the child’s health or well-being.”¹⁵⁷ Assessment of research risk should take into account the probability, magnitude, duration, and reversibility of harm.¹⁵⁸ Risks include both potential harms from the intervention itself as well as those that might occur as a result of the procedures associated with the research. Reviewers should also take into account commonly used assessments of what constitutes minimal risk or a minor increase over minimal risk in making their determination. The level of permissible risk to which children may be exposed under specified circumstances includes, for example, risks of conditions such as redness or moderate soreness at the injection site (both minimal risk), or missing a few days of school due to temporary low fever or malaise (minor increase over minimal risk), or procedures such as drawing blood (minimal risk) or a skin biopsy or chest X-ray (minor increase over minimal risk). Procedures that entail a significant likelihood of greater risks than these (such as lumbar puncture or bronchoscopy) are not acceptable within the context of pre-event pediatric MCM research.

Risk assessment is necessarily based on empirical data, but risks cannot be measured directly. Judgments about risk may be based on adult human data, animal studies, or pediatric use of the product for different indications. If there are insufficient data from these sources to support the conclusion that the intervention poses no more than a minor increase over minimal risk to child research participants, more data should be obtained. Where the data are inconclusive or no additional data can be obtained, the remaining conclusion must be that the risk is more than a minor increase over minimal, and the research should not go forward. The assessment must be based on data in each case, and although empirical certainty in such matters is impossible, decision makers must strive to make the best judgment possible based on the available data.

B. Ethical Research Design

Pre-event pediatric MCM research should be designed and conducted under conditions of the greatest scientific and ethical rigor. Determining whether research is ethical includes evaluating the scientific necessity of the proposed trials, the design of the research plan, the adequacy of available data from prior testing conducted in adults, the benefit of the proposed study over alternatives, and the fairness of subject selection.

i. Scientific Necessity

Research with children is a matter of scientific necessity if the important research question cannot be answered without an ethically permissible study involving children. Pre-event pediatric MCM research reviewed under section 407 should be conducted only if it poses no more than a minor increase over minimal risk and it is necessary to include children in order to learn how to protect children as a subgroup during a bioterrorism attack.¹⁵⁹ As a matter of respect for persons, safeguards must be provided to ensure that children, as members of a vulnerable population, are not exploited through participation in unnecessary research, the results of which could be obtained by other means. This determination should be made using a careful, systematic evaluation of all information, including possible alternatives.¹⁶⁰

ii. Research Plan

To be ethical, human subjects research in general—including pediatric MCM research—should be both scientifically valuable and valid, and conducted in accordance with an ethical research plan. The research plan is a broad, high-level overview of the research, which can encompass multiple studies that collectively inform the overarching research question. In the context of pediatric MCM research assessed under section 407, an ethical research plan and each experiment contained therein must be scientifically valid, minimize risks to child research participants by, for example, conducting small trials using age de-escalation, implement appropriate monitoring, and properly plan for later research—all while maintaining a level of risk that is no more than a minor increase over minimal. Taken together, these considerations contribute to upholding and honoring the principles of beneficence and respect for persons by minimizing and managing foreseeable risks to research participants, quickly identifying and ameliorating the consequences of unforeseen risks, and maximizing the potential benefits by incorporating plans to acquire additional data.

Scientific Validity. Scientific validity is required for ethical human subjects research. In pediatric MCM research, each study should be well designed to answer a specific question of importance to the protection of children; studies should be adequately powered, rigorous in data collection, and feasible.¹⁶¹ The research plan should be peer-reviewed and approved as scientifically valid before moving forward with participant recruitment.

Small Trials and Age De-escalation. An ethical research plan ought to minimize the number of children exposed to research risks while maintaining a large enough group to satisfy the requirements of scientific validity. Testing an appropriate MCM dosage in pediatric populations should take place only after adult trials have been completed to determine dosing, safety, and—for vaccines—immunogenicity. Following adult trials, an ethical research plan will usually start with a very small pediatric trial with the fewest number of children necessary in the oldest age group (typically 10 to 20 participants) to evaluate the safety of the most promising dose and route of administration, based on adult information before expanding to later-stage studies that might involve many more participants.¹⁶² Larger-scale trials conducted to identify

rare adverse events from MCM interventions would not be ethically justified in a pre-event setting. However, adverse event data must be collected in a post-event study, closely monitoring any adverse events after an MCM is deployed. (See Post-event Studies, Chapter 3.)

