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Testing vaccines in pediatric research subjects

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Abstract

Past difficulties encountered in pediatric vaccine research have positively influenced the development of modern regulations of human subjects' research. These regulations permit pediatric research but impose special restrictions on the types of studies to which children may participate, and these restrictions have important implications for modern vaccine trials. These ethical issues pose real but surmountable concerns. Considerations also include the use of placebos, critical for trial design but an impediment to parental permission. Recent pediatric vaccine studies illustrate practical alternatives to placebos that preserve allocation concealment and blinding yet obtain parental support. Vaccine researchers must consider the role parents play, not just in giving formal permission for their children's participation, but also for their roles in active recruitment, successful retention, and data acquisition. Studies of parents' attitudes do identify consistencies among motivating forces that drive parents to participate or refuse their children's participation. These studies should influence how we design and execute pediatric vaccine trials. Finally, ethical considerations and current regulations raise certain issues concerning the remuneration of the research volunteer when that volunteer is a child. The published literature illustrates wide variation in practice. Better understanding of the restrictions in pediatric research, the use of placebos, the attitude of parents, and the concerns with remuneration can better equip the vaccine researcher in pursuing successful studies in children.

Keywords

Vaccines; Human experimentation; Child

1. Introduction

Past difficulties encountered in pediatric vaccine research have positively influenced the development of modern regulations of human subjects' research. As a result, modern regulations permit vaccine research in healthy pediatric volunteers while protecting them as vulnerable research subjects limited in their ability to understand and consent to participation.

The history of modern research regulation dates back to at least the 1930s and the Lübeck vaccine disaster [1]. Back then, in Europe, tuberculosis remained rampant. The Bacillus Calmette-Guérin (BCG) vaccine had become available a decade before, as early as 1921, but its use was still not widely accepted. In 1930, in the northern Germany town of Lübeck, two

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physicians mounted a campaign to vaccinate newborn babies against tuberculosis. They used a vaccine produced locally from a Parisian strain. In the first 2 months, the campaign resulted in 250 infant-vaccinations. The first complications only appeared in the third month of the campaign. Soon after receiving the vaccine, infants were becoming seriously ill and many died. In 12 months, of all the infants vaccinated, 208 became ill with tuberculosis and 77 died. The two physicians were arrested and put on trial. The court eventually found the two physicians guilty of murder. The newspapers publicized the trial throughout Europe, and the news of the disastrous vaccine campaign spread throughout the continent.

This tragedy actually led to the first published discussion on medical research using human subjects, approximately two decades before the Nuremberg Trial and the Code of Nuremberg [1]. Julius Moses, a Member of German Parliament, called for a public accounting of medical science. He charged that the vaccine campaign was in fact not a clinical practice proven safe and effective but rather an experimental trial. Furthermore, he decried the conduct of the campaign as research in humans without their knowledge or permission. Taking a contrary view, Ludwik Fleck, both a medical doctor and philosopher, published a response, arguing both for the need for medical research in humans as well as the need for an improved public understanding for what that research was and why it was needed. Fortunately, Fleck's arguments were successful, facilitating continued efforts in pediatric research.

In 1954, the Francis Field Trials of the Salk polio vaccine successfully enrolled more than 1.8 million young children in the United States [2]. This was a remarkable effort aimed at assessing the effectiveness of an inactivated polio vaccine as a public health measure. It remains the largest medical experiment ever conducted in terms of the numbers of research subjects enrolled. The study's purpose was to assess the effectiveness of vaccines against paralysis or death from polio. Designed as a randomized, double-blind, placebo-controlled trial, approximately 440,000 received the experimental, inactivated polio vaccine, and approximately 220,000 received placebo. The study investigators enrolled an additional 1.2 million children to receive neither the vaccine nor the placebo. The study clearly demonstrated the effectiveness of the vaccine. The trial's findings were announced on April 12, 1955, the anniversary of the death of a famous U.S. polio victim, the late President Franklin Delano Roosevelt. Mass campaigns for polio vaccination ensued. Millions underwent vaccination, leading to a massive reduction by more than 99% in the number of polio cases as a result.

