Table for Consideration of Child Risk in Research

July 28, 2005 SACHRP Chair Letter to HHS Secretary Regarding Recommendations: July 28, 2005 SACHRP Chair Letter to HHS Secretary Regarding Reco

Appendix B: Recommendations regarding risk in research involving children.

Assumptions/ Prerequisites	**Component Analysis**	**404** Minimal Risk	**405** Prospect of direct benefit	**406** Minor increase over minimal risk
"Minimal Risk" (46.102(i) when applied to Subpart D should be interpreted as those risks encountered during daily life by normal, average, ***healthy children living in safe environments*** or during the performance of routine physical or psychological exams or tests.	Multiple cohorts, either by age group, treatments, health status	Well-Child visit as basis for routine medical & psychological, exams or tests.	The IRB ***MUST*** find that: • The risk is justified by the anticipated benefits to the subjects. • The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; ***AND*** • Adequate provisions are made for soliciting the assent of the children & permission of their parents or guardians, as set forth in 46.408	Procedure does not meet minimal risk criteria
Safe environmental in the US should be the standard applied to international studies.	Component of minimal risk should be aged indexed.	Minimal risk should represent the ***upper not lower limits of risk*** to which children can be exposed.	Risk ceiling is proportional to the probability & magnitude of benefits. Acceptable risk should be a ceiling for which no further risk would be acceptable given the probability & magnitude of the benefit.	Investigator has presented sufficient evidence about procedures, population & qualifications of research personnel to assure the IRB the following: *1. Increased probability & magnitude of harm is only slightly more than minimal risk.* *2. Potential harms will be transient & reversible in consideration of the nature of the harm (restricted to time of procedure or short post-experimental period).* • This criteria requires the investigator to provide the IRB sufficient evidenced-base information that enables the IRB to assess risk; and conclude that the probability & magnitude of harm is only ***"slightly more than minimal risk".*** • Information provided could include the qualifications of the individual performing the procedure & data on the experience of similar populations with the procedure. • The investigator should provide sufficient evidenced-based information that supports the judgement that the probability of an adverse event will be reported as severe by the subject is small. • The threshold of "sufficient evidence" should be greater than relying on the opinion of the investigator. • The nature of the setting should also be considered. *3. No or extremely small probability that participants will experience as severe the potential pain, discomfort, stress or harm associated with the procedure.*

	The intention is to make IRBs & investigators think about the merits of each procedure & interventions individually.	Approved as "minimal risk" only if the probability & magnitude of hare are equivalent to or less than the risks of daily life or routine exams with respect to: Duration Cumulative characteristics **AND** Reversibility of harm.	Anticipated benefits must be at least as favorable as available alternative approaches. If expected benefits of the investigational therapy are not as good as the standard therapy then the research should not be approved under 45.405. The evidentiary basis for the risk-benefit decision should be scientifically sound to justify undertaking whatever risk in involved.	Condition interpreted as referring to a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific or clinical evidence has shown to negatively affect children's health & well-being or to increase their risk of developing a health problem in the future. Basically there has to be some grounds or reasonable rationale to expose children to potential harm that is greater than minimal risk. There are times when a cohort of normal healthy children may be considered as having a condition appropriate for research under 46.406.

		Well-Child Procedures: ***These are examples & any one may be greater than minimal risk given the context of the protocol & population.***
		• Physical Exam
		• Measurements of height, weight, head circumference
		• Assessment of obesity with skin fold calipers
		• Collection of blood or voided urine
		• Measurement of heart rate & blood pressure
		• Hearing & vision test
		• Modest changes in diet or schedule
		• Testing of fine & gross motor development
		• Non-invasive physiological monitoring
		• Medical & social history
		• Psychological exam or tests
		• Guidance & education interventions (for child &/or parents)
		• Index routine psychological tests to standardized screening or assessment measurements such as the following:
		  • Child & adolescent intelligence tests
		  • Infant mental & motor scales,
		  • Educational tests, reading & math ability tests, neurological or motor disorder screening,
		  • Social development assessment
		  • Family & peer relationship assessments,
		  • Emotional regulation scales and
		  • Scales to detect feeling of sadness or hopelessness
			Monitoring must be intended, not incidental
			
			Opinions about risks & benefits should be based on evidence NOT on an investigator's hunch.
			
			The evidence could include data from adults & animals.
			
			NOT acceptable to "piggy back" additional procedures of greater than minimal risk in a protocol under the guise of it being a monitoring procedure necessary for the child's care.
				"Vital importance" must have clear & significant scientific evidence that their use is likely to yield generalizable knowledge that would contribute to understanding the etiology, prevention, diagnosis, pathophysiology, amelioration or treatment of a condition or disorder.
				
				Although the children are healthy they have the condition of being a child at risk for the common disease under study.

			Potential benefit of influencing child's management of the disease.	IRBs applying the commensurate criteria should determine that research interventions or procedures are reasonably similar to those procedures & interventions that children with the condition or disorder as a class have or are expected to experience.
			MUST Independently evaluate each research procedure required for benefits & risk to subject.	Commensurate should not be introduced to gage the acceptable level of risk.
			Different procedures in a tiral may be approved or disapproved under different subpart D standards. (Remember Component Analysis)	Level of acceptable risk is determined by the definition of "minor increase over minimal risk."
			IRBs should require strong evidence that study cannot be conducted without each of the non-beneficial procedures.	Commensurate criterion mean that some children **may not be permitted under 406** to experience even a minor increase over minimal risk, either because of their or their parents/guardians' unfamiliarity with the procedure, or the research imposes an unfair burden on the subject.
			The responsibility to demonstrate to the IRB which procedures do or do not have the prospect for direct benefit is the responsibility of the ***INVESTIGATOR.***	
			Phase I pharmacokinetics studies could be included under 46.405 if several conditions are met: • Enrolled subjects had failed alternative treatments a& the intervention offered some potential for benefit, • Providing the risk are proportional to the benefits, • Toxicity & benefits would have to be supported by adults &/or animal studies.	