Executive Summary

Pediatric clinical trials often include interventions and/or procedures that offer the enrolled children a prospect of direct medical benefit, and interventions and/or procedures that are performed for the purpose of obtaining generalizable knowledge and do not directly benefit the enrolled child. Examples of such “research only” nontherapeutic procedures may include a magnetic resonance imaging study to provide a structural correlation with a neurological endpoint, a sham procedure in the control group to maintain blinding of the study, a lumbar puncture to evaluate a biomarker found in the cerebrospinal fluid (CSF), or a bone marrow aspirate to study hematopoietic stem cell markers. With appropriate risk mitigation strategies, many commentators as well as federal advisory panels have opined that nontherapeutic procedures such as a lumbar puncture or bone marrow aspirate may present no more than a minor increase over minimal risk. As such, these procedures would be approvable under 21 CFR 50.53 (discussed below) and/or 45 CFR 46.406 provided that (1) the intervention and/or procedure present experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical situation, and (2) the intervention and/or procedure is likely to yield generalizable knowledge about the subjects disorder or condition that is of vital importance for the understanding or amelioration of the subjects disorder or condition.

Many children, and especially younger children or children with neurocognitive impairments, may be unable to tolerate longer and/or painful procedures absent some form of procedural sedation. The assessment of the level of risk of these nontherapeutic procedures must take into consideration the procedural sedation necessary to either tolerate or complete the procedure. If the procedure itself is nontherapeutic (does not offer a prospect of direct benefit) then the procedural sedation necessary to complete the procedure also must be considered nontherapeutic. Thus, the procedural sedation cannot be approved under 21 CFR 50.52 because it does not offer a prospect of direct benefit. We do not consider the administration of therapeutic doses of sedative or analgesic drugs to present no more than minimal risk; hence the administration of these drugs cannot be approved under 21 CFR 50.51. Absent review by a federal panel under 21 CFR 50.54 and/or 45 CFR 46.407, the risk of the procedural sedation necessary to complete a nontherapeutic procedure must be considered under 21 CFR 50.53. The purpose of this meeting is to discuss whether and under what conditions procedural sedation can be considered to present no more than a minor increase over minimal risk. For the purposes of the discussion, we will assume that the performance of the nontherapeutic intervention and/or procedure satisfies the other criteria for approval under 21 CFR 50.53 and/or 45 CFR 46.406.

FDA is aware of data from animal and observational human studies that general anesthetics may cause neurotoxic changes in the developing brain which later may result in adverse neurodevelopmental outcomes. Specifically, general anesthetics and sedatives that increase inhibitory γ-aminobutyric acid (GABA) receptor activity (e.g., propofol, etomidate, sevoflurane, desflurane, and isoflurane) or block excitatory glutamate receptors (e.g., ketamine) produce neurotoxic effects in laboratory animals. Although the small number of observational studies in
children offer conflicting results and are confounded by multiple factors, the data suggest that some children who underwent anesthesia early in life may have deficits in learning and school performance. Factors that appear to influence the extent of injury include age at the time of drug exposure (e.g., less than 3 years of age) and cumulative anesthetic dose (e.g., exposures exceeding three or four hours). Given these concerns, it is recommended that surgical procedures performed under anesthesia should be avoided in children who are less than 3 years of age unless the situation is urgent or potentially harmful if not attended to (i.e., there is a compelling clinical benefit to warrant exposure to the potential risk of neurotoxicity from the anesthesia).

Prospective randomized clinical trials are necessary to determine whether general anesthesia impairs neurocognitive development. [1, 2] Clearly these risks need to be considered when performing "research only" procedures that require sedation. However, for the present discussion of the risks of procedural sedation, we will assume that the duration of cumulative exposure to general anesthetics and/or sedatives is below the threshold (e.g., less than three hours) or that the children are beyond the age of vulnerability (e.g., over three years) at which these neurotoxic changes in the developing brain may be observed.

21 CFR 50, Subpart D

Title 21 CFR Part 50, subpart D (subpart D) provides additional safeguards to children enrolled in clinical investigations. Before a pediatric trial may proceed, subpart D requires both (1) an assessment of the level of risk that the interventions and/or procedures included in a clinical trial would pose to pediatric subjects (i.e., minimal risk, slightly more than minimal risk, or greater than minimal risk) and (2) of the anticipated outcome or consequence of the interventions and/or procedures (i.e., the prospect of direct clinical benefit to subjects, the development of generalizable knowledge about the subjects’ disorder or condition, or the opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children).

The additional protections for children enrolled in research fall into two main categories: (1) absent any prospect of direct benefit to the enrolled child, the intervention or procedure must present either minimal risk (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53) under the “lower risk” pathway, or (2) the intervention or procedure must present a prospect of direct benefit that is sufficient to justify greater risks (i.e., the "higher" risk pathway under 21 CFR 50.52). A clinical investigation that is not approvable under either the lower or higher risk pathways may be referred by an institutional review board (IRB) for federal panel review under 21 CFR 50.54 for a determination as to whether the clinical investigation meets the requirements of subpart D regulations. Prior to addressing the requirements of these pathways in greater detail below, we will review important considerations regarding minimization of risk that are applicable regardless of the category in 21 CFR 50 subpart D under which a protocol may be considered.

Risk Minimization

Under FDA regulations at 21 CFR 56.111(a)(1), the research risks to human subjects must be minimized. Risk minimization may be particularly important in vulnerable populations. Concerted efforts should be made in pediatric research to minimize risks prior to assessing the protocol under 21 CFR 50 subpart D. For example, investigators may consider reducing the number of invasive procedures by obtaining measurements at fewer time points. Children who
are able to tolerate necessary procedures (e.g. MRI scans) without procedural sedation should be enrolled whenever possible, instead of children who would require sedation to undergo the same procedure. When procedural sedation is required, the depth of sedation should not exceed that which is absolutely necessary to perform the procedure. In addition, consideration should be given to using medications for procedural sedation with the fewest potential risks.

While it may be in the best interests of the child to escalate the level of sedation or the number of agents used when the intervention or procedure provides benefit to the child, when the intervention or procedure offers no direct benefit consideration should be given to withdrawing the child from a study when an appropriate approach to procedural sedation fails. From the literature, seven predictors were significantly associated with failed sedation: (1) upper respiratory infection (P = 0.008); (2) congenital heart disease (P = 0.021); (3) obstructive sleep apnea/snoring (P < 0.001); (4) American Society of Anesthesiology (ASA) risk class of above II (P < 0.001); (5) obesity (P < 0.001); (6) increased weight (P < 0.001); and (7) older age (P < 0.001). [3] Many of these same factors would also increase the risks associated with procedural sedation, as discussed later.

We now turn to a review of the lower and higher risk pathways below. As any given protocol may contain multiple interventions and/or procedures, each intervention and procedure must be evaluated with respect to these two categories, as explained further in the section regarding component analysis.

**Low Risk Pathway**

There is general consensus that a child’s exposure to risk in pediatric research must be low in the absence of direct therapeutic benefit to that child. For example, for research on non-consenting subjects that does not offer direct therapeutic benefit, the International Conference on Harmonisation (ICH) E6 Guidelines specify that “the foreseeable risks to the subjects are low” and that “the negative impact on the subjects’ well-being is minimized and low” [4]. We will review the two categories of research in subpart D that comprise the low risk pathway: “minimal risk” and “minor increase over minimal risk” in the context of no direct benefit for the individual pediatric participant.

**Minimal Risk**

21 CFR 50.51 uses the term “minimal risk” which is defined as “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” (21 CFR 50.3k).

The U.S. National Commission defined minimal risk as the risks normally encountered in the daily life or routine examination of healthy children. [5] The subsequent omission of “healthy children” from the definition may allow for a “relativistic interpretation” indexed to the research participants’ own experiences. However, three national advisory committees (the Secretary’s Advisory Committee on Human Research Protections [SACHRP], the Institute of Medicine [IOM], and the National Human Research Protections Advisory Committee [NHRPAC]) have
agreed that the definition of ‘minimal risk’ should be interpreted as those risks of daily life encountered by normal, average, healthy children living in a safe environment [6]. This interpretation is intended to prevent children who may be exposed to greater risk in their daily lives (e.g. from living in an unsafe environment) from being exposed to greater risk in research than would be allowable for children living in safer environments [7].

