The Standard of Ethical Research Involving Vulnerable Populations: Implications of Korea’s 1997 Japanese Encephalitis Vaccine Trial Incident

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Abstract

This paper examines the 1997 Japanese Encephalitis (JE) Vaccine clinical trials that were conducted in Korea, on a vulnerable population of participants. Reviewing the reactions that emerged shows that critics of the clinical trial focused on the characteristic vulnerability of the participants as the reason the trials were morally problematic. However, the authors of this paper propose that it was actually the presence of undue influence in the consent process, through improper compensation, and lack of additional safeguards for participant rights and welfare, which made the JE Vaccine Trials morally problematic. If these issues are addressed in future research, the authors believe it is possible to conduct ethical research involving vulnerable populations, while still being sensitive to the risk of exploitation.

Keywords: Japanese Encephalitis Vaccine Clinical Trial, Vulnerable Populations, Pediatric Trials, Undue Influence, Exploitation

I. Introduction

Clinical trials are unavoidable in the process of affirming the safety and efficacy of essential vaccines and medications. Yet, they have not always been performed in ways which are consistent with our generally held ethical principles. Following public outrage in the aftermath of several incidents in the medical and scientific communities, several nations such as the United States and South Korea as well as international professional societies like

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the WMA developed ethical guidelines or enacted laws to protect the rights and dignity of the human subjects of clinical trials. Cornerstone documents in the field of Bioethics, such as the Nuremberg Code (1947) and Declaration of Helsinki (1964) are ethics guidelines also developed in response to the definitively unethical and inhumane medical experiments and research scandals.\textsuperscript{1,2} The objective of both documents is to lay out the ethical principles and derivative practices recommended to ensure ethical behavior during the course of designing and conducting research involving human participants. The timeline of events of the widely publicized Tuskegee Syphilis Study provides a clearer example of the tacit link between widespread societal criticism of unethical research practices, the enactment of regulatory laws (The U.S. Department of Health and Human Services Regulations, 1974),\textsuperscript{3} and the publication of a guideline for ethical research involving human participants (The Belmont Report, 1979).\textsuperscript{4} The prominence of these principles and guidelines proposed to promote their normative influence will be further described in the body of this paper (section 3).

In Korea, regulation of human participant research and recommendations grounded in ethical principles are apparent in the Bioethics and Safety Act (2008) and the additional regulation in the form of a Presidential Decree.\textsuperscript{5} The initial piece of legislation took a mainly permissive stance towards regulation of embryonic stem cell research and somatic cell nuclear transfer stem cell research. After it became known that Professor Hwang Woo Suk, who consulted in the process of writing the Bioethics and Safety Act, fraudulently claimed in 2004 and 2005 to have successfully created human embryonic stem cells through somatic cell nuclear transfer, using egg cells donated for scientific use, the law was revised through a Presidential Decree. The revised legislation more stringently regulated somatic cell nuclear transfer stem cell research by specifying limits on the type of egg cells that could

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  \item \textsuperscript{1}Nuremberg Code (n.p., 1947), https://history.nih.gov/research/downloads/nuremberg.pdf.
  \item \textsuperscript{2}World Medical Association, Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (Helsinki, Finland, 1964).
  \item \textsuperscript{3}US Department of Health and Human Services Regulations, 45 C.F.R. § 46 (1974).
\end{itemize}
be used in research. Among the numerous critiques of this research study, the means by which researchers obtained egg cell ‘donations’ raised serious ethical concerns regarding the potential for exploitation and the use of coercive tactics to solicit ova donations from women whose family members suffered from incurable diseases. Here as well, legislation was developed and enacted as a corrective, after the fact, to prevent future misconduct. According to the Presidential Decree, which went into effect in 2008, the embryos used in research could only be ‘leftover’ unused ova extracted or created for the purpose of reproduction through assisted reproduction technology. The articles of the Presidential Decree restricting the conditions under which somatic cell nuclear transfer stem cell research can be conducted aim to limit the potential for exploitation of ova donors, strictly limiting the source of ova to authorized clinical institutions that extract ova.

The research scandals and corresponding regulatory actions references above illustrate how the ethical guidelines or relevant legal regulations evolved as a societal response to the incidents. The body of guidelines that regulate research involving human participants has continued to undergo reform. This reformulation may be a process to meet the demands of emerging technology and growing public awareness. Such a process is controlled by general consensus on what constitutes morally and legally acceptable research practices. Our changing conceptions of ethical conduct in biomedical and behavior research are best encapsulated in the numerous revisions of the Declaration of Helsinki, which are extensive enough to address modern concerns regarding research involving human participants, including data collection and preservation as well as collection and storage of samples of human materials. The Declaration of Helsinki has evolved to meet the demand of appropriate responses to new ethical issues. It is evident that events throughout biomedical and behavioral research history have resulted in this extensive body of ethical norms and related legislation that regulate human participant research. The same is true in the case of research studies involving children and other vulnerable populations (eg. ethnic minorities, prisoners). However, in spite of the Declaration of Helsinki and similar guidelines such as the CIOMS International Ethical Guidelines for Health-related Research Involving Humans (CIOMS Guideline), issues regarding the exploitation of participants and violation of rights persist, particularly in cases where potential participants are socioeconomically disadvantaged or
vulnerable in another significant way, such as being illiterate or having a disability. The appropriate application of core ethical principles and existing participant selection guidelines remains unclear in these situations, despite necessitating additional regulatory action.

