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Chapter 11: Ethical frameworks and regulatory pathways in high-stakes medical research and trials

11.1. Introduction to High-Stakes Medical Research

Research and clinical trials are not always benign. These endeavors can result in significant and irreversible harm to participants, such as organ failure, neurocognitive impairment, and even death. Tragic research decades ago involved participants who suffered severe and permanent effects due to unsafe chemical and drug exposures. Such high-stakes clinical trials are especially troubling when they involve cellular and genetic modifications – and in the past, these interventions have proved one-way, unrecoverable streets. High-stakes medical research includes studies that may cause irreversible medical, psychological, and financial consequences to participants. These negative consequences can arise from particular categories of Phase I clinical trials or involve minimally- or untested cell therapies, gene therapies, genomic enhancements, genetically modified viral vectors, whole-exome sequences without proper protections, germline changes to hereditary risks, implanting electrodes to alter neural circuits, placing microchips for memory and decision-making enhancements, and adding bio-microbricks into organs to enable nonhuman enhancement (Kim et al., 2023; O'Connor et al., 2023; Patel et al., 2025).

Despite the importance of considering ethical, regulatory, recruitment, and access issues, few publications to date have examined such high-stakes research in any serious way. In particular, how many reviews or empirical studies are devoted to addressing issues of informed consent by researchers, universities, research institutions, and industry in these high-stakes contexts? How many journals carefully vet the ethical concerns of papers submitted for publication? Until as late as 2019, the Universal Declaration on Human Rights did not prioritize ethical safeguards either; it still hasn't emphasized oversight and protections for the vulnerable in research contexts. Moreover, as with early orphan

drug development situations, it is often left to vulnerable impoverished participants to shape the field in hopes of better therapies for hard-to-treat indicia of despair – perhaps for their future benefit, but often with little or no personal advantage and much risk (Roberts et al., 2024; Walker et al., 2024).

11.1.1. Overview of High-Stakes Medical Research and Its Significance

Medical research plays an important role in advancing therapeutic interventions used in practice, and more intrusive clinical trials become available as a natural extension of laboratory translation. Such research provides benefits to participants and society more generally, however, this is often at a certain level of risk that can impact on the quality of research itself. High-stakes medical research is that which involves the possibility for both substantial benefits – to individuals or to humanity at large – and also substantial risks, especially those affecting individual participants. It covers activities that are designed with the intention to maximize these factors and which are inherently uncertain. Examples of types of high-stakes medical research include experimental gene editing and viral vector creation, CRISPR research, stem-cell transplant trials, and phase-1 vaccine and drug trials.

Fig 11 . 1 : Medical Innovation and Ethical Boundaries

High-stakes medical research has particular significance in two key areas. Firstly, it often raises ethical and policy questions about reducing the risks of participants or fabricating the benefits promised without good reason. The ethical and policy framework for other clinical research areas often mirrors that of clinical research itself but is more flexible in

moving and defining the zones where risk emanates. This may influence the quality of the research design. It also often concerns populations that are quite particular with unique vulnerabilities and regulatory oversight. Such potential participants may not be ideally placed to advocate for themselves, this creates obvious further responsibilities.

11.2. Historical Context of Medical Research Ethics

The conduct of medical research, often on vulnerable populations, has a morally checkered past. Both voluntary and involuntary human subjects have been subjected to procedures that adhered to no generally acceptable code of ethics, frequently with harmful or fatal consequences. With the rise of modern science in the sixteenth and seventeenth centuries, a number of physical and psychological experiments were conducted that tested the limits of pain on organisms viewed as expendable. More recently, well-documented research atrocities during World War II focused attention on the need for ethical guidelines in research protocol development and review.

In response to abuses perpetrated principally by authors of human medical experiments who had been unrepentant at the War Crime Trials, the Code was promulgated. It was followed by the Declaration which, although criticized for vagueness and lack of enforcement power, evolved into a core foundation that brought ethical standards of practice to the world, especially to developing countries without local ethical guidance. International research organizations, academic and clinical research institutions, and Institutional Review Boards modeled their standards for ethical conduct of research on the principles expressed in these documents. Subsequently, a number of countries developed their own rules and guidelines. More parochially, events including the Syphilis Study, the Hepatitis Study, and the Chronic Disease Hospital Study contributed to an amplified response. With the rise of scientific research on the most basic layers of human existence, a spate of current events, in the United States and elsewhere, undermined public confidence in research ethics. With public trust at risk, the challenge is to navigate a pathway forward that safeguards the interest of patients and volunteers, while optimizing the chances for important new scientific discoveries.