Examples of minimal risk interventions may include “modest changes in diet or schedule, physical examination, obtaining blood and urine specimens …developmental assessments… most questionnaires, observational techniques, noninvasive physiological monitoring, [and] psychological tests and puzzles.” [5] Other examples include “obtaining stool samples, administering electroencephalograms, … [and] a taste test of an excipient or tests of devices involving temperature readings orally or in the ear.” [8] Finally, some limited exposure to radiation from diagnostic procedures may be viewed as minimal risk [9]. However, federal panels clearly indicate that risk may be cumulative. For example, the number of procedures included in a protocol or the number of times that an individual procedure is repeated in a given period of time may be a factor in assessing the risk. “Although a single blood draw by needle stick normally involves minimal harm or discomfort, multiple needle sticks for blood draws in a short period could, depending on the child’s age and other circumstances, present more than minimal risk of harm or discomfort.” [6]

**Minor Increase over Minimal Risk**

FDA regulations also include a category of “minor increase over minimal risk” (21 CFR 50.53). An intervention or procedure approved under this category must also involve “experiences to subjects that are reasonably commensurate with those inherent in their actual or expected… situations” and be “likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition.” According to the National Commission, the increase in risk allowable under this category was intended to be “slight”, and such risks should involve “no significant threat” to the child’s health or wellbeing. “Given this conservative limit, the… promise of [substantial future benefits to children other than the subject] does justify research which goes beyond, but only slightly beyond, minimal risk.” [10] The justification for this classification also includes: 1) the increased risk is warranted due to scientific necessity [6] and 2) conscientious parents can be entrusted with the authority to evaluate this level of non-beneficial risk exposure [11].

According to SACHRP, when evaluating risk an IRB should take into account the proposed procedure, population under study, and the qualifications of the research personal. Echoing the National Commission, SACHRP recommended that the increase in the probability and magnitude of harm should only be “slightly” more than minimal risk, any potential harms associated with the procedure should be “transient and reversible”, and there should be no or an extremely small probability that participants will experience pain, discomfort, stress, or harm associated with the procedure that is severe. [12] Even if the average risk associated with an intervention or procedure is thought to be low, if the risk estimate is unknown, reflects a large degree of variability, or has not been adequately characterized, then the risks of an intervention or procedure cannot be considered only a minor increase over minimal risk. Both NHRPAC and the IOM concluded that what constitutes a minor increase in research involving children should
not allow for a higher threshold for children with high-risk or high-burden conditions than for children with less serious conditions. [6, 13] In addition, the application of this category of research includes several key concepts: “disorder or condition,” “vital importance,” and “reasonably commensurate” as discussed in the following paragraphs.

“Disorder or condition” can be defined as a set of “specific physical, psychological, neurodevelopmental, or social characteristics” that scientific evidence or clinical knowledge has shown to compromise the child’s health or “to increase risk of developing a health problem in the future” [6]. Therefore, a child could be healthy, but “at risk” for the condition that is the object of the research. Healthy (i.e., not-at-risk) children should be excluded from greater than minimal risk research without a prospect of direct benefit absent referral for review under 21 CFR 50.54 [4, 14].

Consistent with this definition, the IOM report listed four examples of “at risk” conditions that may enable the enrollment of otherwise healthy children into research that posed a minor increase over minimal risk. Children who are obese may be considered “at risk” of type 2 diabetes, such that obese children may be allowed to participate in a nonbeneficial experiment to examine the time course and mechanism of insulin resistance. Being a neonate may be a sufficient “condition” to allow a microdosing study to better understand the ontogeny of drug metabolizing enzymes that could be considered a minor increase over minimal risk. The designation of a child as having behavioral problems by a teacher might allow psychological testing for research purposes that is considered to be a minor increase over minimal risk. Although children with acute lymphoblastic leukemia may have the condition of being at risk of relapse, serial nontherapeutic bone marrow aspirates was considered greater than a minor increase over minimal risk. [6]

The requirement for “vital importance” is consistent with the principle of scientific necessity and thus closely tied to the child’s “disorder or condition” [6]. Establishing that medical products are safe and effective in the pediatric population is a critical public health objective which protects children from risk and enhances their wellbeing. In this context, early phase and exploratory trials to better understand the natural history of a particular disease or to develop endpoints for later registrational trials may be crucial to pediatric product development. Nontherapeutic procedures in children that contribute to these important outcomes may meet the vital importance requirement, even if product development is at an early stage.

The National Commission used “reasonably commensurate” to describe research activities that are reasonably similar (but need not be identical) to procedures that prospective research participants may ordinarily experience. The Institute of Medicine noted that “although a child might not have experienced a particular research procedure…the procedure could still be described to the child as potentially presenting levels of pain, immobility, anxiety, time away from home, or other effects that would be similar to those produced by procedures that they have experienced” [6]. The goal is to make the research procedures tangible for the child and parents, thereby improving child assent and parental permission [5, 15].
NHRPAC, SACHRP and IOM all provided examples of interventions or procedures that may be considered a minor increase over minimal risk. For example, NHRPAC produced the following table regarding common procedures and the level of risk each may pose.

<table>
<thead>
<tr>
<th>PROCEDURE*</th>
<th>CATEGORY OF RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venipuncture/fingerstick/heelstick</td>
<td>X</td>
</tr>
<tr>
<td>Urine collection via bag</td>
<td>X</td>
</tr>
<tr>
<td>Urine collection via catheter</td>
<td>X</td>
</tr>
<tr>
<td>Urine collection via suprapubic tap</td>
<td>X</td>
</tr>
<tr>
<td>Chest xray</td>
<td>X</td>
</tr>
<tr>
<td>Bone density test</td>
<td>X</td>
</tr>
<tr>
<td>Wrist xray for bone age</td>
<td>X</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>X</td>
</tr>
<tr>
<td>Collection of saliva</td>
<td>X</td>
</tr>
<tr>
<td>Collection of small sample of hair</td>
<td>X</td>
</tr>
<tr>
<td>Vision testing</td>
<td>X</td>
</tr>
<tr>
<td>Hearing testing</td>
<td>X</td>
</tr>
<tr>
<td>Complete neurological exam</td>
<td>X</td>
</tr>
<tr>
<td>Oral glucose tolerance test</td>
<td>X</td>
</tr>
<tr>
<td>Skin punch biopsy w/topical pain relief</td>
<td>X</td>
</tr>
<tr>
<td>Bone marrow aspirate w/topical pain relief</td>
<td>X</td>
</tr>
<tr>
<td>Organ biopsy</td>
<td>X</td>
</tr>
<tr>
<td>Standard psychological tests</td>
<td>X</td>
</tr>
<tr>
<td>Classroom observation</td>
<td>X</td>
</tr>
</tbody>
</table>

* The category of risk is for a single procedure. Multiple or repetitive procedures are likely to affect the level of risk.

With respect to procedural sedation, the IOM noted that “a research protocol might include an aspiration of bone marrow that would not offer the prospect of direct benefit to the child participant. To be considered for approval, such a “research-only” procedure must present no more than a minor increase over minimal risk. To meet this requirement and also minimize risk, procedural sedation for the aspiration of bone marrow might be restricted to local anesthesia and intravenous medications (e.g., a narcotic and a benzodiazepine). The purpose of the restriction would be to ensure that the level of sedation was moderate, thus preserving protective airway reflexes.” [6] If an intervention or procedure cannot be considered only a minor increase over minimal risk, it would need to be evaluated under the higher risk pathway described in the next section.

**Higher Risk Pathway and Direct Benefit**

The higher risk pathway (21 CFR 50.52) becomes necessary when existing data indicate that the risks of the intervention or procedure are greater than a minor increase over minimal risk, or when insufficient data are available to support a lower risk determination. Critical to this pathway is the requirement that interventions and procedures must “hold out the prospect of direct benefit to individual subjects,” and that this prospect of direct benefit must be sufficient to justify the risks. In addition, this balance of risk and potential benefit must be comparable to the available alternatives, thus setting this judgment in the context of the natural history, prognosis and treatment alternatives for a specific disease.
FDA regulations do not define “direct” benefits, and the literature offers varying views on which benefits are direct. However, the majority view from a previous Pediatric Ethics Subcommittee discussion was that direct benefit must accrue to the individual research participant, and result from the specific research intervention or procedure and not from ancillary benefits such as health care that may be provided in the clinical trial. In addition, generalizable knowledge per se is not considered a direct benefit. [16]

Diagnostic or monitoring procedures (e.g., additional scans, blood draws, or biopsies) may be needed to answer the scientific questions posed by the clinical trial, or to evaluate the safety of other interventions. More recent accounts of direct benefit have explicitly considered these procedures [17-19]. Diagnostic or monitoring procedures may not per se offer a prospect of direct benefit, yet may be critical in evaluating the safety of other interventions that do offer a prospect of direct benefit. If the monitoring procedure is made necessary by the administration of the investigational product, the risks of the monitoring procedure may be justified by the prospect of direct benefit of the experimental intervention. Using this approach, the administration of the investigational product and the monitoring made necessary by that administration could both be considered under the higher risk pathway (i.e., 21 CFR 50.52). In addition, monitoring procedures that may impact on the child’s clinical care may offer a prospect of direct benefit. For example, if clinical monitoring of blood levels in order to adjust drug dosing were necessary, the risks of venipuncture may be justified under a prospect of direct benefit because the information obtained in this way may affect clinical management. Similarly, if safety monitoring of hepatic enzymes might result in the discontinuation of the investigational product for safety reasons, these laboratory tests may be considered to hold out the prospect of direct benefit under 21 CFR 50.52.

