

Ethical Conduction of an International, Pediatric Trial

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Category: Drug Trials

Case Summary:

A basic scientist temporarily discontinued the development of a measles treatment after the approval of a highly effective measles vaccine. However, due to the anti-vaccine movement as well as logistical barriers in underserved countries, it has become clear that the vaccine will not achieve global eradication. Therefore, given the current measles epidemic, the scientist has decided to resume efforts towards the development of the investigational treatment and submit a grant. His plan is to first conduct a phase 1 clinical trial in healthy adults and then to proceed to a phase 1 trial in children with measles. Since one of the few places that children regularly get measles is in developing countries such as India, he would like to conduct the pediatric trial in India. He is proposing a trial that raises three ethical concerns: (1) measles, though it can have long term adverse events such as reduced hearing, is not usually fatal so the risk/ benefit analysis is not easy; (2) he wants to do a trial in sick individuals in the pediatric setting; (3) he wants to do the trial in India. The requestor asked for this research consult to help with writing a grant to fund the clinical trial.

Background:

In 2018, globally, there were 9,759,400 cases of measles, with nearly 140,000 deaths¹. These statistics demonstrate that there is a current measles epidemic that needs to be addressed. Even in the United States, a first-world country in which the measles was declared eradicated in 2000, cases have been on the rise due to travel and transmission to unvaccinated individuals². The United States reported 1,282 cases in 2019—the highest since 1992³. However, the majority of cases are found in poorer countries who have limited access to the Measles, Mumps, and Rubella vaccines, with the most recent CDC report showing India leading the world with the highest number of cases during a one-month period⁴. Limited access to the vaccine in third-world countries contributes to these high statistics⁵ and highlights that despite the fact that a vaccine exists for measles, the current rise in cases demands a treatment that can help mitigate the effects of this deadly and debilitating disease.

Expert Opinion:

What is the benefit/risk analysis for a measles treatment?

While measles only causes death in 1-3 cases per 1000 individuals⁶, the potential adverse events that can occur in both the short-term and long-term indicate that a potential measles treatment may likely provide significant benefit. Contracting measles can cause pneumonia and encephalitis, permanent brain damage, secondary infections, blindness or hearing loss^{1,2,6,7}. Studies have also revealed that there are long-term risks associated with contracting the measles. Subacute sclerosing panencephalitis (SSPE), a rare but fatal disease of the central nervous system and fatal neurological complications^{2,8}, are but two of those risks. Additionally, the CDC noted that 20% of cases in the United States resulted in hospitalization, especially among children under the age of 5 and adults over the age of 20⁶. Therefore, although measles is not usually fatal, an effective treatment could limit the adverse events caused by contracting measles, leading to immense benefits for the survivor.

Ethics of Pediatric Trials

In light of the fact that measles is most commonly contracted in childhood, a pediatric trial appears to be appropriate, but raises ethical concerns as children are a vulnerable population and do not have the capacity to consent. The FDA's categories of acceptable research in pediatrics requires the study to "present risks that are justified by anticipated direct benefits to the child (21 CFR 50.52;45 CFR 46.405)." Therefore, the researcher must have adequate data on both the benefits and risks of the investigational treatment. To get this data, we recommend that the research team first conduct a trial with healthy adult individuals and then if possible, the research team should try to conduct a small trial in adults with measles. However, since measles is predominantly a pediatric disease, if it is not possible to conduct a trial with infected adults, it is imperative that an animal model be used to establish the prospect of direct benefit as well as to assess any possible risk, in addition to the data from healthy adults. If the investigational treatment shows to be effective in the animal models and safe within both the human adult and animal trial, then the investigational treatment may offer direct benefit to child participants, satisfying the FDA's qualifications for pediatric trials. Once meeting this criterion, we suggest that the research team do an age escalation, if possible, starting with older adolescents before including younger children, as older adolescents are more capable than younger children of providing meaningful assent.

Ethics of International trials

Conducting a clinical trial in a developing country is only ethical if six principles are respected. These principles include: collaborative partnership, social value, scientific validity, fair selection of subjects, favorable risk/benefit ratio, independent review and informed consent⁹. Many of these principles will be met by the trial design and implementation as planned, but three of them need further consideration: collaborative partnership, social value and fair selection of subjects. First, we recommend that the research team partner with a community in India that is directly impacted by the current measles epidemic. We suggest the research team collaborate with community leaders in order to determine the community need and interest for this investigational measles treatment. If there is a community need and the researchers choose to open the trial, the team must ensure they respect the community partner's culture and social values, soliciting advice from the community leaders' on how best to conduct the study in their community and how to fairly select subjects. If the investigational treatment is proven to be effective, the research team must ensure that they have the resources needed to make this treatment available to this community after the research project is completed. Through proper community engagement, this proposed trial can respect all the principles for ethical conduct of international trials.

Summary:

While there is an ever-growing need for an effective measles treatment, this proposed trial raises significant ethical concerns. In order to ensure the trial is ethically sound, it is imperative that the researchers gather enough animal and healthy adult data to ensure that there is a good risk/benefit ratio for a pediatric trial and that they collaborate closely with the Indian partner community where they will conduct the research.

References:

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