The issue of exploiting vulnerable populations as research participants and how core principles should be applied to best protect those participants is at the center of the incident to be discussed in this paper, the Japanese Encephalitis Vaccine Scandal of 1998. This event continues the previously noted pattern of a controversial and often deeply morally offensive incident leading to inspection and revision of the legal ‘loopholes’ or absence of regulation that enabled a violation of ethical principles and participant rights. While public outrage surrounding publicized details of the JE Vaccine Study and the legislative action taken to prevent future research ethics violations preceded the passing of Korea’s Bioethics and Safety Act, the concerns that were raised in its aftermath are nonetheless relevant to a discussion of research involving vulnerable populations. In the case at hand, clinical trials for a live-attenuated vaccine were conducted on one to three year old children living in three different orphanages. After reports of this research study were made public, social outrage led to the perception that all research involving vulnerable populations was morally problematic, especially those conducted with children living in institutional environments. While this wariness of exploiting vulnerable individuals appears to be grounded in well-intentioned beliefs, it raises questions about the justification for refraining from such research, and whether this is a proper interpretation of the ideals contained in previously established guidelines and principles that govern research on human participants.

At the time of the incident, Article 26 of The Pharmaceutical Affairs Act stated only that experimental drugs that had been approved for a conditional permit for distribution must conduct clinical trials on the safety and efficacy of the drug, and that those trials must be conducted in accordance with the Ministry of Health and Welfare Regulations. This is less

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specific and restrictive than the current Pharmaceutical Affairs Act (enacted Dec. 23, 2017), which delineates the standards and requirements of the permit approval process and clinical trial process, through prime minister’s decree. So, at the time of the Vaccine Scandal, it is possible that the selection of orphanage children as trial participants was not a violation of established regulations. In the years that followed, however, there was a clear shift towards the categorical exclusion of this group as ethically viable participants, due to associations with this very incident and other concerns of unacceptable risk of exploitation. In her critique of the Vaccine Trial Scandal, Jang argues that the incident necessitated a revision of child welfare laws, in the form of completely prohibiting participation of institutionalized children in research studies. Yet, the authors propose that this action goes beyond what was necessary, in order to address how the vulnerability of the institutionalized children presented a risk of exploitation. Rather than viewing participants’ vulnerability as a reason in and of itself to prohibit inclusions in research studies, the authors examine what additional considerations researchers or IRB members must take into account due to the presence of vulnerability.

This paper examines the reactions that emerged in the aftermath of the Vaccine Scandal, separating the ‘instinctual’ emotional response from a more systematic analysis of the unethical aspects of this research study based on the core principles associated with research on vulnerable populations. For this purpose, the paper will analyze whether such prohibitions of research on vulnerable populations are truly demanded by adherence to existing international ethical guidelines such as CIOMS, and proposes an alternative set of criteria that permits research studies involving human participants from vulnerable populations on the basis of appropriate ethical guidelines and under certain conditions with the establishment of additional protective safeguards.

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II. The Japanese Encephalitis Vaccine Trial Scandal

The unethical clinical trials involved the four-month study of a live attenuated vaccine for Japanese Encephalitis (JE), which had continually posed a considerable epidemic risk to the Korean population, particularly the young and elderly. In 1967, South Korea had imported a small amount of a killed vaccine, the mouse brain-derived formalin-inactivated Nakayama vaccine, and begun producing it locally.\(^{11}\) Despite mass immunization campaigns using this killed vaccine being “successful in attaining high rates of vaccination coverage, JE vaccine-related adverse effects might have been overlooked. A reporting system was not available until 1995, so the incidence of JE vaccine-related adverse effects among South Korean children was not known. However, in 1994, six cases of severe systemic illness after JE vaccination were reported. Two sudden deaths were attributed to anaphylactic reaction to the vaccine, and four cases of severe neurologic illness, including encephalopathy and acute disseminated encephalomyelitis” associated with vaccination using the killed vaccine.\(^{12}\) This cluster of vaccine-related illness incited public concern, in the form of a refusal to vaccinate, lowering the immune coverage rate and once again endangering public health and welfare. In response, the National Compensation Program for Vaccine Injury was established in 1995.\(^{13}\) Due to the lingering public debate over the safety and quality of the domestically produced killed vaccine, the Advisory Committee of the National Immunization Program also announced a change to vaccination schedule, age of initial vaccination, booster schedule, and vaccine strain.\(^{14}\) This new vaccine strain was “live attenuated SA14-14-2 vaccine, which had been used safely and effectively in over 100 million children (between one and six years old) in China since 1988”. Development of the live vaccine had started in the 1970s, with its safety and efficacy being studied by joint researchers at the University of Pennsylvania, the Rockefeller Foundation, and the Sichuan University School of Medicine over 20 years. These researchers concluded that this live attenuated vaccine was superior in both safety and efficacy to the previously standard killed mouse brain-derived vaccine, leading to it being

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\(^{11}\) Sohn, “Japanese Encephalitis.”

