# Hypothetical Case Description: Clinical Trials of Human Neurostem Cells for Neonatal Hypoxic-Ischemic Injury

The following case description uses published information to construct a generic description of a typical clinical investigation that is not unique or specific to any particular product.

## Background

- Hypoxic-ischemic injury is a common cause of neonatal brain injury in preterm and term infants, leading to significant neurological deficits such as learning disabilities, cerebral palsy or mental retardation.
- Injury to oligodendrocyte precursor cells may contribute to the pathogenesis of hypoxic-ischemic injury by disrupting the maturation of myelin-forming oligodendrocytes.

## Pre-Clinical Experience

- As documented in the literature, human neurostem cells (HNSC) have demonstrated the capacity to engraft, proliferate, migrate and differentiate into different neural phenotypes in vitro and in vivo, using neonatal mouse models.

## Study Hypothesis

- These (and other) observations have led to the hypothesis that inserted HNSCs may reduce or reverse the neurological deficit secondary to neonatal brain injury after a hypoxic-ischemic event.

## Potential Animal Models

- There are several experimental animal models of neonatal hypoxic-ischemic injury that are discussed in the literature.
- Perinatal rodent models have been developed as an experimental platform of hypoxic-ischemic injury for preclinical testing of potential therapeutic interventions. However, they do not reproduce the many distinct physiologic features unique to the premature human infant.
- Other models are thus being developed such as the preterm fetal sheep and non-human primate models (e.g., the preterm baboon and rhesus monkey).

## Exploring Future Pediatric Clinical Trials

- Several investigators are currently exploring the role of HNSCs in reducing or reversing hypoxic-ischemic injury in these different models in anticipation of pediatric clinical trials.
- Of necessity, the HNSCs would need to be surgically inserted while a child was under general anesthesia – rendering the experimental intervention greater than minimal risk regardless of the risks of stem cell insertion. In addition, the child may need immunosuppressive medication to assure engraftment.

# Question One

- Please discuss the ethical issues in selecting an appropriate subject population for the initial clinical development plan of these HNSC products.
- Issues you may want to consider include:
  a) differences in the natural history of the disease between adults and pediatric subjects which may influence the timing of HNSC insertion;
  b) whether dosing, safety and/or efficacy should first be established in suitable adult subjects prior to enrolling children; and
  c) differences between pediatric and adult subjects with hypoxic-ischemic brain injury (e.g., possibility of direct benefit, usefulness of safety information, assessment of physiologic response, long-term effects).


# Question Two

- Please discuss the ethical issues in designing a “first-in-children” clinical trial of these HNSC products.
- Issues you may want to consider include:
  a) the need to establish a sufficient prospect of direct benefit to justify the risk of the experimental intervention;
  b) the range of animal models available for pre-clinical studies;
  c) the different types of physiologic changes in response to the experimental product (e.g., structural, functional, disease reversal);
  d) the severity of the disease; and
  e) the availability of alternative treatments.