Interventions and procedures that would not be clinically indicated for diagnosing, monitoring or treating a child’s disease (e.g. “nontherapeutic” blood or CSF studies for research biomarkers) are not approvable under this category of research. Hence, absent referral for a federal panel review under 21 CFR 50.54, nontherapeutic interventions and procedures judged to exceed a minor increase over minimal risk may not be approvable in children.

Federal Panel Review Under 21 CFR 50.54

If an IRB determines that a clinical investigation involving children as subjects does not meet the requirements of 21 CFR 50.51, 50.52 or 50.53, the clinical investigation may proceed only if the IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and refers the protocol to FDA for Federal panel review [14]. The Pediatric Ethics Subcommittee provides advice on the acceptability of the protocol through the Pediatric Advisory Committee to the FDA Commissioner. Based on this advice, the FDA Commissioner makes a final determination on whether the criteria for study acceptability are fulfilled:

- The clinical investigation in fact satisfies 21 CFR 50.51, 50.52 or 50.53, or
- The following three conditions described in 21 CFR 50.54 are met:
The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

The clinical investigation will be conducted in accordance with sound ethical principles; and

Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in §50.55.

Following a discussion of component analysis, we will outline examples of the types of studies reviewed by FDA in which procedural sedation may be necessary for nontherapeutic interventions or procedures in the pediatric population.

Component Analysis

As noted earlier, any given protocol may contain multiple interventions and/or procedures, and each must be evaluated under the categories of Subpart D. In 1978, the U.S. National Commission recommended that “to determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively.”[5] For adult subjects, the risks of research participation can be justified either by the anticipated direct benefits to the subjects or by the importance of the anticipated knowledge. In other words, higher risk procedures may be justified in research involving adult subjects by the knowledge to be gained. This is not the case for research involving children. In pediatric studies, the allowable risk exposure for an intervention or procedure not offering a prospect of direct benefit must be restricted to low risk. Thus, the individual research interventions and procedures that are contained in an investigational protocol must be assessed according to whether they do (21 CFR 50.52) or do not (21 CFR 50.51 or 50.53) offer a prospect of direct benefit - an approach referred to as “component analysis.” While component analysis has been debated in the literature, all parties agree on the importance of assessing interventions or procedures individually as to whether they do or do not hold out a prospect of direct benefit so that the risks of non-beneficial interventions or procedures are not justified through the inclusion of unrelated beneficial interventions or procedures in the same protocol [5, 6, 20].

Component analysis may be approached by applying the following three steps.

1. Analyze the protocol to determine whether each research intervention and/or procedure contained in protocol does or does not offer the enrolled child a prospect of direct benefit.
2. Assess the risk level of those interventions and/or procedures that do not offer the child a prospect of direct benefit. This risk level must not exceed a minor increase over minimal risk (i.e., “low” risk) (21 CFR 50.53).
3. Assess whether the risks of those interventions and/or procedures that do offer a prospect of direct benefit are justified by those potential benefits, and that this balance of risks and potential direct benefits are comparable to any available alternatives (21 CFR 50.52).

Thus, component analysis would require that the risks of an experimental intervention or procedure must be justified by the prospect of direct benefit from that same intervention or procedure, and not by other interventions or procedures included in the protocol. For example, the risks of a lumbar puncture must be justified by the prospect of direct benefit from that same
lumbar puncture. If the lumbar puncture is not being performed for the health benefit of the enrolled child, then the lumbar puncture would be considered nontherapeutic and would need to be evaluated under the lower risk pathway (21 CFR 50.51 or 21 CFR 50.53). The risks of a nontherapeutic lumbar puncture may not be balanced against other health benefits that the child might receive as a result of study participation (e.g. more intensive monitoring of their health condition or free health care.)

To determine whether a procedure may be considered therapeutic or nontherapeutic, both the reason for performing the procedure and timing of the procedure need to be considered. If the specified procedure would generally be performed as part of routine clinical management of children with the given disorder at the same or similar time points as would be required by the investigational protocol, these procedures may be approvable under 21 CFR 50.52 as presenting a prospect of direct clinical benefit. In addition, procedures that might change clinical management of a child’s condition (e.g. therapeutic drug monitoring or follow-up diagnostic imaging) may be considered therapeutic. However, procedures that are performed, for example, solely for the purpose of evaluating research endpoints or measuring research biomarkers and would not routinely be performed in children with the given disorder at the specified time points outside of the study are considered “nontherapeutic”, and thus must be evaluated under the lower risk pathway. The failure to carefully distinguish the different components of a clinical investigation may result in the risks of an intervention or procedure that does not hold out the prospect of direct benefit exceeding the allowable ceiling of a minor increase over minimal risk (absent referral under 21 CFR 50.54).

Examples of Studies Involving Nontherapeutic Procedures the Require Procedural Sedation

Several examples of pediatric protocols that involve nontherapeutic procedures that (in some or all children) may require procedural sedation or analgesia are provided below. Following each example, the procedure(s) that may require sedation will be identified, along with a brief review of these procedures under 21 CFR 50 subpart D.

Example 1: Mucopolysaccharidosis Type IIIA

Sanfilippo syndrome Type A, or Mucopolysaccharidosis (MPS) IIIA, is a rare lysosomal storage disease caused by deficiency of the enzyme heparan N-sulfatase. In the absence of this enzyme, there is an accumulation of the glycosaminoglycan (GAG), heparan sulfate, resulting in progressive neurodegeneration. Symptoms are usually first noted in the 1st or 2nd year of life, although definitive diagnosis is often delayed, with an average age of diagnosis of 4.5 years. The disease is characterized by developmental delays initially, followed by neurodevelopmental arrest, then regression. These developmental deficits are typically associated with severe behavioral disturbances. Patients have a significantly reduced lifespan, with few surviving beyond the 2nd or 3rd decade.

The proposed study is a randomized, open-label, concurrently controlled study in patients with MPS IIIA to evaluate the safety and efficacy of an investigational product in pediatric patients ≥12 months and ≤48 months of age at baseline. Patients will be randomized 1:1:1 to intrathecal administration of the investigational product every two weeks for 48 weeks, every four weeks for
48 weeks, or a no product control. The primary outcome measure is decline in Developmental Quotient. Secondary outcome measures include the change from baseline in cortical grey matter volume and GAGs measured in cerebrospinal fluid (CSF). Cortical grey matter volume is assessed by magnetic resonance imaging (MRI), which generally requires procedural sedation in patients in this age group. Lumbar punctures to administer investigational product and to obtain measurements of CSF GAGs may also require procedural sedation.

We appreciate that the age range of the subjects in the proposed protocol includes children who may be at risk of neurotoxicity associated with the use of anesthetic agents. We do not intend to discuss this issue during this meeting, but include the example to point out that many FDA-regulated studies propose to enroll children who are within an age range in which the possibility of anesthetic-associated neurotoxicity from nontherapeutic procedures is a concern.

**Example 1: Assessment**

Assume for the purposes of this discussion that the risks and benefits of the investigational product were appropriately reviewed and found to be approvable under 21 CFR 50.52. As such, the investigational product would be judged to hold out the prospect of direct medical benefit to any enrolled child who received the product. The risks of any invasive procedures that may be necessary to administer the investigational product (in this case, lumbar punctures with or without procedural sedation) would be judged against the potential benefits of the investigational product as part of the review of the risks and benefits under 21 CFR 50.52. If CSF samples for investigational analyses (e.g. measurements of CSF GAGs) may be obtained at the same time as the investigational product is administered, then the only risk to children of this assessment stems from the volume of CSF withdrawn for the purposes of GAG measurements.