\(^{12}\) Ibid.

\(^{13}\) Ibid.

\(^{14}\) Ibid.
licensed in China in 1988.\(^\text{15}\)

Although the live vaccine’s safety and efficacy could have been inferred from the results of the joint researchers’ reports, affirming its safety and efficacy from prior research studies and its track record in Chinese national immunization programs, the Korean Food & Drug Administration (KFDA) still required data from domestic clinical trials before it would authorize a permit for the import, sale, and public usage of the vaccine domestically. The context of social concern and criticism of immunization programs that were ongoing at the time provides some insight into the concerns that fueled the KFDA’s stricter enforcement of laws regarding authorization for the import and sale of foreign drugs. The Korean pharmaceutical company seeking an import permit for the live vaccine, Boryung Pharmaceuticals, reported that it had “obtained authorization from the Ministry of Health and Welfare in August (1997) to conduct clinical trials based on a conditional permit, received IRB approval of their proposal in September, and legally authorized clinical trials from November to February (1998)”.\(^\text{16}\) These trials involved 84 children of three orphanages, between the ages of one year old and three years old, who were vaccinated with the live vaccine. Some of these children had been abandoned, leaving the orphanage directors their undisputed legal guardians. However, 32 of the vaccine trial’s participants were “children of single mothers or other socioeconomically disadvantaged parents, who had been ‘surrendered’ to the orphanage due to a lack of means to ensure the children’s quality of life”.\(^\text{17}\) While these children were not technically orphans, they still resided at the same orphanage facility as other children without living biological parents, under the care and legal guardianship of the orphanage director and caretakers. This fact was the focus of heavy criticism by the public as well as several National Assembly representatives, who questioned the legality of the orphanage directors’ actions in giving proxy consent for participation of children who still


had living parents, without consulting and obtaining permission from the biological parents.\textsuperscript{18} While the fact that these particular children resided in an orphanage meant that they fell under the legal guardianship and day-to-day care of the orphanage director, and thus the directors were not violating any laws by giving proxy consent to researchers,\textsuperscript{19} later-reported details of the directors’ reasoning give rise to a set of ethical, rather than legal, concerns: In the process of investigating the clinical trial and its proceedings, Ministry of Health and Welfare officials discovered that “orphanage directors were commonly promised up to 1 year of medical support, by the researcher institutions, in exchange for children’s participation in clinical trials.”\textsuperscript{20} Despite the legality of these clinical trials, these factors place the risk of exploitation of vulnerable populations at the forefront of a discussion of the trial’s morality. The incentive offered for research participation in this case seems to exceed the reasonable limit, improperly influencing the orphanage directors’ decision of whether to enroll the children in a clinical trial of the live-attenuated vaccine.

Two stances emerged in response to public awareness of the trials: First was the defensive position that it was necessary to perform the vaccine tests on institutionalized children because of the lack of voluntary participation from the general population.\textsuperscript{21} This shaky reasoning was grounded in the public’s mistrust of experimental trials involving human subjects at the time, due to a history of unethical behavior by researchers, ranging from misinformation to intentional deception, which had cemented the perception of clinical trials as dangerous and disreputable. In addition to this, for many Koreans, the conception of clinical trials involving human subjects had been influenced by knowledge of lethal and unethical human experiments conducted by the Japanese army’s Unit 731 during World War 2, evoking a justifiably negative response to the idea of scientific and medical research involving human subjects. Researchers argued that this climate of mistrust and unwillingness to volunteer for clinical trials, especially in trials requiring the involvement of children,

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\textsuperscript{18} Kim Soo Byung 김수병, “Imsangsilheom yullineun eopseotda” 임상실험에 윤리는 없었다 [There were No Ethics in Clinical Trials]. Hankyoreh\textsuperscript{21} 한겨레\textsuperscript{21}, June 4, 1998, 210th ed., http://legacy.h21.hani.co.kr/h21/data/L980525/1p3p5p0b.html.
\textsuperscript{19} Chae & In, “Yeongawon baeksin” 영아원 백신 [Orphanage Vaccine].
\textsuperscript{20} Ibid.
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created the necessary reality of conducting the clinical trial on children in institutional settings. Sohn, a researcher involved in the trials, called attention to the fact that clinical trials using institutionalized children was also common practice in other countries, and that in this particular case, the vaccine being tested had already been used to vaccinate over a billion children in China over the course of 10 years. His justification for selecting this particular group of children was that the safety of this vaccine was not in question, given the existing foreign data, and that the clinical trial involving the institutionalized children was an unfortunate but practical and low-risk means of obtaining necessary data to satisfy the formal data requirements for approval of a domestic import and sale permit as mandated by the Food and Drug Safety Administration. Since the parents of un-institutionalized children were difficult to convince of the live vaccine’s reputability, in spite of the evidence in favor of its safety and efficacy, the researchers of the clinical trial were ‘forced’ into obtaining participants from this vulnerable population.

