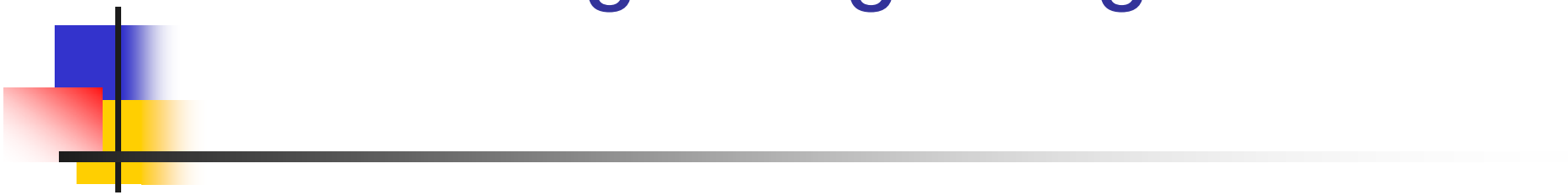
Informed Consents for Clinical Trials Using Integrating Vectors



Discussion Points and Strawman Language

Description of Integration

Retroviral vectors are designed to carry new genetic material into your cells and insert it into your cells' DNA. This process of insertion is known as "integration" and is required for the gene transfer product to produce the intended effect. However, scientists cannot control where integration will occur and cannot predict what portion of your DNA will be affected.

Description - Question

Integration is a characteristic of the biology of many vectors used in gene transfer research. Should model consent language describe the fact and risks of integration in the context of:

- Retroviruses only?
- “High probability integrators” such as retroviruses, lentivirus, and AAV?
- Or all vectors?

Potential Negative Outcomes of Integration

Most integration is not expected to cause harm to the cell or to the patient. It is possible, however, that integration into some parts of your DNA could have a bad effect on neighboring genes. This is known as "insertional mutagenesis" and can cause a change in the way your cells function. For example, if a gene controlling the growth of the cell were disrupted, the cell might multiply uncontrollably, as happens in cancer.

Negative Outcomes - Question

Does this language adequately convey the risks or potential harm of integration?

Evidence of Harm - Part I

A serious adverse event involving cells multiplying out of control occurred in 2002 in a research participant who received a retroviral vector in an experimental human gene transfer study for X-linked Severe Combined Immunodeficiency (SCID). In this instance, the child's white blood cells began multiplying at an abnormally high rate. This problem was found approximately 24 months after receiving the gene transfer intervention.

Evidence of Harm - Part II

A group of experts in this field studied the available data and concluded that the gene transfer [**caused? contributed to?**] this condition, which appears to be [**uncontrolled cell growth? lymphoproliferation? a leukemia-like condition? leukemia? lymphatic cancer?**]. The child has received chemotherapy and his white blood cells decreased significantly in number.

Evidence of Harm - Part III

The participant will continue to undergo extensive testing to determine more about the cause of this serious adverse event. It is not known how he will do in the long term. [**There were 10 other participants in this study, who appear to be doing well. Eight of the subjects showed evidence that their immune systems had been restored.**]

Evidence of Harm - Questions

Should the description of the X-SCID adverse event include:

- Information about other possibly contributing factors, such as the participant's family history of cancer?
- Any mitigating information, such as the apparent benefit to other participants in the X-SCID trial?

Probability of Harm - Part I

Scientists have known from animal studies that the retrovirus's ability to insert genes randomly into DNA could cause serious health problems. Therefore, the vectors used in human studies were designed specifically to minimize this risk. Up until the serious adverse event in the X-SCID study, the occurrence of integration-related health problems in humans was theoretical.

Probability of Harm - Part II

The X-SCID event is the first evidence of this problem in humans. The risk of [**uncontrolled cell growth? lymphoproliferation? a leukemia-like condition? leukemia? lymphatic cancer?**], or another health problem caused by integration, developing in your child is [**low? unknown?**].

Probability of Harm - Part III

[**The event that occurred in the X-SCID trial is the only such event known to have occurred in a human among the [number?] of [X-SCID? Retroviral? All?] trials that have taken place to date**]. It is also possible that a health problem related to integration may occur long after the gene transfer product is administered.

Probability of Harm - Questions

Should the proposed informed consent language address the probability of an adverse health event arising from integration? If so, should this be expressed qualitatively or quantitatively? If some quantitative sense of the risk should be portrayed, what should the denominator for risk calculation be? Or, instead, should the probability of an adverse health outcome from viral integration be described as “unknown”?

Monitoring - Part I

Because the risk and timing of any integration-related health problems is unknown, the researchers conducting this project will ask to monitor your child, even after the active phase of the trial is over. The researchers will want to conduct tests to see if your child develops any symptoms that might suggest a health problem caused by the gene transfer. This monitoring will include: [**specify procedures – protocol specific**].

Monitoring - Part II

Your child will be monitored [**specify frequency – protocol specific**] for [**specify duration, including the post-trial phase – protocol specific**]. While such monitoring is important for scientific and safety reasons, your child's participation is completely voluntary.

Monitoring - Question

Though the details of monitoring are protocol specific, statements about monitoring in *model* consent language may be important to signal to investigators the need to inform participants about this aspect of the trial. What should be said in model language about monitoring?