When appropriate, ethical MCM research with pediatric populations should also incorporate age de-escalation, a process by which MCMs that have been deemed safe in adults are tested first with older pediatric populations, followed by successively younger children in multiple steps, based on development-specific characteristics, as the risks are classified and minimized.¹⁶³ When age de-escalation is used, trials with each new age range are informed by the results of the earlier trials so that trends observed in dosage (e.g., per body weight) or adverse events in each age group are used to determine how to alter the experimental design to maximize safety for the next group of participants. Inferring risks from young adults to older children is discussed in greater detail above. (See Pre-event Studies Posing No More Than Minimal Risk Approvable under Section 404, Chapter 3.)

Appropriate Monitoring. Minimizing risks to participants—as required by beneficence, non-maleficence, and respect for persons—can be accomplished, in part, through appropriate monitoring. The safety of participants in certain studies should be monitored through a data safety monitoring board, an independent group of experts tasked with monitoring study data and participant safety while the research is underway. In addition, the use of a medical monitor—a pediatrician (or team of pediatricians) independent of the research team who monitors trial participants—should be included in the study design to monitor participants. Monitoring should include extensive patient follow-up, particularly when experimental interventions could carry lasting effects that might otherwise escape detection. Because pediatric MCM research reviewed under section 407 exposes children who cannot consent to a minor increase over minimal risk, rigorous safety monitoring—with a medical monitor and a data safety monitoring board—is necessary.

Proper Planning for Post-event Research. In the context of research responsive to the threat of a bioterrorism attack, ethical research planning must also include appropriate plans for post-event testing, either through a post-event research arm (when pre-event testing is ethically appropriate) or through a

separate post-event study proposal. To plan adequately for post-event research, pre-event approval and plans for post-event access to funding and expertise should be in place. (See Post-event Studies, Chapter 3.)

iii. Prior Adult Testing to Minimize Risk to Children

To minimize risks to potential research participants in pre-event pediatric MCM research, any proposed intervention should, to the extent possible, be thoroughly tested and found acceptably safe in adults with regard to the same issues that would be studied with children. Information learned from prior testing with adults—along with information from computer models, animal models, and prior comparable MCMs—can help identify proper dosing for initial testing in pediatric populations and characterize the risk level such research might impose. The condition of prior testing with adults is a matter both of non-maleficence—that is, not imposing unnecessary risks on more vulnerable individuals—and of respect for persons—which calls upon testing those who can consent before turning to more vulnerable populations who cannot. This condition applies to the extent that research with adults can be conducted ethically. Prior testing of an intervention with adult populations might not be possible or ethical if, for example, the intervention is only clinically indicated for children, is expected to cause serious adverse events in adults but not in children, or is otherwise not appropriate for use in adults.¹⁶⁴ Requiring that any proposed intervention be tested in advance with adults when appropriate helps to ensure that child research participants who enter into adulthood before the tested MCM is needed will have access to an adult formulation of the intervention if ever necessary.

iv. Sufficient Benefit over Alternatives

In the context of 407 review, a proposed pediatric MCM study must be expected to generate knowledge that would confer a sufficiently greater overall benefit to children as a class than would the most beneficial alternative, if any, that does not impose greater than minimal risk without the prospect of direct benefit.¹⁶⁵ Assessing comparators is required as a matter of beneficence, which dictates that we strive to minimize risks while maximizing benefits in the present and the future. Pre-event MCM research assessed under section 407 is only justified by beneficence if it imposes less risk of harming participants

than alternatives, including risks of other pre- and post-event research or current preparedness contingency plans for children.