But this position lacks moral justification, as it would allow the exploitation of vulnerability. In addition, this position may lead to rationalizing the exchange of consent for medical support. But this exchange is also problematic as it supports the argument that the orphanage directors were persuaded to enroll the children as participants based on external factors, beyond the facts about the drug in question. In this case it would appear that selection of the institutionalized children as research participants falls into the category of exploitatively selecting vulnerable populations for the ease of the researchers, in obtaining consent or conducting research, that the ‘normal’ population would not give consent to participate in.

The second position saw the clinical trials as undeniably wrong and criticized the practice of conducting clinical trials with children in institutional settings, whose ‘consent’ to participate could have been granted against their own desire by the actions of their legal custodian. Opposition to the vaccine trial from this perspective relied on the ‘instinctive’ emotional reaction to perceived exploitation of vulnerable institutionalized children, the majority who had no strong advocates for their individual interests, since they did not have parents to prevent their participation in these clinical trials. As a critic of the subject selection


23 Jang, “Adongingwon boho daean chajaya” 아동인권 보호 대안 찾아야 [Finding Alternatives for Protection of Children’s Rights].
process in these trials, Jang voiced the opinion that any parent who had learned the truth about these clinical trials would feel distress just from imagining their own child in the same situation. Her argument condemning the manner in which this trial had been conducted questioned why these disadvantaged children had to be used as clinical trial subjects for the benefit of others. Additionally, she argues that if the researchers had ever thought that it could be their own children, they would have been unable to continue conducting the vaccine trial in the same manner, appearing to reveal the presumption that all clinical trials involving children are inherently dangerous and unacceptable. She concludes somewhat inconsistently, by stating that participant selection should have been based on voluntary consent by parents of regular pediatric patients, and that no matter how difficult the task, the researchers should have explained the safety and efficacy of the vaccine to routine patients to obtain their individual consent (that of their parents) to participate in clinical trials of the new live attenuated vaccine.

Her argument grounded in the orphanage children’s lack of individual advocates seems reasonable. But given the orphanage director’s status as legal guardian of all children of the facility and responsibility for their collective welfare, her conclusion that the selection process should have persisted in seeking out non-institutionalized children seems to establish an impossible standard for ethical participation in clinical trials.

Both of these stances speak of the negative effect on the ‘emotions of society’ (사회 정서) that resulted from reports of the trial as the key determinant of its ‘wrongness’ –that the problem with this clinical trial was emotional in nature and a matter of how it was received by the public, rather than a matter of a moral concern regarding specific facts of the clinical trial. Sohn’s justification for the necessity or unavoidability of the participant selection, as it occurred, appeals to the lack of volunteers or other consenting participants from ‘non-vulnerable’ subsets of the population. The reasonably known fact of the vaccine’s safety and efficacy are mitigating factors, yet do not change that the children selected for this trial were chosen for the ease of obtaining (proxy) consent. He concludes that the prevalent criticism indicated the need to halt the practice of clinical trials with institutionalized children. His conclusion does not specifically highlight the reason, only that the public order was disturbed by becoming aware of unethical research practices. For Jang, the vaccine trial was a reflection of faults in Korean society’s moral conscience and indicated the need to improve welfare policy standards regarding the rights of children, particularly those residing...
in institutional settings without discussing significant safeguards to protect their interests. Though this particular clinical trial had been conducted with the approval of an Institutional Review Board, and there was reputable data to support the safety and efficacy of the vaccine in question, there remain some problematic aspects due to the factors surrounding selection of this subgroup due to the comparable ease of obtaining consent. Jang’s strain of justification for the subsequent prohibitory regulations appears to be based on the widespread emotional reaction, which misses the mark for proper protection of vulnerable populations. Simply objecting to the way the clinical trial was conducted on this vulnerable population, and discouraging all future research on similar groups based on a moral objection to clinical trials involving children does not provide a viable solution for future research. To depart from such emotional judgments on the moral aspects of this incident requires an analysis of how the ethical principles such as respect for persons, beneficence, and justice, enshrined in more formal guidelines such as the CIOMS Guideline, applied specifically to vulnerable populations, are relevant to identifying the specific needs and protections required by these populations in the context of research. Examining this research scandal from the starting point of these ethical principles and guidelines will indicate how to better promote protection of members of vulnerable populations in research without enacting a complete ban on all research where selected participants are members of vulnerable populations.

