

Medical Researchers' Ethical Awareness of Transgenic Monkeys with Human Genes: A Quantitative Case Study from China

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Abstract

Background: In 2019, a Chinese medical research team constructed a human MCPH1 gene transgenic rhesus monkey model to understand the human genetic mechanism in the developing brain. The case has attracted worldwide attention and raised a heated ethical debate, but the voices of Chinese medical researchers have not been heard. This study is an attempt to assess Chinese medical researchers' ethical awareness of transgenic monkeys with human genes.

Methods: A questionnaire that consisted of two parts was developed. The first part surveyed demographic information. The second part surveyed ethical awareness. The premise of all the questions in the second part is that "The researchers transferred a specific human brain gene, MCPH1, into rhesus monkeys to create a transgenic rhesus monkey with human genes to understand how the human gene works in the developing brain". ☒ Are there ethical issues in this study? ☒ What ethical problems do you think exist in this study? ☒ Do you agree that it can be carried out as long as it is approved by the ethics committee of their own organization? Between April 1 and 15, 2020, the questionnaire was distributed to members of all research institutions across the National Natural Science Foundation of China system. Basic descriptive statistical analyses were performed.

Results: In total, 70.9% of Chinese medical researchers believe that there are ethical problems in using transgenic monkeys for medical research. Chinese medical researchers believe that the three most important ethical issues involved were unacceptable risk-benefit ratio (49.1%), harm to rhesus monkeys (33.7%) and inadequate scientific evidence (26.7%). A total of 68.9% disagreed that it could be carried out as long as it was approved by the ethics committee of their organization.

Conclusions: Chinese medical researchers are wary of using transgenic monkeys for medical research, and their greatest concerns are the risk-benefit ratio, the harm to rhesus monkeys and the lack of scientific evidence supporting the study. It is necessary to strictly implement 3R in the medical research of transgenic monkeys with human genes.

Introduction

Monkeys have long been the experimental animals of choice for some medical research because of their high degree of genetic and physiological similarity to humans. Scientists have been trying to find the best animal model for studying human disease. For example, transplanting human stem cells into non-ape primate hosts, could create human-primate chimeras that could transcend the limitations of current animal models [1].

Meanwhile, the mixing of human and animal genes for medical research has aroused a heated debate in both the public and the academic circles [2]. Currently, medical research using transgenic non-human primates with human genes can be approved in some countries, including the United States and China[3, 4]. 59% of the American public would accept the injection of human-induced pluripotent stem cells into transgenic pig embryos [5].

In 2019, a Chinese team successfully generated transgenic rhesus monkeys with human gene MCPH1 to explore brain development and evolution[6]. The head of the study, Bing Su, announced that all their animal procedures were conducted following international ethical standards and were approved by the Institutional Animal Care and Use Committee of Kunming Institute of Zoology, Chinese Academy of Sciences and Yunnan Key Laboratory of Primate Biomedical Research. There are no ethical problems in this challenging experiment according to the authors. However, several Western scientists questioned the ethics of using transgenic monkeys with human genes for medical research.

However, the ethical and regulatory perspectives of researchers in China on this controversial study have not been made public. We do not know about the views of Chinese medical researchers on the ethical governance issues involved. This study was designed to investigate attitudes among leading medical researchers in China towards using transgenic monkeys in medical research.

Methods

Survey development

Survey items were developed by an interdisciplinary team with backgrounds in clinical medicine, bioethics, and science policy research. The authors have various professional backgrounds and divergent sociopolitical identities, which ensures that the interpretation of the data incorporates a number of analytical and interpretative perspectives. The questionnaire was divided into two parts: (1) demographics and (2) attitudes about ethical issues associated with transgenic monkeys with human genes. The detailed content of the questionnaire is provided in Table 1.

The Chinese Academy of Medical Sciences Ethics Committee reviewed the protocol and determined that this study was exempt from continued review due to participant anonymity. The study was conducted in accordance with the Chinese National regulation “Ethical Review Guidelines on Biomedical Research Involving Human Subjects” and the Helsinki Declaration.

This electronic questionnaire was distributed online, and the respondents answered the questionnaire anonymously. So, there was no real name signature. In order to obtain the informed consent, at the beginning of the questionnaire, the respondents were asked to choose whether they are voluntary to complete the survey or not. If they chose yes, they will see follow-up research questions; if they chose not, they will automatically drop out of the questionnaire.