However, the protocol also proposes to obtain measurements of CSF GAGs in children in the control group who would not otherwise undergo lumbar punctures. In addition, MRI scans to assess cortical grey matter volume would be required in all enrolled children to obtain data that may be used for further exploratory studies and endpoint development. These procedures would not be clinically indicated outside of research participation, and would not be considered to offer enrolled children a prospect of direct benefit. Because there is no prospect of direct benefit, these procedures cannot be assessed under the higher risk pathway (21 CFR 50.52), as this category stipulates that interventions and procedures must hold out the prospect of direct benefit. However, the risk of the procedures (LP and/or MRI) along with any procedural sedation that may be necessary to perform these procedures in this age group may be considered under 21 CFR 50.53, as procedures evaluated under this category are not required to offer children the prospect of direct benefit. In the proposed study, all children on whom these nontherapeutic procedures will be performed have a “disorder or condition” of MPS IIIA which is the object of the research. As such, the nontherapeutic procedures along with any necessary procedural sedation may be considered under a “minor increase over minimal risk” (21 CFR 50.53).

As outlined earlier, the criteria for approval of research under this subpart include the following: (a) the risk represents a minor increase over minimal risk; (b) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; (c) the
intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (d) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians. To be approvable under this pathway, the risks of the nontherapeutic interventions and procedures and the procedural sedation necessary to perform them must not exceed a minor increase over minimal risk. In addition, the procedures and sedation must also meet criteria under (b-d) above regarding commensurability, vital importance, and appropriate permission and assent.

If some forms of procedural sedation are determined to pose more than a “minor increase over minimal risk” to enrolled children (or are otherwise not approvable under 21 CFR 50.53), then the only remaining option for performing the study is for an IRB to refer the protocol for Federal panel review under the 21 CFR 50.54 process.

**Example 2: Spinal Muscular Atrophy**

Spinal muscular atrophy is an autosomal recessive disease caused by a deletion or point mutation in the survival of motor neuron (SMN) 1 gene, leading to a deficiency in functional SMN protein. A functional deficiency in this protein results in muscle atrophy due to a loss of function in neurons in the anterior (motor) horn of the spinal cord. Muscles in the lower extremities are usually affected first, and proximal muscles are affected earlier. However, the age at onset and disease phenotype is variable, and depends on the number of copies of a nearly identical protein in chromosome 5, SMN2. Due to variation in a single nucleotide, only 10-20% of SMN2 transcripts result in a functional SMN protein. In patients affected prior to 18 months of age, respiratory compromise is a major concern.

A Phase 3 multicenter, double-blind, randomized, sham-procedure controlled study of an investigational product in patients 2 to 12 years of age at baseline with onset of SMA symptoms at greater than six months of age is planned. Subjects will be randomized 2:1 to receive intrathecal investigational product or a sham procedure control, respectively. The sham comparator will consist of a needle prick in the lower back at the location where an intrathecal injection is normally made. The primary outcome measure is the change from baseline in Hammersmith Functional Motor Scale. Secondary outcome measures include number of new motor milestones achieved, and change from baseline in the upper limb module test. Anesthesia and/or sedation may be used for study procedures, such as the intrathecal administration of the investigational product.

We appreciate that the age range of the subjects in the proposed protocol includes children who may be at risk of neurotoxicity associated with the use of anesthetic agents. We do not intend to discuss this issue during this meeting, but include the example to point out that many FDA-regulated studies propose to enroll children who are within an age range in which the possibility of anesthetic-associated neurotoxicity from nontherapeutic procedures is a concern.
Example 2: Assessment

As in the prior example, the risks of lumbar punctures and procedural sedation would be assessed against the potential benefits of the investigational product among children who are randomized to receive this product. However, in children who are not randomized to the investigational product, the sham procedure poses risks that are without any compensating benefits. As such, the risks of the sham procedure cannot be considered under 21 CFR 50.52.

As before, all enrolled children in the study will have a “disorder or condition” (spinal muscular atrophy) that is the object of the research. As such, the risks of the sham procedure may be considered under the “minor increase over minimal risk” category (21 CFR 50.53). In general, a sham procedure is intended to mimic the actual procedure in every way, including pre-procedure routine, anesthesia, and post-procedure follow-up. Thus, the only difference between the sham procedure and a true lumbar puncture is that the spinal canal would not be punctured, eliminating any risk of headache or remote risk of central nervous system infection that may otherwise be associated with entering the spinal canal. However, procedural sedation for this nontherapeutic procedure may still be necessary in these participants to maintain blinding of the study. Thus, as before, the approach to procedural sedation would need to be approvable under criteria for a minor increase over minimal risk (21 CFR 50.53) absent referral of the protocol for Federal panel review.

Example 3: Limb-Girdle Muscular Dystrophy Type 2D

Limb-Girdle Muscular Dystrophy type 2D (LGMD2D) is an autosomal recessive disorder causing progressive weakness of muscles in the hip, shoulder, and abdomen. Disease onset is often before the age of 10 years, but in some patients may be later. Approximately 20% of patients with the disorder have cardiomyopathy. In some patients, the disease may be fatal early in the second decade of life, often from cardiac or respiratory compromise. The proposed clinical trial is a dose escalation study of a gene transfer product in LGMD2D subjects ages 7 years and older delivered via a major lower limb artery of each leg sequentially by modified isolated limb perfusion and isolated limb infusion. Two cohorts will undergo gene transfer in a standard three-six dose escalation scheme to establish the maximum tolerated dose.

The primary objective of this study is to assess the safety of intravascular administration of the gene transfer product delivered via the femoral artery to both lower extremities in LGMD2D subjects. Safety monitoring during recirculation will include: activated clotting times, limb gases, real time monitoring of arterial and venous access pressures, and perfusate temperature. Safety endpoints will be assessed by changes in hematology, serum chemistry, and urinalysis, immunologic response to gene transfer products, and reported history and observations of symptoms. The six minute walk test will be used as secondary outcome. An exploratory measure will include direct muscle testing for strength of lower limb muscles. Subjects will be evaluated at baseline, infusion visit (days 0-2), and return for follow up visits on days 7, 14, 30, 60, 90, 180 and at the end of 1st and 2nd years. The study requires muscle biopsies to be performed at baseline screening and at day 180 for the purpose of establishing the size of muscle fibers and determining the effects of gene transfer. Procedural sedation and anesthesia is required for the muscle biopsies.
Example 3: Assessment

Whether the muscle biopsies performed at baseline and at day 180 could be considered therapeutic is doubtful. Many clinicians may choose not to perform repeated biopsies in this patient population, and without further details regarding the nature of the investigational product, it is not clear whether such biopsies would be required for therapeutic monitoring of the investigational product with subsequent changes to the child's clinical care. As with the other examples, all enrolled children in the proposed study have a “disorder or condition” (LGMD2D) that is the object of the research. Hence, the muscle biopsy and procedural sedation could be evaluated as to whether they present no more than a “minor increase over minimal risk” under 21 CFR 50.53. If the biopsy and/or sedation were not approvable under this category, then as before the protocol could be referred for Federal panel review under 21 CFR 50.54.

Review of Published Literature Regarding Procedural Sedation

Procedural sedation involves the administration of sedative or analgesic medications to intentionally suppress a patient’s level of consciousness to facilitate performing diagnostic or therapeutic procedures. The intended depth of sedation may vary according to the needs of the procedure. Sedation levels of “mild,” “moderate,” and “deep” levels of altered consciousness are frequently cited in the medical literature, although many studies (reviewed below) do not use these descriptors. A level of minimal sedation describes a patient with a near-baseline level of alertness, in which patients respond normally to verbal commands, but cognitive function and coordination may be impaired. Moderate sedation is characterized by purposeful response to verbal commands, either alone or in combination with light tactile stimulation. Event amnesia will frequently occur. No interventions are generally required to maintain a patent airway and ventilation and cardiovascular function is usually adequate. Moderate sedation is commonly achieved with a benzodiazepine in combination with an opioid such as fentanyl (F). Dissociative sedation is a trance-like cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability. Particularly in the emergency department, ketamine (K) is commonly administered to children as a dissociative agent to facilitate moderate to severely painful procedures such as fracture reduction, as well as procedures requiring immobilization. Deep sedation means that patients cannot easily be aroused but respond purposefully after repeated or painful stimulation. The ability to independently maintain ventilatory function, a patent airway and spontaneous ventilation may be impaired, although cardiovascular function is usually maintained. Deep sedation is commonly achieved with short-acting sedative agents such as propofol (P), with an opioid in concert with the sedative for painful procedures. [21]

Thus, it is important to recognize that procedural sedation is on a continuum with general anesthesia, and it is not always possible to predict how individual patients receiving sedative and/or analgesic medications will respond. Accordingly, the Joint Commission for Hospital Accreditation Standards stipulates that “individuals administering moderate or deep sedation and anesthesia are qualified and have credentials to manage and rescue patients at whatever level of sedation or anesthesia is achieved, either intentionally or unintentionally.” [22] As such, hospitals may have a sedation team comprised of individuals with experience and expertise in
selecting appropriate agents for sedation and in monitoring and managing any potential complications.