III. Morally Problematic Aspects of the JE Vaccine Trial

Since the clinical trial proceeded with the approval of the relevant institutions and in alignment with the procedural safeguards, it is difficult to question its legal status at the time of the study’s publication. However, the main questions raised by this incident which are the focus of this paper are the ethical concerns, rather than a debate over the study’s legality. That a clinical trial that evoked such social and moral debate had been conducted within the boundaries of the law was a clear motivator of the Ministry of Health and Welfare and the Korean FDA’s subsequent push to strengthen regulations and guidelines governing clinical trials and other research involving human participants, addressing the apparent lapse in legislative boundaries that had allowed the vaccine trials to proceed. This was consistent

24 Chae & Gyo, “Yeongawon baeksin” 영아원 백신 [Orphanage Vaccine].
with Jang’s argument that the problematic vaccine trial indicated faults with the bodies of laws, which had allowed the research to proceed and should have been remedied with stronger regulations.

However, the authors of this paper counter that the issues with the vaccine trial were not a matter to be approached with legal solutions, as in the subsequent government actions, but rather, moral issues concerning the improper interpretation and application of ethical principles and guidelines within the extant legal framework. Thus, a clearer determination of how this particular research trial was morally problematic can be gained through examining the ways ethical principles such as respect for rights and welfare and concern for justice or fairness are entrenched in the existing literature and guidelines which govern human subject research, particularly research involving vulnerable populations. This examination reveals aspects of the JE clinical trial that emerge as morally problematic.

Foremost among the morally problematic aspects of the trial was the issue of fairness or justice with regards to participant selection: not only were matters of compensation for participation handled inappropriately, but in light of this issue, participant selection was also based on morally questionable grounds reflecting an inequitable distribution of burdens and benefits. This leads to discussion of an additional morally problematic aspect of the JE Vaccine trial, concerning respect for the rights and welfare of vulnerable participants, considering how the inherent vulnerability of child participants was compounded by the vulnerability of their low-resource setting. Analyzing how the research design and researcher conduct were inconsistent with the relevant CIOMS Guidelines regarding human research will provide a more structured approach to critiquing the JE Vaccine Trial, in contrast to the previously referenced emotional or ‘intuition based’ judgments that dominated the push to revise Korean legislation to take a prohibitive stance against participation of institutionalized children and vulnerable populations in clinical research.

The CIOMS Guidelines clearly delineate the boundaries for acceptable compensation for participants of clinical trials and other human subject research. While it is acceptable for participants to receive monetary or non-monetary compensation to cover the costs directly incurred during the research, such as travel costs, it is meant to compensate participants for inconvenience and time rather than the risks the participants agree to undertake. Additionally, “compensation must also not be so large as to induce potential participants to consent
to participate in the research against their better judgment”.\textsuperscript{25} It is this guideline that the researchers of the JE Vaccine Trial violated, by offering the orphanage directors a year of medical support for their charges. Even if it was the case that orphanage directors granted proxy consent based on an evaluation of the known safety and efficacy of the vaccine and the potential risks of participation, the undue inducement opens their decision and the vaccine trial to criticism of unreasonable enticement. In making the choice to grant consent to participation, the directors would have been forced to consider the welfare of all children under their care, who could benefit from a year of medical support, rather than limit their decision-making criteria simply to the risks and potential benefits that would apply to the participating children. Furthermore, Guideline 13 states that in regards to compensation for persons who are incapable of giving informed consent, such as children, “a legally authorized representative asked to give permission on behalf of a person who is incapable of giving informed consent must be offered no compensation other than reimbursement for travel and other direct or indirect expenses.”\textsuperscript{26} This clearly applies to the scenario in question, and makes it apparent that compensation in the JE Vaccine Trials was problematic. The reasoning for limiting compensation in instances of participants who cannot directly give informed consent is to prevent the risk of exploitation for financial gain by guardians. Although the offer of medical support was a non-monetary form of compensation, the participating children may have been exploited by orphanage directors in the interest of the ‘greater good’ of providing stable medical care for other children of the institution they were responsible for.

The presence of an undue incentive in acquiring consent also leads to discussion of morally problematic aspects of participant selection. Specifically, that participant selection in the JE Vaccine Trials was improperly influenced by the comparative ease (for researchers) of obtaining proxy consent for institutionalized children’s participation as mentioned earlier. This is a clear violation of Guideline 3 of the CIOMS Guideline, concerning the equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research, stating that “groups, communities, and individuals invited to participate in research must be selected for scientific reasons and not because they are easy to recruit

\textsuperscript{25} Council for International Organizations of Medical Sciences (CIOMS), \textit{International Ethical}, 53.

\textsuperscript{26} Ibid., 54.
because of their compromised social or economic position or their ease of manipulation”. Participant selection in the JE Vaccine Trial was based on questionable justification that institutionalized children were the only population from which researchers could obtain proxy consent for participation. Which instigated the emotional reactions as we saw. Even though the scientific research into the safety and efficacy of the JE live-vaccine would have benefited all young children of that age group, the burden of risk for confirming the vaccine’s safety and efficacy was relegated to this particular subgroup of children, not for scientifically relevant reasons but for logistical or practical reasons regarding which group it was more convenient to obtain consent from.