Study Participants

Our target population was senior medical researchers. All applicants for National Natural Science Foundation of China medical projects are well trained in specific fields of medicine and could be clinicians, epidemiologists, basic medical researchers or interdisciplinary researchers. This study utilized a convenience sample of individuals who applied to the National Natural Science Foundation of China medical project in 2019. Between April 1 and 15, 2020, e-mail invitations were distributed to members of

all research institutions across the National Natural Science Foundation of China system. No compensation was provided for participation.

Data processing and analysis

Data were analysed using IBM SPSS 26.0 (IBM, Armonk, NY, USA). Surveys were included if at least three-quarters of the questionnaire was complete. Descriptive statistics summarize responses to each item.

Results

1. Demographics

We sent questionnaires to 72,218 applicants through the National Natural Science Foundation of China; 16,439 responses were initially received, 11,164 were deemed eligible and were included in the final analysis, and the effective recovery rate was 67.9%. Exclusion criteria: More than 25 percent of the participants' questions were unanswered. A total of 55.4% of the respondents were women (n = 6,183), and the majority, i.e., 44.8% (n = 5,001), worked in clinical medicine, followed by basic medicine, accounting for 22.4%. A total of 57.5% of the respondents came from medical institutions, one-third from universities, 7.7% from scientific research institutes, and only a few from enterprises. A total of 35.6% were aged 35 or below, 40.1% were aged 36–45, 18.4% were aged 46–55, and 5.1% were aged over 55. Approximately two-thirds considered themselves to be mid-level or higher, and 82.1% possessed a doctorate in their respective fields. The majority, i.e., 58% (n = 6,475), worked within the eastern provinces of mainland China, and 57.5% (n = 6,419) worked within a hospital. Please see Fig. 1 and Supplementary Material-Table S1 for further demographic data.

2. Attitudes about ethical issues associated with transgenic monkeys with human genes

2.1 Overall, 70.9% of Chinese medical researchers believe there were ethical issues.

According to the survey, 70.9% of Chinese medical researchers think there are ethical problems in the study, 16.1% think there are no ethical problems, and 12.9% are undecided. The respondents from hospitals were the most likely to say that the study had ethical problems; the rate of 73.0% in this population was higher than that of researchers from institutions of science and technology (65.8%), universities (68.7%) and private companies (68.5%). Please see Fig. 2 and Supplementary Material-Table S2 for further demographic data.

2.2 The unacceptable risk-benefit ratio is the primary ethical concern.

According to the survey, 49.1% believed that the study had an unacceptable risk-benefit ratio, 33.7% believed that the study had harmed rhesus monkeys, 26.7% believed that the scientific basis of the study was inadequate, 23.6% believed that the study was offensive to human dignity, and 11.3% believed that the study violated the principle of informed consent. The participants from hospitals and private companies reported higher rates of unacceptable risk-benefit ratios than the participants from institutions

of science and technology and universities. Please see Fig. 3 and Supplementary Material-Table S3 for further demographic data.

2.3 Overall, 68.9% of Chinese medical researchers opposed the use of transgenic rhesus monkeys, even if the protocol was approved by the Institute's Ethics Committee.

According to the survey, 31.1% of respondents said they could conduct the research as long as it was approved by their organization's ethics committee, while 68.9% opposed it. The respondents from hospitals were the most likely to disagree that it can be carried out, even if it was approved by the ethics committee of the relevant organization, and the rate of 71.6% was higher than that of researchers from institutes of science and technology (62.4%), universities (65.4%) and private companies (67.6%). Among the respondents from research institutes, 37.6% believed that transgenic monkey research could be carried out as long as it was approved by the ethics committee of their organization, which was higher than the 28.4% in medical institutions. Please see Fig. 4 and Supplementary Material-Table S4 for further demographic data.

Discussions

1. Most Chinese medical researchers were aware of the ethical issues related to using transgenic monkeys with human genes for medical research.