Determining an appropriate comparator requires assessing various scenarios, such as the use of alternative existing therapies that have already been tested with children; administration of therapies that have not been tested with children, but are approved for use by adults; or even the prospect of a next-generation intervention not yet approved or in advanced development, but likely to be authorized at the time such an intervention might be necessary.¹⁶⁶

v. Fair Subject Selection

Fair subject selection is a necessary condition of ethical research, and is a particularly important safeguard in the context of pediatric research because all children are vulnerable. The principles of beneficence and justice require that the selection of research participants is fair, minimizes risks to and enhances benefits for individual participants, and fairly distributes research risks and benefits more broadly.¹⁶⁷ Rather than selecting subjects on the basis of vulnerability, privilege, or convenience, fair subject selection requires that a study's particular research goals be the primary basis for determining who should be enrolled in research.¹⁶⁸

In considering potential pediatric research participants for pre-event MCM research, the question becomes which members of this vulnerable class should be selected for inclusion. Certain standards provide guidance. For example, we should not include children who are burdened with multi-faceted vulnerabilities, such as those who are “institutionalized, cognitively or physically disabled, or wards of the state.”¹⁶⁹

Children enrolled as research participants should be at least as likely to benefit from the results of the proposed study as children who are not participating in research. Determining appropriate populations to accord with this standard is context dependent and should include considerations such as geography, parents' occupation, or other risk factors. Certain populations—for example, children living in urban centers—might be at greater risk of future exposure because they live near targets of bioterrorism and therefore might be more likely to benefit from the results of pediatric MCM research in the event of an exposure. In selecting sites for clinical trials, researchers should consider

locations in which participants are likely to be at elevated risk of exposure to the agent under investigation. Selection of particular sites could increase the chances that research participants would be among those likely to benefit from an intervention should an attack occur.¹⁷⁰ Other populations—including first responders who advocate that their families be among the first to receive MCMs in an emergency—might have a greater potential to benefit from pediatric MCM research as well.¹⁷¹

Additionally, in research that is particularly complex, and in which children are expected to take on more than minimal risk for no prospect of direct benefit, researchers should seek to enroll research participants who are best equipped to understand the consequences of participation. Enrolling children of parents who are particularly well informed about the purpose and limits of pediatric MCM research, for example, could mitigate some of the heightened concerns about such research. This might include children of MCM researchers, policy makers, and subject matter experts.

Some have also suggested that another group—families of military personnel—might be particularly well informed in situations where military personnel have already received the MCM being studied.¹⁷² Other factors, however, caution against selective enrollment of children of military personnel in pediatric MCM research. Military personnel work in environments with clear chains of command, and so might interpret encouragement to enroll their children in research as a tacit manifestation of duty. Military parents, their children, or both, might feel inappropriate pressure to participate given the hierarchical social structures that they inhabit. Further, while service members have volunteered to be exposed to higher risks than most civilians, their children have not. This is not to say that children of military personnel should be ineligible to enroll in pediatric MCM studies, just that they should not be singled out for participation, and it should be clear that there are no positive or negative repercussions in deciding whether to enroll one's child.

C. Post-trial Requirements to Ensure Ethical Treatment of Children and Their Families

Justice, which requires that the benefits and burdens of research be equitably distributed, gives rise to certain post-trial obligations to ensure that participants in pre-event pediatric MCM research reviewed under section 407 are

not disproportionately burdened as a result of their participation in research. First, there should be an adequate plan in place to equitably distribute interventions shown to be successful through research to all exposed children in the event they are needed. Second, compensation and care should be guaranteed for any child who incurs a research-related injury during participation in a pediatric MCM trial.

i. Distribution Protocol for All Children Tested or Assured

Pre-event pediatric MCM research is conducted to ensure that, in the event of an attack, children have access to the benefit and protection of tested MCMs at appropriate dosages. Accordingly, children who participate in pediatric MCM research assume the risks of research that promises no prospect of direct benefit, but that might benefit all children as a class in the future. Given its ethical grounding in the potential for future benefit, pediatric MCM research cannot be justified unless the presumed benefit to children as a class is assured—that is, a documented plan must be in place for the wide and equitable distribution of the intervention (should research support its use) to children that need it in the event of an attack.¹⁷³ Moreover, in order to respect those who agree to participate in pediatric research and to create a just distribution of benefits and burdens, those who participate must have access to the potential benefits of that research when appropriate. The assurance of an equitable and just distribution protocol guarantees delivery of the intervention to children in need, including any that participated in pre-event research.