In the United States, federal regulations (45 CFR 46) restrict research in children primarily to three possible circumstances [3]. The first is where the research does not expose the child to more than minimal risk. The second is research that is greater than minimal risk but presents the prospect of direct benefit to the individual subjects. The third is research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. The legacy of the Francis Field Trial and its study of healthy children for the public good is preserved as a fourth circumstance, rarely pursued but still available, which permits the consideration of medical research studies in children that fail to fulfill one of the first three circumstances but are necessary or important for public health [4].

2. Regulations and children

In the United States, regulation of pediatric research as formulated in 45 CFR 46, parents actually have less than a straightforward power-of-attorney in making choices regarding their children's participation in human subject research [3]. The regulations actually limit what studies the parents may actually enter their children. The parents are not simply acting in place for their children but instead have a limited role. Instead, as stipulated by the 45 CFR 46, the Institutional Review Board (IRB) acts *in loco parentis* with children by prohibiting children's

participation in studies it would permit for adults. In all of these, 45 CFR 46 not only calls for parental permission but also the assent of the child when appropriate.

Similar to the 45 CFR 46, the Declaration of Helsinki, approved by the World Medical Assembly, provides a basis for regulating human subjects research [5]. Many countries, not including the United States, did adopt this Declaration for its own medical research regulation. Unlike 45 CFR 46, the Declaration of Helsinki does not specify specific levels for pediatric research. Instead, it calls for special attention to vulnerable subjects and includes among those it identifies as vulnerable those individuals who cannot give informed consent. Similar to the IRBs specified by 45 CFR 46, the Declaration calls for the formation of Independent Ethical Review Committees (IECs) to provide oversight and to restrict research with vulnerable subjects. The restrictions on research for these vulnerable subjects hold that the research must offer generalizable knowledge that outweighs the risk. The Declaration also requires that the IECs give special consideration when there is no direct benefit or when the research is combined with medical care. Similar to the 45 CFR 46, the Declaration of Helsinki also calls for the assent of the incompetent individual when appropriate.

Unlike the Declaration of Helsinki, the third major body of regulation, the statement of Good Clinical Practice (GCP) as developed by the International Committee of Harmonization (ICH), specifically identifies minors as an example of vulnerable subjects who are incapable of consent [6]. The ICH GCP calls for IRBs and IECs to safeguard the rights of human subjects with special attention to vulnerable subjects with specific restrictions on non-therapeutic trials. The ICH GCP also calls for the use of a legally acceptable representative in provide permission for a vulnerable subject's participation. Finally, similar to 45 CFR 46 and the Declaration of Helsinki, the ICH GCP also states that to the extent possible such a vulnerable subject should be informed and when capable sign and date the consent form (in addition to the legal representative).

3. Placebos and children

While most recognize the need for research to advance medical care for children, those not closely familiar with the field might pause or even involuntarily recoil at the notion of randomizing children as research subjects to receive placebos. This is even more of an issue than in vaccine trials, where one usually injects vaccines rather than give them orally.

While 45 CFR 46 never mentions placebos specifically [3], the U.S. Food and Drug Administration has however provided specific guidance regarding placebos [7]. The FDA encourages the use of placebos and provides a conceptual basis for the practice. The FDA however does not specifically address placebos in children or other vulnerable subjects.

Unlike the FDA, the Declaration of Helsinki implicitly discourages placebos by articulating exceptions when placebos may be used in research rather than a general endorsement [5]. It specifically addresses the need for the investigator to take extreme care when using placebos and to limit the use of placebos to situations where there is an absence of existing proven therapies. The ICH GCP also specifically addresses the use of placebos but neither encourages nor discourages their use [6].

None of these regulations excludes placebos and their use for children. In fact, the American Academy of Pediatrics (AAP) in its "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations" specifically states, "In general, placebos should be used when data cannot be obtained by comparing the efficacy and safety of the drug under study with either a commonly used therapeutic agent for that condition or the natural course of the disease as described from clinical studies." [8] The AAP guidelines list five situations when placebos in pediatric research are ethically acceptable. These include (1) when no intervention is

currently accepted, (2) when the current intervention lacks proven benefit, (3) when the current intervention is unsafe, (4) when the addition of the proposed therapy to a standard therapy might prove unsafe, and (5) when the course of the condition under treatment varies widely in severity in a given individual.