According to the survey, more than seventy percent of the respondents thought there were ethical issues in using transgenic monkeys with human genes for medical research. At least three kinds of arguments have been advanced against the creation of human-nonhuman chimaeras, such as creating transgenic monkeys with human genes: a dignity-related argument, a moral status argument, and the playing god argument. First, the dignity-related argument claims that the chimaera could possess human-like mental capacities, which would undermine human dignity. In our study, 23.6% of the respondents thought it was an affront to human dignity. Second, farming human-pig chimaeras for their organs risks perpetrating a serious moral wrong because the moral status of human-pig chimaeras is uncertain and potentially significant, as Koplin and Wilkinson pointed out [7]. Finally, the playing god argument holds that human beings are not gods and have no right to create genetically modified monkeys that show a disregard for animals. Of course, not all agree with the above arguments. For instance, Palacios-González criticized that these arguments confuse the ethical assessment of the creation of chimaeras with the ethical assessment of how such creatures should be treated in specific contexts (e.g., in the laboratory)[8].

2. The unacceptable risk-benefit ratio is the biggest ethical issue.

The survey shows that the “unacceptable risk-benefit ratio” was transgenic monkeys. Professor Wieland Huttner, who led the study that transferred the ARHGAP11B gene into marmosets, said their experiment was stopped because of the gene's unforeseen potential effect on brain function after the monkeys were born. Monkeys, once equipped with human genes, might be as advanced as humans or even smarter, so their research was stopped at the embryo stage. If such studies found that the gene improves memory

and promotes intelligence, increasing skills of observation, memory, imagination, understanding, analysis, judgement, thinking, strain capacity, etc., it cannot be ruled out that introducing such genes opens the risk that scientists make experimental animals more powerful, even becoming superhuman. Such experiments have even been called human death experiments. James Sikela, a geneticist at the University of Colorado, argues that such experiments constitute a classic slippery slope issue in that the experiment shows disregard for the animals and will soon lead to more extreme modifications [9].

Overall, 33.7% of Chinese medical researchers believe that using genetically engineered monkeys for medical research harms the monkeys; this was the second-most reported ethical concern. There is irrefutable evidence that monkeys have rich social and mental capacities. Using transgenic monkeys with human genes for medical research destroys their original way of life, potentially causing them greater social and mental suffering than that experienced by other experimental animals. Recognition of the moral status and intrinsic value of nonhuman primates must be reflected in research programs involving the use of nonhuman primates. The use of genetically modified monkeys for medical research does them no good, only harm. By transferring genes unique to humans to monkeys, such research blurs the line between humans and animals. Transgenic monkeys with human genes might have human-like characteristics, but they do not have human rights. They will not receive a level of protection and care befitting their moral status[10].

Given that nonhuman primates have the ability to feel pain, are conscious and self-aware and have the ability to communicate socially but cannot easily communicate with humans, we recommend considering them to be similar to human “vulnerable groups”, which would require primate zoologists or experienced animal management to be hired as their guardians and participate in the animal ethical review committee or for them to participate in the research decision making. Representatives of animal protection organizations may also be invited to participate as independent consultants in the review meetings of the Ethical Committee for Animal Experiments. Scientists need to clearly articulate the scientific and translational benefits of human-monkey chimaeras to society so that any ethical or moral risks can be properly weighed.

3. Overall, 70% opposed allowing medical research using human genes to be carried out, even with the approval of their own organizations.

According to the survey, approximately 70% disagreed that medical research on genetically modified monkeys could be carried out if approved by the ethics committee of the organization in which it was conducted. For such a world-first medical study with ethically controversial implications and the biological safety risks associated with major cutting-edge research, approval by only the sponsoring scientific research institution and head of the ethics committee is not enough; approval should also be granted by the regional ethics committee, the national science and technology ethics committee, the competent department of health at or above the provincial level, or a comparable temporary committee of experts following sufficient argumentation and evaluation.

4. The use of transgenic monkeys in medical research needs to more rigorously implement 3 R content

As nonhuman primates possess cognitive and emotional abilities similar to those of humans, they have computational, memory and problem-solving skills. Their abilities make them highly sensitive to pain, and confining them in a laboratory for research results in extreme harm[11]. Therefore, animal research committees play a primary role in evaluating experimental research protocols, from their feasibility to the rational use of animals, primarily to ensure animal welfare by following the principle of the three Rs (replacement, reduction, and refinement)^[12].