A common method noted in the literature for indicating the degree of sedation is the Ramsay Sedation Scale. [23] The sedation scale has the following elements:

1. Patient is anxious and agitated or restless, or both
2. Patient is co-operative, oriented, and tranquil
3. Patient responds to commands only
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6. Patient exhibits no response

There appears to be no necessary relationship between the ‘mild’, ‘moderate’, and ‘deep’ levels of sedation described above and the Ramsay scale, though ‘mild’ sedation appears to correspond to Ramsey levels 1 and 2, ‘moderate’ sedation to Ramsay levels 3 and perhaps 4, and deep sedation to Ramsay level 5. As persons who are deeply sedated should respond purposefully to repeated or painful stimuli, a Ramsay level 6 appears to describe a patient who is oversedated.

**American Society for Anesthesiologists Classification**

The American Society of Anesthesiologists (ASA) uses a classification system to assign risk for anesthesia, which has become an essential part of the pre-operative evaluation for general anesthesia. [24]

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Normal healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 2</td>
<td>Patient with mild systemic disease</td>
</tr>
<tr>
<td>Class 3</td>
<td>Patient with severe systemic disease</td>
</tr>
<tr>
<td>Class 4</td>
<td>Patient with severe systemic disease that is a threat to life</td>
</tr>
<tr>
<td>Class 5</td>
<td>Morbid patient who is not expected to survive without the operation</td>
</tr>
</tbody>
</table>

A recent study of risk assessment using 863,349 patients records from the National Surgical Quality Improvement Program database found that the single highest preoperative risk factor for mortality or surgical complication out of 66 preoperative variables recorded was ASA classification [25]. ASA classification is a parameter that is routinely recorded by most sedation services, and limited data (discussed below) indicate that a higher ASA classification is associated with a greater complication rate for procedural sedation as well as for general anesthesia.

A prospectively collected database of children aged 0 to 21 years undergoing procedural sedation in the emergency department of an urban, tertiary care, children's hospital was retrospectively reviewed. Complications were defined *a priori* as persistent oxygen desaturation (SpO2) on pulse oximetry to less than 93% requiring supplemental oxygen, bronchospasm, dizziness, apnea, seizure, hiccoughs, laryngospasm, stridor, arrhythmia, hypotension, rash, vomiting, aspiration, or a disinhibition/agitation/dysphoria emergence reaction. The main outcome measure was the incidence of complications relative to ASA class. Nine hundred eighty-eight patients were classified as ASA class 1, whereas 214 were classified as ASA class 2 or greater. There were a total of 215 adverse events in the study population. Most of these were hypoxia (185 total) and
were more likely to occur in patients with an ASA class 2 or greater (p = 0.021). No hypoxic episode required intubation to resolve. Children with ASA class 2 or greater were also more likely to be admitted to the hospital than children with ASA class 1 (p = 0.005), and have a longer recovery time (p = 0.016) [26].

A retrospective study of the Clinical Outcomes Research Initiative database reported on 1,318,495 individual adults undergoing endoscopic procedures. The study found that increasing ASA class was associated with higher prevalence and a stepwise increase in the odds ratio of serious adverse events for esophagastroduodenoscopy (II: 1.54 [95% confidence interval (CI), 1.31-1.82]; III: 3.90 [95% CI, 3.27-4.64]; IV/V: 12.02 [95% CI, 9.62-15.01]); and colonoscopy (II: 0.92 [95% CI, 0.85-1.01]; III: 1.66 [95% CI, 1.46-1.87]; IV/V: 4.93 [95% CI, 3.66-66.3]) [27].

Several additional studies in children also found an association between ASA classification and the adverse events associated with procedural sedation. A retrospective cohort study of children (primarily ASA classes II and III) receiving P for research imaging studies demonstrated an association between adverse events as described below and ASA classification (odds ratio [OR] 2.92; 95% CI, 1.24-6.88) [28]. An increased odds ratio for respiratory complications with ASA classification (OR: 2.60, P = 0.04) was found in a study of children undergoing procedural sedation with intramuscular or intravenous K [29]. Another retrospective study of children sedated with P found an association between respiratory events and ASA class II (OR 2.30, 95% CI 1.22-4.33) [30]. Finally, an increased risk of hypoxemia was found in a series of children with ASA class 3 or 4 who underwent either procedural sedation or general anesthesia for radiologic studies [31].

**Propofol**

A study from the Pediatric Research Sedation Consortium (PRSC) reports on nearly 50,000 P sedation/anesthesia encounters from 37 centers from July 1, 2004 until September 1, 2007. Cardiopulmonary resuscitation and epinephrine administration was required for one case of apnea and asystole and another of severe bradycardia, but there were no deaths. Aspiration during sedation/anesthesia occurred four times. Unplanned intubation occurred 53 times, unplanned laryngeal mask airway placement occurred 50 times, and unplanned nasopharyngeal airway placement occurred 211 times per 10,000 sedation/anesthesia administrations. Other adverse events were more common. SpO₂ below 90% for more than 30 seconds occurred 154 times per 10,000 sedation/anesthesia administrations. Central apnea or airway obstruction occurred 575 times per 10,000 sedation/anesthesia administrations. Stridor, laryngospasm, excessive secretions, and vomiting had frequencies of 50, 96, 341, and 49 per 10,000 encounters, respectively. Unexpected admissions (increases in levels of care required) occurred at a rate of 7.1 per 10,000 encounters [32].

A subsequent study from the PRSC reported on > 90,000 encounters where procedural sedation using P was provided by pediatric critical care physicians. Most encounters (80.9%) were performed in dedicated sedation or radiology units, and most patients were not at increased risk of complications (81.9% were ASA class I or II). A P bolus alone was used in 52.8%, and 41.7% received a bolus plus continuous infusion. Commonly used adjunctive medications were lidocaine (35.3%), opioids (23.3%), and benzodiazepines (16.4%). The overall adverse event
incidence was 5.0% (95% CI, 4.9-5.2%), which included airway obstruction (1.6%), desaturation (1.5%), coughing (1.0%), and emergent airway intervention (0.7%). No deaths and a single cardiac arrest occurred, with no untoward neurologic sequelae. Risk factors associated with adverse events included: location of sedation, number of adjunctive medications, upper and lower respiratory diagnosis, prematurity diagnosis, weight, American Society of Anesthesiologists status, and painful procedure[33].

A third study from the PRSC reported on > 25,000 encounters with procedural sedation using P by emergency physicians from 2004-2008, with 76% performed in a radiology department. More serious adverse events (defined as airway obstruction, desaturation, apnea, laryngospasm, aspiration, unplanned admission, cardiac arrest, emergency call for anesthesiologist, unplanned intubation, or death) occurred in 581 (2.28%) of encounters. There were two episodes of aspiration, one cardiac arrest, and one unplanned intubation. The risk of adverse events was increased in children with ASA classification > 2, children ≤ 5 kg, those given adjunctive opioids, K, or benzodiazepines, and those with a primary diagnosis of either upper airway disease or prematurity. The risk among children administered anticholinergics was also increased, but the use of anticholinergics may be used prophylactically in patients with more risk factors [34].

Another study evaluated all outpatient pediatric procedures using P sedation over a 6-year period (2001-2007) that was provided by pediatric intensivists at a single institution. In all, 4716 procedures were recorded during the study period. Approximately 5% of patients were less than a year of age, 59% were 1 to 10 years of age, and 36% were older than 10 years of age. Minor complications (e.g. transient requirement of oxygen by nasal cannula or positive pressure ventilation by mask, airway repositioning by jaw thrust, or oropharyngeal suctioning to improve SpO2) were common, occurring in 15% of procedures. Major complications (e.g. endotracheal intubations, unplanned admission, or early termination of the procedure) occurred in only 0.1% of procedures. All patients experiencing a major complication recovered [35].

Another study reported on a retrospective review of 1649 charts of patients sedated with P by pediatric hospitalists at St Louis Children's Hospital between January 2005 and September 2009. Major complications included 2 patients with aspiration and 1 patient intubated to complete the study. Predictors of respiratory events were history of snoring (OR, 2.40; 95% CI, 1.52-3.80), ASA physical status classification of ASA 3 (OR, 2.30; 95% CI, 1.22-4.33), age >12 years (OR, 4.01; 95% CI, 2.02-7.98), premedication with midazolam (M) (OR, 1.85; 95% CI, 1.15-2.98), and use of adjuvant glycopyrrolate (OR, 4.70; 95% CI, 2.35-9.40). All except ASA 3 status were also predictors for airway intervention [30].