In developing a plan that equitably and adequately accounts for the interests of research participants and future children, researchers and government officials should use successful extant distribution plans for existing MCMs as models to distribute the experimental intervention in the event of an emergency. To the extent possible, this plan should be proven and should include provision for adequate quantities of MCMs.¹⁷⁴

Children who participate in research also should not be disadvantaged by such participation beyond the imposition of research risks. To the extent possible, the research protocol should ensure that research participants are not disadvantaged in an emergency situation as a result of their participation in pediatric MCM research. For instance, participation in a pediatric MCM trial for an experimental vaccine should not preclude a child from receiving the

eventual approved vaccine in the event of an attack, even if the vaccine supply is low, due to the assumption that the child might have residual immunity from their participation in the earlier research. Research participants should have the same access to the vaccine as other children who have been exposed to an agent; otherwise, participants would be penalized for volunteering to participate in the MCM research.

ii. Compensation for Research-Related Injury

Justice requires that children who participate in pediatric MCM research, which primarily aims to benefit other children and society more broadly, be treated or compensated for research-related injuries so that they do not bear a disproportionate share of the burdens of research. In addition, the principles of beneficence and respect for persons require that risks to participants be minimized; in this context, such risks include additional medical or financial harm resulting from research-related injuries. These ethical principles warranting treatment or compensation are particularly acute in the case of research-related injuries stemming from pre-event pediatric MCM research that is greater than minimal risk—children, who cannot legally or ethically consent to the research, are bearing greater risk than ordinarily permitted in order to potentially benefit future children in the event of a bioterrorism attack.¹⁷⁵

The argument that compensation for research-related injuries is not required because participants willingly accept the risk lacks force in the case of pediatric research.¹⁷⁶ Pediatric research participants are unable to provide valid informed consent, and therefore cannot fully accept the risks of research in the same way that adult research participants might. This fact weakens the argument that children enrolled in pre-event MCM research have waived any claim to care or compensation for research-related injuries by agreeing to participate.

Before approving pre-event pediatric MCM research under section 407, reviewers must ensure that researchers have assured that a plan is in place to treat or compensate injured pediatric research participants. The strong ethical obligation to provide care or compensation for injuries resulting from participation in pre-event MCM research entails providing injured research participants with needed medical care, including any available medications or interventions. Monetary compensation might also be necessary in the event of severe or long-term injury.

Although the likelihood of severe or long-term injury from pre-event MCM research is, under this framework, extremely low—particularly from interventions that have already been found safe in adults—the very assurance of compensation is both ethically and practically important.¹⁷⁷ (See Threshold of Acceptable Risk and Adequate Protection from Harm, Chapter 3.) It is important to note that compensation for research-related injuries, as discussed here, does not extend to incentives to participate in research. In pre-event pediatric MCM research, monetary reimbursement for costs outside of research-related injuries should be limited to reimbursement for participation costs, such as transportation and parking.

The Bioethics Commission reaffirmed its previous conclusion, noted in *Moral Science: Protecting Participants in Human Subjects Research*, that “subjects harmed in the course of human subjects research ought not individually bear the costs of care required to treat qualified harms resulting directly from that research.”¹⁷⁸ Particularly because of their vulnerable nature, children who enroll in pre-event pediatric MCM research, and become injured as a result of their participation, should be guaranteed all necessary medical care and appropriate compensation for such injuries.

Because this type of research is exceptional (and rare), the cost of compensation for research-related injuries is expected to be limited and would likely not require any major new federal infrastructure. As articulated in *Moral Science*, there is currently no overarching federal policy to ensure that injured research participants receive treatment or compensation.¹⁷⁹ However, there are some existing targeted federal programs, such as the National Vaccine Injury Compensation Program (NVICP) and the Covered Countermeasure Process Fund established by the PREP Act.¹⁸⁰

NVICP is the primary mechanism through which those injured by vaccines receive compensation in the United States. In the context of most MCMs, the NVICP is inadequate because the program only provides compensation for injuries resulting from vaccines listed in the Vaccine Injury Table or recommended by CDC for routine administration.¹⁸¹ Most vaccines used as MCMs are not listed on the Vaccine Injury Table. Accordingly, injuries caused by these MCMs would not be eligible for compensation under the NVICP. Moreover, not all MCMs are vaccines; MCMs can be any FDA-regulated product intended

to treat or prevent harm (or diagnose a condition) from the effects of chemical, biological, radiological, or nuclear attacks.