Guideline 3 elaborates three reasons why a disproportionate selection of disadvantaged or convenient populations is morally problematic: “First, it is unjust to selectively invite poor or marginalized individuals or groups to participate in research because this concentrates the risks and burdens of research on people who already experience increased risks and burdens from social and economic disadvantage. Second, these individuals and groups are also the most likely to be excluded from, or to have difficulty accessing, the benefits of research. Third, the broad inclusion of different social groups helps ensure that research is conducted in a socially and ethically acceptable manner.” Applying these reasons to the incident of orphanage children trials reveals that participant selection manifested an unfair and thus morally problematic distribution of the burdens of research.

Aside from issues of justice or fairness, the JE Vaccine Trial as it was conducted can also be criticized on the grounds of respect for participants’ welfare and rights. The minimal risk principle is the standard applied to pediatric studies, in order to ascertain whether it is appropriate to expose participating children to the interventions required by the research. This standard permits institutional review boards (IRBs) to approve pediatric research studies in cases where the risks posed by participation do not exceed the risks that participating children would face in daily life or during routine examinations. Regarding the minimal risk principle, David Wendler has argued that “children should be enrolled in clinical research only when it offers a compensating potential benefit or poses sufficiently low risks.”

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27 Ibid., 7.
28 Ibid., 8.
could be argued that since the selected children could expect the potential direct benefit of immunity from Japanese Encephalitis through vaccination, and that the safety of the vaccine could have been reasonably assumed based on data from foreign studies of the same vaccine, it was acceptable to condone a ‘minor increase over minimal’ level of risk. So criticism that emerged in the aftermath of public awareness of the JE Vaccine Trial that the research was morally problematic due to the risks participating children were exposed to are not specific to this trial, but concern the ethics of any and all instances of pediatric trials more generally.

Yet, minimal risk and ‘minor increase over minimal’ risk still present a problem in this particular study due to the vulnerability of the selected participant group. CIOMS Guideline 15, regarding research involving vulnerable persons and groups, requires that “when vulnerable individuals and groups are considered for recruitment in research, researchers and research ethics committees must ensure that specific protections are in place to safeguard the rights and welfare of these individuals and groups in the conduct of the research.” The participants of this study were vulnerable due to their lack of capacity to give informed consent and the economic and social disadvantages of living in an institutional environment. Given the inherent vulnerability of children, in combination with the situational vulnerability arising from their residing under the care of orphanage directors rather than a conventional family environment, commitment to representing the interests of the children themselves should have emerged as the primary point of concern regarding the appropriateness of participant selection in this study. However it is not clear that an effort was made to determine whether the infants and toddlers selected as participants assented to the research, or that other safeguards to ensure the protection of the participating children’s welfare and rights were put into place. Since legal minors, especially children, may not have the cognitive capacity to fully understand information about risks and benefits, they are treated as individuals incapable of giving informed consent, instead applying the concept of ‘assent.’ Unlike informed consent, assent is not always legally required to proceed with research, but is used as an indicator that children agree or disagree (if they dissent) to participate. However, the CIOMS Guideline, as well as Declaration of Helsinki state that IRB panels

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30 Council for International Organizations of Medical Sciences (CIOMS), *International Ethical*, 57.
should ensure that the assent of child participants is obtained prior to beginning research.\textsuperscript{31,32} This is in addition to other recommendations of special protection of vulnerable participants, such as the appointment of a representative specifically committed to the protection of participants’ interests, or requiring that research on vulnerable populations be carried out only when the research targets conditions that affect these groups.\textsuperscript{33}

Examining these problems from an ethical standpoint yields interesting and conflicting perspectives: What was primarily ethically at fault in the 1997 Vaccine Trials was the creation of a coercive situation; the quid pro quo transaction of proxy consent to participation in exchange for medical support. It may seem counterintuitive that the trials could have been more ethical if the researchers had removed or reduced the compensation offered for participation. But without this undue incentive, the potential for exploitation of vulnerable participants would have lessened, and the morally problematic aspects of participant selection and respect for participating children’s rights would have diminished. Orphanage directors would have been left to make an informed decision of the direct benefits and risks to potential participants based solely on what was known about the vaccine at the time – the same information given to parents of the researchers’ normal patients – instead of having to weigh the additional and significant potential benefit to all the other children within their care. Thus, examining the resulting ban on clinical trials involving institutionalized children raises the question of whether subsequent legislative action was the most coherent response to addressing the morally problematic characteristics of the JE Vaccine Trial. The criticism of those who condemned the clinical trials was based on the vulnerability of these children, because of their lack of familial or parental legal guardians. To evaluate this position then requires contemplation on the moral acceptability of any and all clinical trials involving children, not just those in orphanages or other institutional environments. If we are able to conceive of a scenario in which a reasonable weighing of the benefits and risks of participation would lead a parent to conclude that participating in a clinical trial is consistent with the child’s best interest (such as in clinical trials of experimental treatment for rare

\textsuperscript{31} Ibid., 65.