A single study from the NIH Clinical Center reported on P procedural sedation specifically in the clinical research context. Whether these procedures were considered “therapeutic” or “nontherapeutic” was not reported. The article reports on 1480 encounters with 607 children, and in 70% of cases the children had severe disease and significant disabilities (ASA III). In all cases, sedation was provided by an anesthesiologist. In 12.5% of procedures, an airway device was necessary. There were 98 notable respiratory, cardiovascular, and other events in 79 anesthetic procedures, with a rate of 534 per 10,000 anesthetic procedures with 1 or more adverse events. There were no deaths and no long-term complications. The ASA classification,
anesthetic effect duration, and presence of airway abnormalities were independently associated with adverse events during anesthetic use [28].

A prospective study of P sedation by ED physicians reported 291 sedation events in 87 patients. All patients received supplemental oxygen. Sedation depth and vital signs were monitored while P was manually titrated to the desired level of sedation. Median patient age was 6 years; 57% were male patients and 72% were oncology patients. Most commonly performed procedures included lumbar puncture (43%), intrathecal chemotherapy administration (31%), bone marrow aspiration (19%), and bone biopsy (3%). Median total P dose was 3.5 mg/kg. Median systolic and diastolic blood pressures were lowered 22 mm Hg (range 0 to 65 mm Hg) and 21 mm Hg (range 0 to 62 mm Hg), respectively. Partial airway obstruction requiring brief jaw-thrust maneuver was noted for 4% of patient sedations, whereas transient apnea requiring bag-valve-mask ventilation occurred in 1% of patient sedations [36].

**Controlled Trials Comparing Propofol with Other Agents**

In the sections below, studies of multiple agents for procedural sedation are described as reported in the original articles. In some cases, the order in which the drugs are reported corresponds to the order in which they were administered.

In another study in the critical care department, 105 persons with an ASA class I-III aged 1 month to 28 years were randomized by procedure date to either P (2.5 mg/kg or 3 mg/kg bolus for infants, with maintenance of 200 µg/kg/min) or a combination of M (0.1 mg/kg)-K (2 mg/kg)-F (2 µg/kg) (M/K/F) [37]. Apnea that did not spontaneously resolve and required bag and mask ventilation occurred in ten patients in the P group and in three patients in the K group (p = 0.17). One child in the K group experienced respiratory depression, resulting in an unplanned endotracheal intubation for the remainder of the procedure. Hypotension (defined as a decrease in systolic blood pressure to less than the fifth percentile for age) occurred in six patients (10.3%) in the P group and in two patients in the K group (p = 0.29).

A prospective cohort study enrolled 200 children <14 years of age undergoing procedural sedation for diagnostic procedures. The patients received either P (2 mg/kg bolus plus a maintenance dose of 100 µg/kg/min) or M (0.15 mg/kg bolus) to achieve sedation. Arterial blood pressures decreased significantly in both groups (numeric decreases not reported). The patients receiving P experienced a greater difference in diastolic blood pressure. Sedation scores in the P group reached the appropriate sedation level in a shorter time. Likewise, recovery time of patients was shorter in patients receiving P. Hypoxia (defined as SpO2 < 90%) was found to be more common in the P group, but the difference was not significant [38].

Another prospective study in a pediatric teaching hospital compared the efficiency of P versus a combination of midazolam and fentanyl (M/F) for endoscopy by measuring elapsed times between initial intravenous administration and patient discharge. The study was not randomized, and patients who received P sedation were significantly more likely to have been assigned ASA class 2 rather than 1. Of patients sedated with P, 34% underwent elective endotracheal intubation before the procedure. All patients who received P sedation were reported to achieve a Ramsay level 5 of sedation, and no patients who received M/F were reported to become more deeply
sedated than a Ramsay level 4. The study found that anesthesiologist-administered P sedation in a pediatric teaching endoscopy unit did not lead to faster hospital discharge times when compared with endoscopist-administered M/F [39].

Other Propofol-Containing Regimens

Several RCTs have reported on the use of P containing regimens. A combination of P (0.5 mg/kg)-F (1 µg/kg) (P/F) was compared to P (0.5 mg/kg)-F (1 µg/kg)-K (0.5 mg/kg) (P/F/K) in 60 ASA class I-III patients ages 1-16 undergoing interventional radiology procedures [40]. The authors reported no cases of apnea, but there were three cases (10%) of SpO2 in the P/F/K group and 9 cases in the P/F group (p = 0.052). There was no evidence for a difference in the sedation scores except at 15 minutes after induction, the group receiving K remained more sedated than the group who did not.

In another randomized study, a combination of P (1 mg/kg)-F (1-2 µg/kg) (P/F) was compared with K (1-2 mg/kg) and M (0.05 mg/kg to a maximum of 2 mg) (K/M) in 113 patients ages 3-18 for orthopedic procedures in the emergency department [41]. Transient desaturation occurred in 18 of 59 (31%) patients in the P/F group and in 4 of 54 patients (7%) in the K/M group. No patient in either group had apnea. Emergence agitation and emesis were seen in 5 of 54 patients in the K/M group. In the P/F group, there was a single episode of hypotension (74/49), a single episode of laryngospasm, and a single episode of stridor with cough and desaturation to 88%. All resolved without complication.

In another study, a total of 136 ASA class I and II children (aged 2 to 17 years) requiring procedural sedation and analgesia for management of an isolated orthopedic injury were randomized to receive either a combination of K/P (0.5 mg/kg and 0.5 mg/kg followed by P 0.5 mg/kg every 2 minutes, titrated to deep sedation) or K alone (1.0 mg/kg and placebo every two minutes, as required). Physicians, nurses, research assistants, and patients were blinded to treatment assignment. Median total sedation time and recovery time was shorter with K/P than with K alone. There was less vomiting in the K/P group compared with the K group. No patients in either group required bag-valve-mask ventilation, endotracheal intubation, or any airway intervention other than airway repositioning or increased supplemental oxygen. Patient, physician, and nurse satisfaction scores were higher with K/P than with K alone [42].

Ketamine, Midazolam, and Fentanyl

Less data have been systematically collected regarding approaches to procedural sedation with other agents. These studies are generally small, conducted in a wide variety of settings, and with variable definitions of adverse events or serious adverse events. In addition, most of the reported studies use a combination of agents, making adverse event data more difficult to attribute to particular agents.

A randomized, controlled study in a Turkish hospital compared a combination of K/M (1 mg/kg and 0.1 mg/kg) versus K (1 mg/kg) alone in 99 children ages 2-14 years requiring sedation for lumbar puncture. Desaturation was not observed in the K group, whereas three patients in the K/M group required supplemental oxygen. Dizziness was reported by 10 patients in the K/M
group and 5 patients in the K group. In the K/M group, a single episode of hypotension was observed. Nausea and/or vomiting was more frequent in the K group, as were nightmares or crying spells. The mean time to sedation was shorter in the K/M group, as was parental satisfaction. Recovery time did not differ between groups [43].

One hundred ASA class I children between the ages of 2 and 7 years who required sedation for dental procedures performed under local anesthesia were administered either a combination of K/M (5 mg/kg and 0.35 mg/kg) or M alone (1 mg/kg) rectally 30 minutes prior to the procedure. Pulse rate, respiratory rate, arterial pressure, SpO2, adverse reactions, postoperative recovery, and behavior were recorded. Thirty minutes after drug administration, the K/M group demonstrated higher values than M alone for blood pressure and heart rate. Respiratory rate and SpO2 did not differ between groups. Excessive salivation occurred in 26% of children receiving the combination of drugs, compared with 14% receiving M alone. Seven (14%) of the children receiving the combination of drugs hallucinated, compared with 21 (42%) receiving M alone. Both drug groups had reliably good anxiolysis and sedation without loss of respiratory drive or protective airway reflexes [44].