For intramuscular and subcutaneous vaccinations, injections of sterile normal saline may serve as placebos, but researchers frequently choose other comparative agents. A review of the most recently published trials involving vaccines for children found a variety of comparators that took the place of placebos in children. For example, a recent study of pneumococcal conjugate vaccine with nine serotypes (PCV-9) used as its comparator an active vaccine [9]. Specifically, the PCV-9 was reconstituted with the DTP-Hib vaccine. The comparator was vaccine-diluent mixed with the same DTP-Hib vaccine. In another study, a novel, bivalent, heat-killed, whole-cell oral cholera vaccine is compared to a similarly manufactured, heat-killed *Escherichia coli* K12 vaccine-a vaccine of no therapeutic benefit [10]. In a third, recent study of a pneumococcal conjugate vaccine with seven stereotypes paired serially with a 23-valent, pneumococcal polysaccharide vaccine, the investigators used as the comparator hepatitis A or B vaccines [11]. In a fourth study, the study vaccine consisted of a *Pseudomonas aeruginosa* flagellar protein combined with aluminum hydroxide and thimerosal [12]. The comparator consisted of just aluminum hydroxide combined with thimerosal.

4. Parents and pediatric research

Much less controversial, at least for institutions and regulatory bodies, perhaps, is the concept of randomized controlled trials with pediatric research subjects. History has certainly validated their use; regulation certainly permits them. But what do parents think? Harth and Thong studied 110 parents who participated in a British study of children with asthma [13]. The study randomized children to receive drug or placebo. The investigators interviewed both the mothers and father who permitted their children's participation and the mothers and fathers who refused. The mothers were as educated in both groups but the fathers were less educated among those permitting the study. The mothers permitting the study were less likely to work outside the home as compared to those who refused. The fathers were less likely to work in a profession as compared to those who refused. Finally, the parents and children were more likely to use National Health Services.

The investigators found among those parents who gave permission for the children to participate a number of commonly held reasons for their decision [13]. All 68 surveyed endorsed the concept that they did this to contribute to medical research. All but one cited that they did this to benefit others. Ninety percent specifically stated that this was to benefit their own child, while 82% expressed dissatisfaction with the current treatments available to their child. Seventy-five percent gave permission to learn more about medical treatment, and 72% endorsed as a reason for volunteering that they like the people conducting the trial. Along the same lines, 66% endorsed as a reason for participating their desire to meet other people.

Harth and Thong also examined the reasons for those 42 parents refusing participation in the study [13]. The reasons endorsed by 50% or more of the refusers included fear of the side effects of a new drug (95%), the inconvenience of frequent visits (83%), the dislike of becoming involved (79%), the lack of time (55%), and the distrust of modern medicine (52%).

In a survey of 505 parents, Tait et al. published a study where they had recruited parents who were previously approached to participate in a randomized control trial [14]. Among the 505 parents, 411 volunteered their children in the study and 94 refused. The investigators found permitting parents were more certain about their decisions and believed their environment was more conducive to giving their permission (in terms of time available for consideration, lack of pressure to decide, and privacy to make the decision). Finally, those parents giving their

permission expressed a sense of having better relations with the researcher. The investigators asked specifically among the consenters what would have changed their minds to reject the study. Eighty-three percent endorsed that they would have refused the study if there were an increased risk, while 72% stated they would have refused if the study turned out to be more difficult to understand. Sixty-five percent stated they would have refused if they felt pressure to consent, and 49% would have refused if they felt uncomfortable with the researcher, as would the same percent if there was a placebo. Finally, 40% would have refused if there less time to decide.

Morris et al. conducted both quantitative and qualitative studies in 136 family caregivers in a major urban tertiary care teaching hospital [15]. The investigators asked how the family caregivers regarded medical research in general. Forty-nine percent answered positively, 6% answered negatively, and 45% were neutral. The investigators also asked if it were good for a patient to be involved in medical research. Sixty-one percent answered yes, and 5% answered no. The investigators also found that race, gender, past experience with research, and education did not matter. In their qualitative analysis, they found fears held in common that novel treatments might not work and that novel treatments may have unanticipated adverse affects. The parents also expressed concern for medications that were developed for adults as they may hurt children.