Children injured as a result of participating in MCM research will, however, have access to, but may be insufficiently protected by, the PREP Act. The PREP Act—passed to limit the liability of manufacturers, distributors, and others who develop, prescribe, administer, test, or dispense a countermeasure—provides limited access to compensation for those injured as a result of receiving an MCM.¹⁸² Individuals injured as a result of receiving an MCM can seek compensation through the “Covered Countermeasure Process Fund,” a pool of funds that comes into existence once the Secretary of HHS declares an emergency.¹⁸³ The PREP Act permits those who suffer “serious physical injury or death” to recover from the fund; those who suffer more minor injuries will be ineligible for compensation.¹⁸⁴ The PREP Act also establishes a statute of limitations of one year; injuries that manifest more than one year after administration are not entitled to compensation.¹⁸⁵ The Covered Countermeasure Process Fund is funded through congressional appropriations; it is unclear, however, whether Congress has ever appropriated funds.¹⁸⁶ As of December 2009, 24 letters of intent requesting benefits had been submitted under the PREP Act.¹⁸⁷ It is anticipated that any claims would be paid out of emergency appropriations.¹⁸⁸

Regardless of whether researchers rely on an established government mechanism, a system particular to the research funder, or a plan specific to a research site, they must ensure that a treatment and compensation plan is in place for any particular proposed study. The costs of any resulting harm or injury—whether or not it is severe—should not fall on child research participants or their families.

D. Community Engagement in Pre-event Research

The principle of democratic deliberation endorses respectful and inclusive collaborative decision making—a process that includes community engagement.¹⁸⁹ In the context of pre-event pediatric MCM research, engaging the community serves multiple ethical goals. The aims of community engagement include educating the public about the proposed research, providing relevant communities with opportunities to educate researchers about community-specific concerns, and encouraging community members to take advantage

of research products should the need arise. Community engagement helps build transparent, meaningful, collaborative, and mutually beneficial relationships among those considering or conducting research and the relevant communities.¹⁹⁰ Moreover, it helps to ensure that research is a joint enterprise, influenced by all relevant stakeholders, and that research is not directed solely by those who have a financial or professional interest in the results.

The process of community engagement is the responsibility of researchers, and should involve the public at every stage of research; address concerns and prevent unnecessary misgivings about the research; and strive to preempt any potential underuse of MCMs by the community in which they are tested. In the case of pre-event pediatric MCM research, community engagement is particularly important to address misgivings or mistrust because individual children within the community are exposed to risk for the potential benefit of other children in the community and the broader population. Community engagement in post-event research is discussed in greater detail below.¹⁹¹

In order for community engagement to be successful, researchers must identify key stakeholders.¹⁹² Stakeholders are individuals or groups who can influence or who are “affected by the conduct or outcome” of a biomedical research trial.¹⁹³ Examples of potential stakeholders in pediatric MCM research are illustrated in Figure 3.1. In the context of pediatric MCM research, relevant communities might be geographic—such as urban populations at potentially higher risk of a bioterrorism attack—or affiliated by special interests—such as first responders whose families might be the first to access MCMs in the event of an attack.

Once key stakeholders have been identified, researchers should engage them early and cooperate with them throughout the entire lifecycle of pre-event pediatric MCM research, from conceptualization through protocol development, execution, and communication of research results. Engaging marginalized communities along with the general public and other relevant stakeholders in the planning and conduct of this research will help to ensure ethical study design, implementation, and access to benefits should the need arise. The guidelines set forth in the Joint United Nations Programme on HIV/AIDS and the AVAC *Good Participatory Practice Guidelines* provide a useful framework for engaging relevant communities that might serve as a