4.1 Replacement: Current ethical guidelines dictate that a substantial benefit must be demonstrated for the creation of transgenic monkeys using human genes or those of related nonhuman primates (and their cloned counterparts) [13]. The use of nonhuman primates for biomedical research is mostly unnecessary to achieve scientific goals [14], and approximately 9% of the studies are of little significance but cause great pain to the primates[15]. In 2008, a rhesus macaque that expressed hallmark features of Huntington's disease became the first transgenic monkey model of human disease[16]. The 3Rs state that animals should be used only if there is no alternative[17]. For using transgenic monkeys with human genes for medical research, it is recommended that nonhuman primate research be evaluated on the basis of its scientific value, the likelihood of medical or other benefits, the availability of other alternatives, and the probability and extent of animal suffering[15].

Currently, with the progress of science and technology, the 21st century has already seen the development of promising, high-tech nonanimal models, such as organs-on-a-chip and computational approaches that, in our view, will replace animals as the default option in biomedical experimentation[18]. There are other alternatives to primate models, such as using brain imaging, noninvasive electrophysiological techniques, in vitro and computer simulations, and even human subjects.

4.2 Reduction: The 3Rs state that animals should be used only if there is no alternative, and when animals are necessary, only the most humane methods should be used on the smallest number of animals required for scientific validity[17]. Studies should also reduce the number of primates needed for research by sharing data, publishing all research results (including negative results), and regularly checking the outcome benefits and effects of studies to avoid unnecessary duplication. The ideal future will allow appropriate alternative animal models to be developed using an array of techniques, from humanizing other model organisms through genome editing to computational approaches, thus reducing the use of nonhuman primates as much as possible.

4.3 Refinement: Unlike rodents, nonhuman primates suffer not only great physical harm but also serious mental harm in experiments or studies. Providing welfare for nonhuman primates is challenging and requires a good environment to ensure their mental health. There are many issues that need to be addressed, including group placement, improving the environment, and caring for infants and young children, as well as individuals who show signs of mental problems. China has been discussing animal rights issues since 2002. In 2012, The Chinese Center for Disease Control and Prevention issued the Regulations on Ethical Review of Experimental Animal Welfare in Nonhuman Primate Experiments and Animal Experiments in International Cooperation Projects (Trial). In 2016, the national standard

"Experimental Animals: Guidelines for Welfare Ethics Review (Draft for Comments)" was released. This process shows that China also paid attention to animal welfare and ethical issues related to animal experiments.

Conclusions

More than seventy percent of Chinese medical researchers believe that there are ethical problems in using transgenic rhesus monkeys for research. Approximately fifty percent believe that the unacceptable risk-benefit ratio is the most important ethical issue. Above seventy percent object that it can be carried out as long as it is approved by the ethics committee of their organization. Chinese medical researchers are wary of using transgenic rhesus monkeys for medical research, and their greatest concern is the risk-benefit ratio, the harm to the monkeys and the lack of scientific evidence supporting the study. It is necessary to strictly implement the 3Rs in medical research using transgenic monkeys with human genes.

Declarations

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Authors' contributions

YYD, JYZ, and JBZ designed the study and wrote the preliminary manuscript; XQZ and GYW reviewed and revised the manuscript. All the authors approved the final version.

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Availability of data and materials

The datasets generated and/or analysed during the current study have not been made publicly available to protect the participants' identities. However, the data are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the Chinese National regulation "Ethical Review Guidelines on Biomedical Research Involving Human Subjects" and the Helsinki Declaration. The Chinese Academy of Medical Sciences Ethics Committee reviewed the protocol and determined that this study was exempt from continued review due to participant anonymity. This electronic questionnaire was distributed online, and the respondents answered the questionnaire anonymously. So, there was no real name signature. In order to obtain the informed consent, at the beginning of the questionnaire, the respondents were asked

to choose whether they are voluntary to complete the survey or not. If they chose yes, they will see follow-up research questions; if they chose not, they will automatically drop out of the questionnaire.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table 1

Table 1 The questionnaire questions.

