

Ethical considerations in clinical investigation

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As hemophilia-related research moves forward, the investigative methods we will need for evidence-based clinical practice and therapeutic advance will present some important ethical dilemmas, said Dr. Donna DiMichele.

Looking ahead, she identified three areas that merit consideration: (1) the therapeutic misconception in all clinical research and the randomized clinical trial in particular; (2) high-risk and potentially non-beneficial research in children; and (3) research in the developing world.

The “therapeutic misconception” and the randomized trial

As prospective randomized trials (such as the Joint Outcome Study, the International ITI Study, and the FEIBA NovoSeven Comparative [FENOC] Study) have started to contribute to the evidence base and inform the current standard of care, they’ve also raised a familiar question: “Is the randomized clinical trial (RCT) ethical?”

Historically, clinical research was categorized as either *therapeutic* (where the intention is to “treat” the patient-subject with the expectation of medical benefit) or *non-therapeutic* (where the purpose is to acquire scientific knowledge for future use), and each type of trial was governed by different ethical standards, DiMichele explained. In the RCT – “the ‘paradigm’ of therapeutic research” – the ethical requirement was the achievement of *collective equipoise*, i.e. that there is genuine uncertainty about the superiority of any one treatment (or no treatment, in the case of a placebo-controlled trial) under investigation.

In the 1980s, a new concept called *therapeutic misconception* was raised. This principle stated that medical research and clinical care are inherently different, and that the ethical principles that guide each must be distinguished. “While clinical care is guided by patient-centred standards of ‘do no harm’, clinical research carries with it the inherent possibility of exploiting the individual participant for future good,” DiMichele said. An alternate classification was proposed in which *beneficial* research is distinguished from *non-beneficial research*, based on the expectation of personal medical benefit from participation in the trial. “In the design of clinical trials, minimizing risk therefore becomes extremely important,” DiMichele noted.

To this end, the US National Institutes of Health has established seven ethical requirements for all clinical research:

1. Social / scientific value
2. Scientific validity
3. Fair subject selection
4. Favorable risk benefit ratio
5. Independent review
6. Informed consent
7. Respect for potential/enrolled subjects

As we move forward in hemophilia research, recognizing the difference between clinical care and research and adopting an appropriate set of guiding principles for each will become very important, particularly in the design of trials involving children and those conducted in the developing world.

High-risk pediatric research

The future of hemophilia therapy lies in novel technologies such as “modified” factor concentrates and gene transfer. Finding a cure for hemophilia remains the ultimate goal, and gene transfer seems the most likely way to achieve it.

The timing of gene transfer is critically important to its success. Targeting infants and young children seems to be the best way to maximize the benefit relative to risk, which means that they would be required to participate in the clinical trials needed to evaluate this new technology. “High-risk research in children is a moral and ethical challenge, but we should look at it as a stimulus for dialogue,” DiMichele said.

Informed assent and fair subject selection are two aspects of trial design that need special attention in pediatric research, she noted. “Getting a child’s informed assent would depend on his/her chronological age, maturity and capacity for altruism, and should include ongoing discussions of the potential risks and benefits of participation in the trial in a way the child can understand,” she said. “The child must also be aware that it’s possible to opt out of the trial at any time.”

Although vulnerable subjects should not be specifically targeted for research, they shouldn’t be specifically excluded, either. Some argue that research in children is essential to avoid creating so-called “therapeutic orphans” (if you only conduct studies in adults, you can’t guarantee the same results in children). If we are to include children, every effort must be made to minimize their vulnerability, which includes minimizing potential risk and maximizing benefit through rigorous trial design.

Current gene transfer technology carries both short and long-term risks, so investigating other, safer methods of gene transfer is an important first step, DiMichele said. Others include gathering as much toxicology data as possible, minimizing invasive procedures, and incorporating a minimum 15-year follow-up study to assess long-term risk.

“Risk must be judged against quantity and quality of life as well as against the existing standard of care,” DiMichele said. The problem with hemophilia is that in the developed world, the standard of care is excellent: symptoms are controlled, therapy is safe and there’s a normal life expectancy. The increased morbidity and diminished quantity and/or quality of life (particularly for children in the developing world and those with persistent inhibitors) may be what lend moral justification to pediatric gene transfer trials, she said.

Research in the developing world

In 1990, the UN Commission on Health Research reported that 90% of the world research dollars went towards diseases that affect 10% of global population, all of whom live in the wealthiest countries. Philanthropic government-sponsored/private

partnerships are now working towards reversing this trend, which means investigators must conduct trials in the countries in which these diseases are prominent, DiMichele said. She identified four main ethical challenges to conducting research in the developing world:

1. The potential for exploitation of participants / human rights violations
2. Obtaining informed consent in a way that's acceptable in the host country
3. The obligation of researchers to provide the standard of care
4. The extent to which the research sponsor is responsible for making sure the host country benefits in some way from their participation.

Although the NIH principles previously listed (see page 1) would theoretically protect research participants in the developing world from being exploited, the regulatory bodies and oversight needed to enforce them isn't always available. For this reason, an eighth requirement has been added to ensure a collaborative partnership between the research sponsors and the host country. This principle allows the host country to determine the acceptability of the proposed research in relation to the community's healthcare needs, DiMichele said, adding that this is an important consideration in assessing the distinct priorities for hemophilia-related research in the developing world.

To ensure voluntary consent within this partnership, the local community must be involved in deciding how subjects will be recruited. The disclosure information and the consent process must be delivered to participants in a socially relevant way, DiMichele said. Getting the community and family's consent to have an individual participate in the research has also been proposed as a safeguard. Finally, the participant must be informed of their right to refuse to join or to withdraw from the study at any time.

Ethical research must also ensure that all participants receive the standard of care, which can be an important challenge, DiMichele noted. "In designing a trial, the 'worldwide best' is what you need. On the other hand, the worldwide best can be overridden and informed by issues of scientific and social relevance to the study outcome, as well as the cost of providing the 'best'," she said, so that control arms can be more in line with the local reality.

In terms of the sponsor's obligation to the host community, the responsibility is to ensure a favourable risk:benefit ratio for study participants. In certain instances, the potential for greater benefit may justify greater risk, but on the other hand, the greater risk inherent to the research may require greater compensatory benefit. This, DiMichele noted, is especially relevant if we are to conduct research on new hemophilia therapies in the developing world.

"Even though research translates imperfectly into clinical care, the host country must gain some enduring benefit from their participation," DiMichele said. In an ideal world, that benefit would be predetermined in the collaborative sponsorship and could include an improved delivery of health services, training of health personnel and, at the very least, sharing the study outcomes in a culturally and linguistically sensitive way.

The promise of improved evidence-based clinical practice is certain, DiMichele concluded. "The challenge will be to ensure an ethical means to that end with the inclusion of all stakeholders in mapping the way forward."