\textsuperscript{33} Council for International Organizations of Medical Sciences (CIOMS), \textit{International Ethical}, 59.
diseases, or observational trials with low risk and high benefit), we cannot automatically dismiss the possibility that a legal guardian who is not biologically related to the child, such as an orphanage director, could arrive at the same judgment. But while lack of genetic relation does not necessarily disqualify a legal guardian from being able to make decisions that express the child’s best interest, to claim this was true of the JE Vaccine Trial seems to be a dubious claim. Nevertheless, if clinical trials involving children are generally accepted as morally permissible in the earlier mentioned cases, it would be unjust to ban participation by institutionalized children in the interest of preventing exploitation and harm, as argued by Jang and several critics of the Vaccine Trial within government and media institutes. Not only would this violate the other dimension of fairness in participant selection, requiring equity in distribution of the benefits of research, it would likely engender similar consequences as the protectionist stance previously taken towards the participation of women in clinical trials, which has stifled the progress of gender-specific medicine.

Instead, efforts to reduce risks of harm and exploitation should have occurred throughout the IRB approval process, by inspecting the following conditions: (1) whether there was justification for why the trial needed to be conducted with ‘particularly more’ vulnerable children, rather than less economically or socially vulnerable children of the same age range; (2) whether there was a direct benefit to participating children; (3) whether there would be long-term or future benefits to that vulnerable population, and whether the scientific and social gains of research would be accessible to the same population; (4) whether there were elements of coercion or undue influence in the process of obtaining consent. Due to the range of disadvantages that vulnerable individuals and groups may face, they may consent to research that comparatively not-vulnerable populations may not, based on concern that they will face direct or indirect negative consequences because of their circumstances. As such, IRBs must pay close attention to these risk factors when examining the researcher’s process of obtaining participants’ informed consent, and identify measures to improve research proposals or consent procedures that do not meet these conditions.

In the future, preventing research scandals similar to the JE Vaccine Trial will require a balance between discouraging exploitation and still ensuring equal access to the potential benefits of participation in human subject research. International guidelines make note of several of the risk factors mentioned here, which may increase the vulnerability of participants, but they do not summarily dismiss the possibility that research involving these
individuals or groups may be conducted, so long as supplementary measures are enforced to respect participants’ rights and welfare. By regulating the participant selection criteria and consent process, and establishing stricter standards for IRB approval that satisfies a more comprehensive set of criteria, ethical research involving vulnerable populations may still be possible. This goal can be achieved through a combination of supplementing IRB approval procedures themselves as well strengthening the regulatory authority of IRB panels. To that end, the following section will consider alternative or supplemental means of facilitating ethical research involving vulnerable populations and proxy consent.

**IV. Considerations for Future Regulations to Ensure Ethical Research Involving Vulnerable Participants**

Legislation to protect the rights and interests of vulnerable populations could be better constructed by focusing regulatory efforts on specific aspects of clinical trials that pose a real risk for exploitation, rather than regulations that take a paternalistic exclusionary approach. These additional risks are not necessarily of greater potential for harm, but rather of other threats to the participant’s rights or welfare due to the disadvantages related to their vulnerability. In the case of the JE Vaccine clinical trials, the degree of potential harm that participating children would have faced from adverse reaction to vaccination would have remained the same, had the participants not been institutionalized children; yet participating children were still exposed to greater injustice due to the way their vulnerability intersected with the coercive incentive for consent and unfairness in participant selection. Had the JE Vaccine Trials been conducted without offering improper compensation in the consent process this would have eliminated the criticism of an unethical transaction between researchers and orphanage directors. Or if an advocate solely invested in representing the interests and rights of participating children had been involved in the IRB approval process, the decision to consent would have been supported by an unbiased party’s evaluation of the proposed risks and direct benefits to participants. If this had been the case, the JE Vaccine Trial could have satisfied many of the current conditions that research involving vulnerable populations must satisfy: ethical trials should entail a minimal level of harm to participants while offering moderate to high potential benefits; that there be a direct benefit to the
participating individual, in addition to the possibility of benefit to society (whether through scientific development or accumulation of new knowledge); that participant selection constitute an equitable distribution of the burdens and benefits of participation (in the sense that vulnerable participants do not bear a disproportionate burden for research gains they would later find inaccessible); that there be no coercive influence when seeking consent or assent; that there be an acceptable reason, relevant to the research, for selecting vulnerable participants rather than from the general population more broadly.