<p>Researchers transferred a specific human brain gene, MCPH1, into rhesus monkeys to create a transgenic rhesus monkey with human genes to understand how the human gene works in the developing brain.</p>	
<p><input type="checkbox"/> Are there ethical issues in this study? (single choice)</p>	<p>A. Yes B. No C. I do not know</p>
<p><input type="checkbox"/> What ethical problems do you think exist in this study? (multiple choice)</p>	<p>A. Violation of the principle of informed consent B. Unacceptable risk-benefit ratio C. Offence to human dignity D. Hurt rhesus monkeys E. Scientific evidence is inadequate F. I am not clear</p>
<p><input type="checkbox"/> Do you agree that it can be carried out as long as it is approved by the ethics committee of your organization? (single choice)</p>	<p>A. Yes B. No</p>

Figures

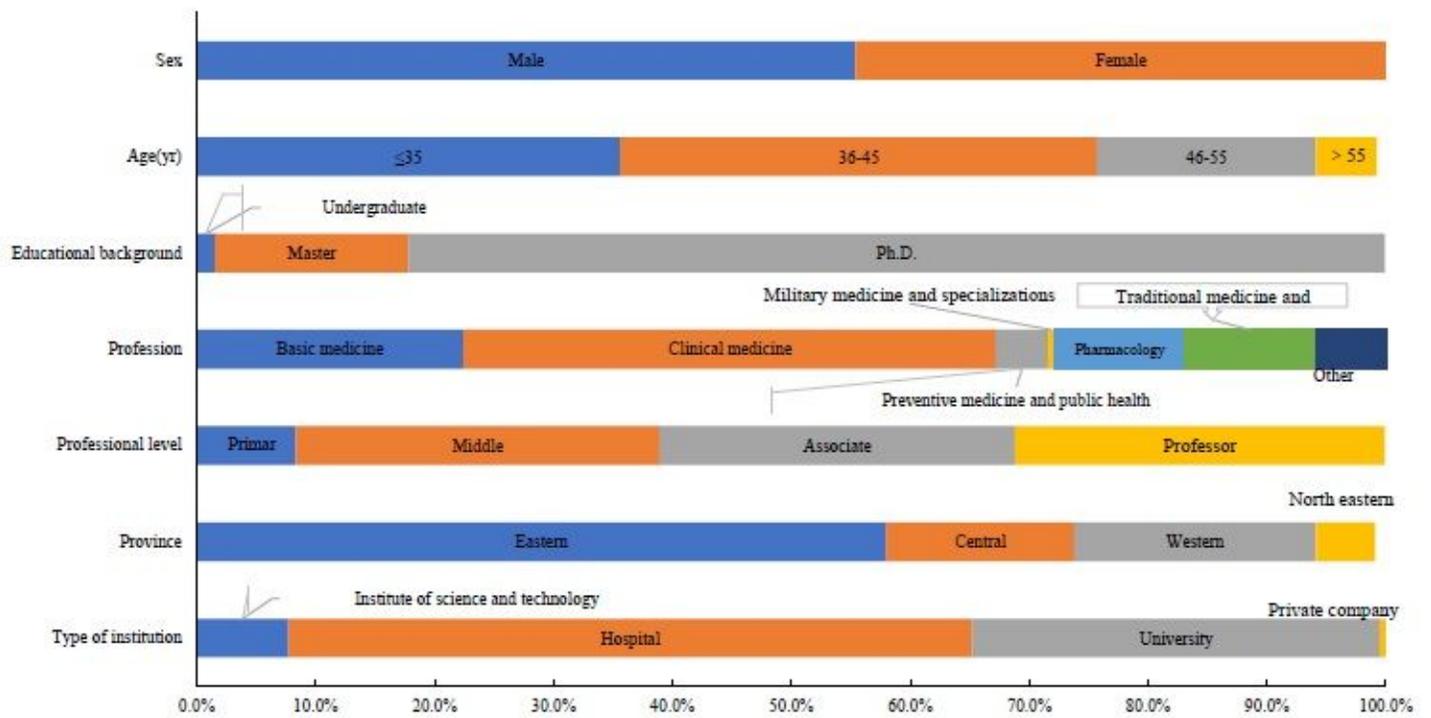


Figure 1

Demographics

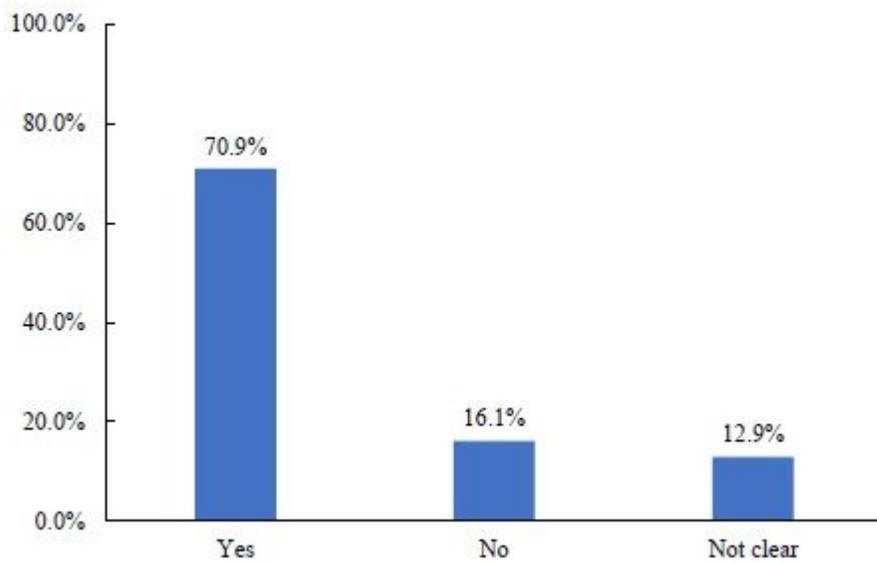


Figure 2

Are there ethical issues in this study?

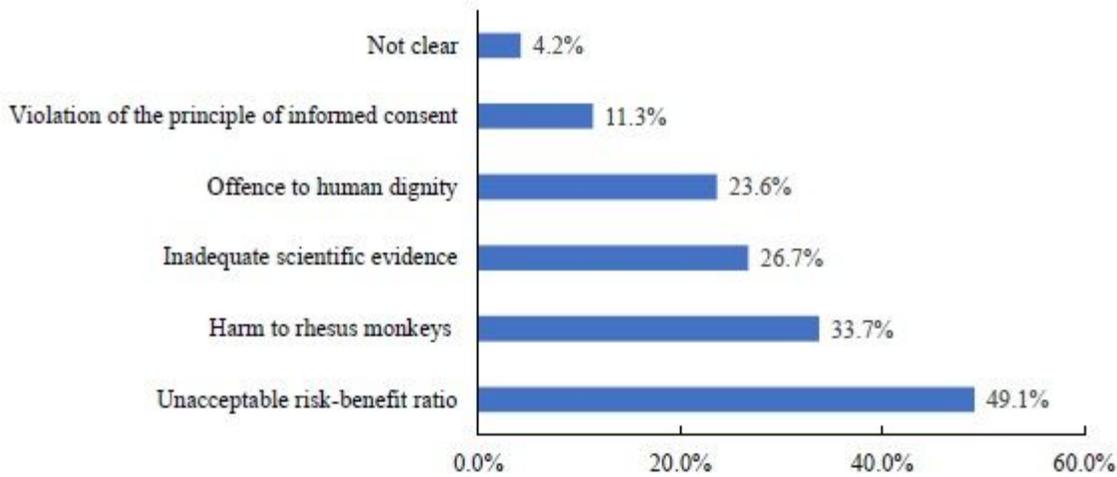


Figure 3

What ethical problems do you think exist in this study?

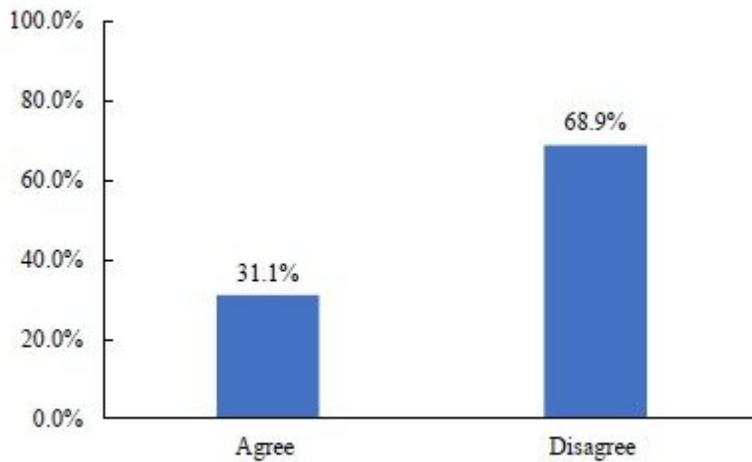


Figure 4

Do you agree that it can be carried out as long as it is approved by the ethics committee of your organization?

Supplementary Files

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