5. Remuneration and children

Few studies have examined the role of remuneration in research, much less remuneration in *pediatric* research. Furthermore, published trials of vaccine research rarely, if ever, mention remuneration, much less specify the amounts given.

The Food and Drug Administration recognizes that the practice of payment for research participation is common but holds that these payments should not be considered benefits of participation [16]. Instead, the FDA holds that these should be recognized instead as recruitment incentives. The FDA stipulates that the IRB should review payment amounts and remuneration plans to avoid undo influence. The FDA also holds the consent form used should specify the payment scheme and that investigator should prorate the amount for length of participation.

Neither 45 CFR 46 [3] nor the FDA's 21 CFR 50 [17] specifically mention payment to subjects other than that "no inducement, monetary or otherwise, may be offered to terminate a pregnancy." The Declaration of Helsinki also makes no specific mention of monetary compensation [5]. Both 45 CFR 46 and the Declaration, however, state that informed consent should occur "without coercion or undo influence." The ICH GCP does address remuneration, however, and states that the IRB (or IEC) should review the plans for payment including the amounts, method, and timing and make sure that the payments do not create issues, again, with "coercion or undue influence." [6] Furthermore the payments should be prorated for the duration of participation and that the consent form describe the details of the payment plan including the proration.

The American Academy of Pediatrics in 1995 published guidelines for including children in research studies regarding pharmaceuticals [8]. The guidelines actually are much stronger than the regulatory language in the previously reviewed documents. The AAP holds that the IRB should evaluate and make a decision regarding monetary compensation. Furthermore, the IRB should do this taking concern for undue influence and coercion. The AAP further holds that payment to an adult for a minor's participation is ethically problematic and the amount should represent just a token gesture of gratitude. Also, the AAP holds that the payment to the child should not be discussed before completion of the study as that would influence the child's

participation in the study. The AAP does, however, suggest that the investigator should consider waiving the medical costs involved in the care of the child.

The AAP also specifies that the compensation for expenses include both the direct and the indirect expenses and that the investigator should make arrangements that are fair but do not serve as an inducement of coercion [8]. The AAP recommends that the IRBs review the plan for compensation. In addition, the AAP addresses indemnification. The AAP holds that investigators at the institution must be able to provide emergency care and state whether investigators will cover the expense or other expenses related to the care of injury or illness to the participation [8]. Furthermore, the consent form should convey this information.

Kimberly et al. did a quasi-experimental retrospective evaluation surveying 69 studies across 59 IRBs [18]. The IRBs considered three standardized multi-centers studies. The investigators reviewed the decisions the IRBs made in approving compensation. Forty-eight approved compensation; 11% did not. Thirty-three percent approved compensation for travel, food, or parking, and 22% approved compensation for subject inconvenience while 13% approved compensation for subject time. The dollar-values of the compensation ranged eightfold. The smallest amount approved was $80 for study completion. The largest approved for the same study was $1425. The IRBs varied in whether the recipient was the parent or the child and whether the form of compensation was in-kind, cash, check, or otherwise.

6. Concluding remarks

Historically, both the scientific community and the public have supported research with pediatric subjects and in particular vaccine research. This is despite the ethical issues raised by randomizing healthy children in double-blinded studies and possibly to a placebo-comparison study arm. Parents do support and accept the role of children in medical research and do permit their children to enroll. Studies demonstrate consistent trends for both those parents who choose to permit their children to participate as well as for those parents who decline. While not identified by parents in studies of the motivations for their permission, remuneration for participation poses a potential concern for undo coercion. While we have guidance for using remuneration, authorities' recommendations vary widely as do actual practices.

In summary, individual investigators must understand the special restrictions placed on research in children and design studies accordingly. While regulations permit placebos in children, investigators often creatively seek alternative comparators to improve recruitment and retention. Reviewing the data regarding parental reasons for giving or refusing permission for their children to participate will help individual investigators design more successful recruiting efforts as well as more successful studies. Understanding the conflicting guidance regarding remuneration as well as considering the wide variation in practice should temper investigators' use of remuneration as a recruitment incentive and instead encourage design elements that would otherwise foster recruitment and retention.

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