The JE Vaccine Trial’s ethical problem of an undue incentive has already been rectified in numerous international and domestic guidelines and regulations, dictating what type and extent of compensation is appropriate for participation in a study. However, this measure to deter exploitation of vulnerable participants could be supplemented by more consistently enforcing the CIOMS Guideline recommendation that an independent child advocate be involved in research.34 It is possible that this advocate may have reached the same decision as the orphanage directors had, if they judged that participation offered direct benefits to the children and the risk of harm was only a minor increase over minimal risk. However, the key difference would have been that this advocate would not have been responsible for the welfare of other non-participating children in the institutions, therefore their decision-making process could remain unaffected by the undue compensation that was offered to the orphanage directors. Advocates for participants’ interests are referenced in the context of child participants, and of other vulnerable individuals and groups more generally,35 but as a special protective measure rather than a mandatory condition. Future studies could solidify moral justification for research on vulnerable participants, particularly children, by implementing this safeguard as a standard, rather than special protection against the risk of exploitation.

Whether the assent of participating children was obtained, in addition to the consent of orphanage directors, was undetermined in the JE Vaccine Trial. Because the participating children were so young (1 to 3 years old), while it is possible that assent was not seen as necessary, current guidelines reinforce the importance of explaining information about the study in language and terms the child can understand before asking whether they approve or

34 Ibid., 68.

35 World Medical Association, Declaration of Helsinki.
disapprove of participation.\textsuperscript{36,37} In situations where the child expresses deliberate objection to participation in the study, this should override the parent or legal guardian’s consent for participation, unless proceeding with study is in the best medical interest of the child. Obtaining assent when the participant is a child or legal minor is required by some IRB panels, in addition to the parent or legal guardian’s consent. But this is not always the case, and the ages of children for which assent is suggested or required also varies from country to country. In Europe, the defined age range suggested or required for assent can differ as greatly as requiring separate written consent as soon as the child is literate, in Finland; applying increasing standards of assent from 0-5 years old, 6-10 years old, and 11-15 years old, in the UK; or not having any regulations defining what age it becomes necessary to obtain the assent of child participants.\textsuperscript{38} Clarifying these standards, and instituting a uniform requirement for IRB panels to confirm that child participants of pediatric studies have assented to participation in research would remove some of the uncertainties involved in determining whether the child participants themselves express approval to enter or continue with research.

Additionally, confidence in the IRB deliberation and approval process could be reinforced by ensuring that there are a greater number of individuals placed on the IRB panels have some professional experience or specialized knowledge regarding the trial’s subject matter, increasing the likelihood that approval of proposals involving research with vulnerable populations is subjected to greater scrutiny and only allowed after greater consideration. Several guidelines and regulations already mandate conditions of diversity and expertise in IRB panels.\textsuperscript{39} Yet, the IRB panels’ authority to claim moral justification for research involving vulnerable participants would benefit from greater involvement of community representatives or independent advocates in the deliberation and approval process, not to mention throughout research. As seen with the recommendation that independent child advocates be appointed in pediatric studies, future research involving vulnerable participants

\textsuperscript{36} Council for International Organizations of Medical Sciences (CIOMS), \textit{International Ethical}, 65.

\textsuperscript{37} World Medical Association, \textit{Declaration of Helsinki}.


\textsuperscript{39} Ibid.
could avoid the morally problematic aspects of previous research scandals by considering this condition a requirement rather than a suggestion.

Had the current standard for IRB approval or the above proposed additional criteria been the established protocol in 1997, the JE Vaccine Trial likely would not have been justified in proceeding with research. However, future research involving vulnerable populations and children under the care of non-familial legal guardians may still be able to claim moral justification, by implementing the above proposed participant selection criteria. Reexamining and restructuring current legislation by taking into account these additional safeguards offers a means of facilitating ethical research involving vulnerable participants, while still preventing violation of rights and minimizing the risk of exploitation that motivates such legislation to begin with.

V. Conclusion

The 1997 JE Vaccine Trial shocked the Korean public with the knowledge that young children, living in a socially and economically disadvantaged environment, had been recruited as clinical study participants under morally questionable circumstances. The criticism that emerged in the aftermath of public awareness largely focused on the particulars of the children’s vulnerability; that not only were they young children, but they relied on the care of an orphanage director who had the authority to give consent for their participation in a study that the vast majority of parents had denied. This ‘gut feeling’ of wrongness spurred social outrage that was used to argue for a prohibition of all research involving institutionalized children. However, examining what was morally problematic about the JE Vaccine Trials reveals the specific faults lay with the introduction of undue influence in the consent process, thereby calling into question the grounds for justifying participant selection, and ultimately casting doubt on whether the rights and welfare of children chosen to participate were the foremost concern of the researchers or guardians who gave consent. These faults with the JE Vaccine Trial could have been remedied if the current guidelines and regulations regarding clinical research with vulnerable populations had been in place then, without requiring a prohibitive ‘all or nothing’ approach to protecting participants rights and welfare. Despite the positive influence the body of international guidelines and national
laws have had in protecting vulnerable participants from harm or exploitation, they could be improved by implementing a stronger interpretation of those regulations, as substantial ethical requirements rather than simple recommendations; this would enable vulnerable populations to continue being included in the direct benefits of participating in research, without placing them at further risk or subjecting them to disproportionate burdens.

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