A total of 260 ASA Class I or II patients ages 5 to 15 years needing emergency fracture or joint reduction were randomized to receive intravenous M (≤0.1 mg/kg, maximum 2.5 mg every 3 minutes, titrated to effect) followed by either F (≤0.5µg/kg every 3 minutes, titrated to effect) or K (≤0.5 mg/kg every 3 minutes, titrated to effect). Measures of efficacy were observational distress scores and self- and parental-report of patient satisfaction. Measures of safety were frequency of abnormalities in and need for support of cardiopulmonary function and other adverse effects. During reduction, M/K subjects had lower distress scores and parental ratings of pain and anxiety than did M/F subjects. Although both regimens were judged to equally facilitate reductions, deep sedation, and procedural amnesia, orthopedists favored M/K. Recovery was 14 minutes longer for M/K. Fewer M/K subjects had hypoxia (6% vs 25%), needed breathing cues (1% vs 12%), or required oxygen (10% vs 20%) than did M/F subjects. Two M/K subjects required bag-valve-mask-positive pressure ventilation briefly. More M/K subjects vomited. Adverse emergence reactions were rare but equivalent between regimens [45].

A total of 57 ASA class II-IV children were prospectively randomized to receive either M/F (0.24 +/- 0.11 mg/kg and 1.68 +/- 0.83 µg/kg) or K/M (0.26 +/- 0.09 mg/kg and 1.40 +/- 0.72 mg/kg) to facilitate central venous catheter insertion for nonintubated children in the pediatric intensive care unit. The groups were similar in age, weight, ASA risk classification, recovery time and sedation level. Median total sedation times did not differ between regimens. Minor complications (excessive secretions, desaturation, hiccups, transient partial airway obstruction) occurred in 3.5% (M/F) vs 20.7% (K/M) (p = 0.03). M/F resulted in a greater reduction in respiratory rate (p = 0.005), but no patient had a <90% SpO2. The adverse events either resolved spontaneously, required suction of the airways, or responded to increased oxygen flow [46].

Another study reported on the results of a program at a single institution in which hematology/oncology and critical care staff began using a combination of M and K for necessary procedures among their patient population. A total of 350 procedures (74 lumbar punctures, 97 bone marrow aspirations or biopsies, 84 radiotherapy sessions, and 95 imaging studies) were reported. The procedures involved 68 children, 4 months to 17 years of age, in both inpatient and
ambulatory settings. Patients were sedated initially with M (0.05 to 0.1 mg/kg intravenously; maximum single dose of 2 mg, maximum total dose of 4 mg), followed by K (1 to 2 mg/kg intravenously). During lengthy procedures, additional doses of K (0.5 to 1 mg/kg) were given as necessary. All patients were effectively sedated with this regimen. Four patients experienced transient decrease in O₂ saturation (<85%) requiring temporary interruption of the procedure and supplemental oxygen. Two patients experienced significant agitation during recovery from sedation. Twenty-four lumbar punctures were associated with transient decrease in O₂ saturation (88% to 92%), which improved by relief of neck flexion and/or supplemental oxygen. No hypotension, bradycardia, or respiratory depression requiring respiratory support or reversal of sedation was noted [47].

The records of patients who received an intravenous K/M combination for painful procedures in the pediatric sedation unit of a Turkish university hospital over a 3 year period were retrospectively reviewed. All children received atropine to minimize secretions. Sedation was initiated with M at a dose of 0.05 mg/kg (maximum 2.5 mg) IV. For all children, the mean total dose of K was 1.8 ± 0.8 mg/kg (range 1 – 6 mg) and titrated to deep sedation. A total of 227 children ages 4 months to 18 years with ASA class I-III had a total of 356 procedures. The indications for procedural sedation and analgesia included bone marrow aspiration or biopsy (50.8%), central venous catheter insertion (27%), and other (22%). A total of 46 adverse events (12.9%) were observed. These adverse events included SpO₂ below 85% without apnea that responded to maneuvers to open the airway or painful stimuli (n = 14), apnea requiring short-term bag and mask ventilation (n = 3), transient stridor (n = 2), transient hypertension and tachycardia (n = 8), hypersalivation (n = 6), vomiting (n = 5), hallucinatory emergence reaction (n = 4), and rash (n = 4). [48].

A database of consecutive patients receiving parenteral procedural sedation and analgesia was prospectively generated with the intent of monitoring safety in a single tertiary care emergency department. A retrospective analysis was performed based on sedation drugs used. A total of 2,500 patients (2,279, intravenous; 221, intramuscular) was included in the analysis. Ages ranged from 19 days to 32 years (median, 6.7 years). Four major drug combinations were used: K alone (n = 1,492; 59.7%), K/M (n = 299; 12.0%), M/F (n = 336; 13.4%), and M alone (n = 260; 10.4%). A total of 113 patients (4.5%) received various other combinations of drugs. A total of 458 adverse events were observed in 426 patients (17%). Respiratory adverse events (SpO₂ <90%, apnea, or laryngospasm) occurred as follows: K alone, 91 patients (6.1%); K/M, 30 patients (10%); M/F, 65 patients (19.3%); M alone, 15 patients (5.8%). No patients required intubation. Vomiting occurred as follows: K alone, 151 patients (10.1%); K/M, 16 patients (5.4%); M/F, six patients (1.8%); M alone, two patients (0.8%) [49].

Another study attempted to establish the timing of adverse events in a cohort of procedural sedation patients from a prospectively generated database. The most common medications used for procedural sedation included M/F, K/M, and M alone. In 1341 sedation events, there were 184 (13.7%) adverse effects, of which 159 (11.9%) were serious (e.g. hypoxia, stridor, hypotension). The median age of children with and without adverse effects was similar (64 months in both groups). Most adverse effects occurred during the procedure (92%) rather than after the procedure (8%). Serious adverse events occurred a median of 2 minutes after final medication dose. Serious adverse events rarely occurred after 25 minutes from the final
medication administration. Those that did occur this late were all preceded by a separate similar adverse event during the expected peak drug effect [50].

A single-center prospective case series of 1200 children documented adverse events with procedural sedation using F and M. Serious adverse events (apnea) were noted in 2 patients (0.2%). Mild or moderate adverse events included desaturation below 92% for less than 20 seconds (100 patients, 9%), vomiting (64 patients, 5%), agitation (15 patients, 1%), desaturation below 92% for greater than 20 seconds (12 patients, 0.7%), and rash (8 patients, 0.7%). No cardiopulmonary resuscitation or sedation reversal was necessary. No patients required hospitalization. Patients younger than 6 years were more likely to develop a respiratory adverse event (P < .01) [51].

Finally, one studies compared the frequency of respiratory adverse events between patients who received intramuscular versus intravenous K. In the case-control study, adverse events were defined as apnea, hypoxemia (oximetry <93%), hypoventilation, laryngospasm, and other upper airway obstruction. Serious adverse events were defined by the level of intervention and included those cases that required positive pressure ventilation, insertion of an oral or nasal airway, or endotracheal intubation. Minor adverse events were respiratory events requiring minimal intervention (stimulation, supplemental O₂, airway repositioning). Controls (2:1) were selected by the next chronological patient in the data set who received K but had no respiratory adverse event. Four thousand two hundred fifty-two patients received K; 102 cases (2.4%) had respiratory adverse events, including 38 patients with severe adverse events (0.9%). Intramuscular IM K was associated with increased likelihood of adverse events (odds ratio 2.1, 95% CI, 1.3-3). Twenty (69%) of the 29 patients with laryngospasm received IM K (OR, 5.2; 95% CI, 2.3-11.9) and 20 (53%) of the 38 patients who had severe events were administered IM (OR, 2.4; 95% CI, 1.2-4.9) [52].

Center and Practitioner Skill

A clear limitation, particularly of the studies from the PRSC and the NIH Clinical Center, is that these data may not be representative of all sites in which P may be used. PRSC sites have providers from a variety of specialties that are part of an organized sedation service. As such, these physicians regardless of specialty are likely to have particular training and expertise in airway management. In addition, PRSC study sites are referral centers and/or academic medical centers with a high volume of cases. A study performed by the PRSC recorded 131,751 pediatric procedural sedation cases, with 122 major complications (aspiration, death, cardiac arrest, unplanned admission to the hospital, an increase in a patient’s level-of-care, or a requirement for emergency anesthesia consultation) and no deaths. Major complication rates and 95% confidence intervals per 10 000 sedations were as follows: anesthesiologists, 7.6 (4.6-12.8); emergency medicine, 7.8 (5.5-11.2); intensivist, 9.6 (7.3-12.6); pediatrician, 12.4 (6.9-20.4); and other, 10.2 (5.1-18.3). There was no statistical difference (p > .05) among provider's complication rates either before or after adjustment for potential confounding variables [53]. Another retrospective study of 690 patients conducted at a tertiary children’s emergency department reported no patients requiring bag mask ventilation or intubation whether procedural sedation was managed by nurse practitioners with training in procedural sedation or emergency physicians/pediatric emergency medicine fellows [54].
A second analysis of the PRSC data noted above evaluated patient demographics, medications used, diagnoses, complications, and procedures involved when pediatric generalists or specialists provided sedation. A total of 12,113 sedations performed by pediatricians or pediatric subspecialists that do not focus on airway management were submitted from 1 July 2004 to 31 December 2008, compared to 119,665 cases performed by physicians and other staff with expertise in airway management (anesthesiologists, intensivists, emergency physicians, PAs, etc.) Patients cared for by pediatricians were more frequently non-emergency ASA class I or II, aged 2-8 years old, with a neurologic primary diagnosis, and being sedated for a radiologic procedure. Due to the dissimilarity between the medications used and patient demographics between patients treated by pediatricians and other providers, direct comparisons between groups regarding complication rates is likely to be confounded [55].