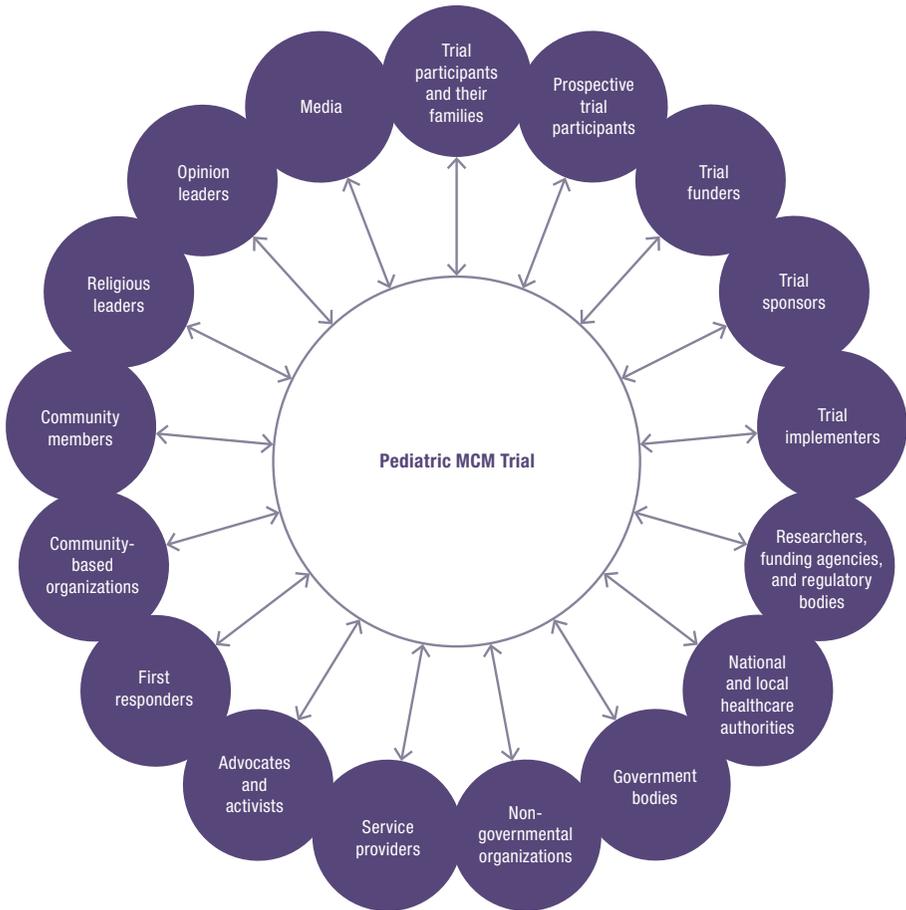


Figure 3.1 Potential Stakeholders to Engage in Pediatric MCM Research

Adapted from: MacQueen, K.M., et al. (2012). Stakeholder Engagement Toolkit for HIV Prevention Trials. Washington, DC: FHI360, p. ix. Retrieved from [http://www.fhi360.org/sites/default/files/media/documents/Stakeholder EngagementToolkit for HIV Prevention Trials.pdf](http://www.fhi360.org/sites/default/files/media/documents/Stakeholder%20EngagementToolkit%20for%20HIV%20Prevention%20Trials.pdf); Joint United Nations Program on HIV/AIDS. (2011). *Good Participatory Practices: Guidelines for Biomedical HIV Prevention Trials 2011, Second Edition*, p.14. Retrieved from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdf

model in this context.¹⁹⁴ Alternatively, researchers might adopt the community advisory board model employed by the Framingham Heart Study or the HIV Vaccine Trials Network, which provides a forum for community member and research participant insight and input.¹⁹⁵

E. Transparency and Accountability

The review, approval, and conduct of pre-event pediatric MCM research that poses more than minimal risk should be transparent in order to enhance public accountability. As the Bioethics Commission recognized in *Moral Science*, “[i]nsufficient access to research information allows studies and results to be hidden and can result in injuries to human subjects, wasted resources, and unethical exposure to unnecessary risk.”¹⁹⁶ In keeping with the principles of democratic deliberation and beneficence, pre-event research that presents a minor increase over minimal risk and no prospect for direct benefit that is reviewed under section 407 should not be hidden from public view; rather, because it is fundamentally designed to benefit the public in the event of an unpredictable bioterrorism attack, and not to benefit directly the child participants, the Secretary should take special care to engage in robust and clear communications about pre-event pediatric MCM research projects. This research, which is conducted for the public good, should engage the public and remain transparent and accountable to them throughout the life of the project.