A prospective single-blind nonrandomized Israeli study compared the rate of procedural sedation-related adverse events of pediatric residents with specific training in "patient safety during sedation" and pediatric emergency physicians (PEPs) who completed the same course or were teaching faculty for the course. Sedations over 12 consecutive months were recorded. Varieties of methods for procedural sedation were used, and were chosen by the treating physician. Adverse events were defined as transient hypoxia (SpO₂ < or = 90%) or apnea. A total of 984 eligible sedations were recorded, 635 by unsupervised residents and 349 by PEPs. The total adverse event rate was 24/984 (2.44%). When the two groups used similar types of drugs, residents had 8/635 (1.26%) events, compared to 11/328 (3.35%) by PEPs. There was no statistically significant difference in the rates of hypoxia or apnea between the two groups, and no patients required intubation or hospitalization [56]. However, this design was open to selection bias, not only about the patients who required procedural sedation, but whether such patients were assigned to residents or PEPs.

We found one study comparing the quality of a standard benzodiazepine/opiate regimen administered by the endoscopy team to P administered by a dedicated anesthesiologist. Clearly, the analysis of sedation regimen is confounded in this study by the difference in providers. Twenty-five adults undergoing upper endoscopic ultrasound were enrolled in each group, and the procedure was videotaped. Expert quantitative analysis of the video was performed using the Dartmouth Operative Conditions Scale to compare the quality of sedation provided by the different sedation protocols. The analysis revealed that 52% (13/25) of the standard group exhibited an uncontrolled patient state (significant undersedation and/or oversedation) on 1 or more occasion during their endoscopic procedure compared with 28% (7/25) of the P group. Patients in the standard group spent 7.1% of the procedure in an uncontrolled state, whereas patients in the P group experienced an uncontrolled state approximately 1.0% of the procedure time. Overall efficiency as measured by time in both the procedure room and in recovery was superior in the P group [57].

Smaller studies report outcomes of procedural sedation in community settings. A registry study using community hospital emergency room data reported on total of 1028 procedural sedations, with 341 procedures performed in patients younger than 21 years. Most procedures involved fracture reductions, relocations, or laceration repair. Medications used included K (n = 141, 41%), M (n = 10, 32%), etomidate (n = 54, 16%), F (n = 51, 15%), and P (n = 47, 14%).
Complications were reported in 2 cases (0.6%), 1 episode of apnea requiring a reversal agent and 1 episode of hypoxia responsive to supplemental oxygen [58].

A second study reported on 654 consecutive sedations provided in a single year by pediatric critical care and pediatric emergency medicine physicians at a freestanding imaging center in a local community. The site has resuscitation equipment and medications, yet limited staffing and no proximity to hospital support. There were no serious adverse events (based on definitions used by the PRSC), no episodes of cardiac arrest or need for intubation, and no patient required transfer to a hospital. The majority (91.8%) of patients were ASA type I or II. P was used in 98% of cases. Overall, 267 events requiring intervention occurred in 164 patient encounters (25.1%). After adjustment for changes from expected physiological response to the sedative, the rate of events was 10.2%. Seventy-five (11.5%) patients had SpO2 requiring supplemental oxygen, nasopharyngeal tube or oral airway placement (5.2%), continuous positive airway pressure (1.8%) or brief bag valve mask ventilation (4.4%). Eleven (1.7%) had apnea that resolved with continuous positive airway pressure or bag valve mask ventilation. One patient had bradycardia that resolved with nasopharyngeal tube placement and continuous positive airway pressure. Fifteen (2.3%) patients had hypotension requiring adjustment of the sedation drip but no fluid bolus [59].

**Therapeutic Index and Reversal Agents**

Although more technical definitions exist, the therapeutic index of a product can be thought of as the difference between the drug exposure that results in the desired therapeutic effect and the drug exposure that results in unwanted adverse effects. The therapeutic index of P is often considered quite narrow. The literature makes clear that small changes in either the total dose administered or the rate at which P is administered may substantially alter the response to the drug. Typical reported bolus doses of propofol as a single agent range from 2-3 mg/kg, with maintenance of 100-200 µg/kg/min. The popularity of P with both patients and providers appears to relate to the rapid rate at which patients recover from its effects. However, there is no agent that can specifically reverse the effects of excessive P administration.

In contrast, both M and F have reversal agents that may partially or completely reverse the effects of the drug, and the therapeutic index appears wider. The range of indicated doses of both agents is considerably wider than is true of P. For intravenous administration of M for sedation, the initial recommended dose in pediatric patients 6 months to 5 years of age is 0.05 to 0.1 mg/kg. A total dose up to 0.6 mg/kg may be necessary to reach the desired endpoint, but the label further specifies that the required dose usually does not exceed 6 mg. For children 6 to 12 years of age, the initial dose is 0.025 to 0.05 mg/kg, with total dose up to 0.4 mg/kg which usually does not exceed 10 mg. Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. There are anecdotal reports of reversal of adverse hemodynamic responses associated with M as well following administration of flumazenil to children.

In adolescents and adults, 2 µg/kg IV (0.002 mg/kg) is the dose of F labeled for minor, but painful, surgical procedures, and may be sufficient, particularly when used as an adjunct to other agents such as benzodiazepines. The risk of respiratory compromise with this dose is low.
According to the label, adequate facilities for monitoring respiratory status and intervening when necessary are needed when moderate or high doses are used (above 10 μg/kg when used as a single agent), although use of F with benzodiazepines clearly potentiates the risk of respiratory suppression, even at lower doses. However, a reversal agent (naloxone) is available. In addition, naloxone administration can reverse respiratory depression caused by opioid analgesics.

Summary and Questions for the Pediatric Ethics Subcommittee

Pediatric clinical trials often include interventions and/or procedures that offer the enrolled children a prospect of direct medical benefit, and interventions and/or procedures that are performed for the purpose of obtaining generalizable knowledge and do not directly benefit the enrolled child. The assessment of the level of risk of these nontherapeutic procedures must take into consideration the procedural sedation necessary to tolerate and/or complete the procedure. If the procedure itself is nontherapeutic (i.e., does not offer a prospect of direct benefit), the procedural sedation necessary to complete the procedure must be considered nontherapeutic. Under these circumstances, the procedural sedation cannot be approved under 21 CFR 50.52 because it does not offer a prospect of direct benefit. The administration of therapeutic doses of sedative or analgesic drugs is not minimal risk, hence the administration of these drugs cannot be approved under 21 CFR 50.51. Absent review by a federal panel under 21 CFR 50.54 and/or 45 CFR 46.407, the risk of the procedural sedation necessary to complete a nontherapeutic procedure must be considered under 21 CFR 50.53. The purpose of this meeting is to discuss whether and under what conditions procedural sedation can be considered to present no more than a minor increase over minimal risk.

DISCUSSION:

Please discuss the factors which should be taken into account when designing a protocol to provide procedural sedation for nontherapeutic procedures in pediatric clinical investigations. Among the factors that may be considered are: the American Society of Anesthesiology (ASA) risk classification, the therapeutic index of the different drugs commonly used for procedural sedation, the availability of reversal agents for those drugs and/or the speed with which the drug effect dissipates, the nature and seriousness of the adverse events associated with the different drugs, the targeted depth of sedation needed to complete the procedure, the type of airway support that may be necessary, the planned monitoring, and the skill of the practitioner(s) and context of use. In light of these (and any other) factors, please comment on how the risks of procedural sedation may be minimized. In addition, please comment on how these factors may influence your assessment of whether one or more approaches to procedural sedation may be considered a minor increase over minimal risk.

QUESTION:

Assuming the risks have been minimized, are there one or more approaches to procedural sedation that would present no more than a minor increase over minimal risk? (Yes/No)

Following the vote you will have the opportunity to comment individually on the factors you considered in making your assessment.
References