The Secretary should first ensure—as required by section 407—that there is adequate “opportunity for public review and comment” during the national-level review process, including the evaluation and communication of all anticipated risks and benefits that might be incurred in a proposed study. In making a decision to approve research, the Secretary should not rely solely on the advice of scientists, who might be predisposed to favor research, but should also consider the opinion of lay people, both as members of the 407 panel and as members of the public.

To achieve the goals of transparency and accountability, it is important to bear in mind that the appropriate composition of national-level review panels convened under section 407 will in itself provide a significantly influential means of community engagement and public accountability. By including several members of the public who do not harbor any specific bias, it is possible to reduce the likelihood that such panels might be compromised by

individuals who have conflicts of commitment or conflicts of interest, which include those financial, fiduciary, and other affiliations that might compromise the objectivity of, or public confidence in, the deliberative process. To avoid marginalizing community views, it is important that these panels include more than one community member and also recognize that not only the community members are expected to advocate for the interests of both research participants and the public good that is served by research.¹⁹⁷ All review panel members should be selected based on expertise and experience, which lends them independence—that is, a lack of vested interest in skewing the deliberations either toward or away from approval of a particular research protocol.

Moreover, after making a determination, the Secretary should publicly communicate the ethical rationale for approving or rejecting any pre-event pediatric MCM research proposal. Before proceeding with testing, the Secretary must provide clear communication of expected risks and benefits of the research. In addition, equally clear reasons must be publicly stated that justify the government ethically seeking the informed permission of parents and the meaningful assent of children to participate in this research.

Finally, throughout the study, the Secretary should provide periodic updates to and communication with the stakeholder communities and the U.S. public. (See Community Engagement in Pre-event Research, Chapter 3.) At the conclusion of the study, the study's findings should be made available to the public. Those community members who belong to a community directly affected by the research trial should be kept abreast of research results and have the opportunity to benefit from the understanding gained through participation and engagement with the researchers throughout the process.

* * *

All of these rigorous conditions are necessary to ensure that research approved under section 407 is conducted in accordance with “sound ethical principles.” These conditions, while necessary, are not sufficient. Informed parental permission and meaningful child assent also remain critical.

3. Are Adequate Provisions Made for Soliciting the Permission of Parents or Guardians and the Meaningful Assent of Children?

The third condition of section 407 requires that “adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.”¹⁹⁸ Informed consent (or its moral equivalent) is a fundamental protection for research participants. Respect for persons requires that individuals be given the opportunity to make a voluntary, informed decision to participate in research to the extent they are able.¹⁹⁹ Although children are not legally competent to give consent, whatever level of partial autonomy they have must be respected and they must be given the “opportunity to choose to the extent they are able, whether or not to participate in research.”²⁰⁰ Researchers must not equate parental permission and child assent with the legal consent of adults.²⁰¹ Only competent adults have the legal authority to consent to participate in research or, in the context of research with children, to provide permission for their children to participate.²⁰²

An informed decision to permit one’s child to participate in research requires that parents understand specific information, including the purpose of the research, any risks and anticipated benefits, and alternative available protocols. Both parents and children should be given an opportunity to ask questions and should be informed that they may withdraw from the study at any time.²⁰³ Additionally, research participants and their parents must be informed of the extent to which confidentiality can be expected and should receive an explanation of the system in place to treat and provide compensation for any research-related injury or harm.²⁰⁴

Pediatric MCM research introduces additional layers of complexity to the informed consent process. Typical concerns about the quality of informed consent are magnified both by the fact that pediatric participants are not competent to consent, and by the heightened risks and uncertainties involved in MCM research. Researchers and persons independent of the research team whose responsibility it is to conduct the informed consent process for research studies must communicate these aspects of research to child participants in a developmentally appropriate manner.

Meaningful Assent. By definition, pediatric research involves participants who are legally and ethically unable to give valid consent due to their age; but where meaningful assent (or dissent) can be obtained, researchers should strive to include children in the decision making process. Although parental permission