11.2.1. Evolution of Ethical Guidelines in Medical Research

The escalation of high-stakes medical research activities in the first half of the 20th century was not solely a consequence of the advances in medical science, but also of the lack of regulatory oversight and ethical scrutiny. Rules governing the boundaries of responsible conduct in human experimentation evolved as both a consequence of egregious acts in the name of research and as an expression of collective outrage against perverse actions that exploited vulnerable subjects. The basic principles for the ethical

conduct of clinical research established the framework for imposing moral restraints on human experimentation, particularly in the context of health research where subjects were from disadvantaged groups. These rallied to ethical standards of accountability, respect for persons, risk-benefit ratio, and fairness.

Enforcement of these ethical standards during the conduct of, and subsequent public engagement with, clinical research was initially achieved through scrutiny by peer institutions and imperfect self-governance. Decades later, mandatory Institutional Review Board oversight eventually became codified in U.S. regulations, which mandated that an IRB review research proposals for humans and approval for investigational clinical studies intended to collect and evaluate data for new drugs or for new indications or new dosages of approved drugs before the study began. Later, similar regulatory requirements were implemented in Europe and other countries establishing Good Clinical Practice guidelines.

11.3. Key Ethical Principles in Medical Research

Research involving human subjects is predicated on ethical principles enshrined in ethical guidelines and is usually enforced through legal regulations and institutional review boards. The four main principles of medical research relate to respect for persons, beneficence, non-maleficence, and justice. Individualistic liberalism, based on a Kantian understanding of moral philosophy, grounds respect for persons to the extent that it requires that research protocols not coerce or mislead participants. This requirement leads to specific ethical mandates, such as requiring valid informed consent, allowing subjects to withdraw from research without penalty, and protecting the privacy of research participants. Respect for persons does not allow researchers to act arbitrarily toward research participants – to do so would violate the ethical requirement of not harming participants. Beneficence, the obligation to promote the welfare of others, represents in part the positive corollary to the prohibition of harm grounded in non-maleficence. In particular, the obligation to provide perspective benefit should be understood among respectful researchers as providing participants with counseling and/or clinical referral to established resources for any psychological or social problems that do arise during the length of the research study, without unnecessary delays. The principle of justice prohibits unfairly imposing research risks on vulnerable subjects and denying them the benefits of research. The principles of justice arise in different ways in the context of research, compared to clinical care. With research, risks may be unequal across groups – for example, a non-therapeutic clinical trial involving inducement could risk economic instability for impoverished people despite their being paid for participation. Yet, those non-therapeutic research risks would not be borne by other participants – wealthy people – who would not engage in the risk-laden research.

11.3.1. Autonomy

Research into human subjects must prioritize respect for persons, which recognizes personal autonomy and the necessity of checking the potential bias introduced by diminished autonomy. Autonomy means the liberty of individuals to make informed decisions regarding their persons. This respect for autonomous individuals is a recognition of their dignity and conveys the belief that they are capable of understanding their situations and of working toward goals with some degree of consistency. First, the research subjects must give consent, which is voluntary, informed, and adequately documented. Second, if the research subjects are individuals without decision-making capacity, any research should be preceded by appropriate approval from a recognized institutional committee.

Should the acceptance of this principle create an absolute ban on research in classes of individuals with diminished autonomy? Several prominent ethicists answer in the negative. Yet, this would leave wide open the relevant mosquito net to allow arbitrary decisions by ethics committees. Autonomy may also refer to the ability to make decisions about one’s health needs or treatments; autonomy requires that such health-related decisions be respected. This requires that people not suffer interference from others and have the capacity to decide for themselves. In practical terms, this means that patients have the right to refuse any offered treatment, a choice made freely and with thought, and that healthcare personnel follow this decision.

11.3.2. Beneficence

"Beneficence" is commonly interpreted as the principle of producing good or at least having the intention to do good. Much debate has been devoted to defining the "good". The simplest interpretation is that the "benefit" means reducing the risk of serious harm, and increasing the probability of viable treatment; this is known as the "positive benefit" interpretation. However, some have suggested that beneficence is more relevant to providing certain basic goods, such as access to a viable therapeutic option or some other compensation instead of enhancing one's chances of survival. Following a different interpretation, some argue that beneficence should focus on more than just the benefit provided by research; it should also relate to the good offered by the use of the new knowledge.

The two models of research ethics are heavily influenced by beneficence, either in the form of achieving a therapeutic "good" through research, or of providing benefits to

future participants and communities through research. Medical research is done in the name of creating knowledge that is meant to help others, meaning that researchers need to balance the risks people assume in providing samples, data, and other forms of participation against the benefits of that knowledge creation. Beneficence is the guiding principle for that balancing act. Researchers can never sacrifice research participants to bring forth new knowledge, no matter how grand the reward may be. Research ethics rests on that sacred trust: when people volunteer, it is not for self-gain, and it is not for altruistic purposes of curing humanity; it is to allow the researchers to work. How the costs and benefits relate to each other, and how those questions address the fact-specific questions of a particular research project, are the defining ethical issues in research.

11.3.3. Non-maleficence

The guiding ethical principles for permissible medical research and acceptable conduct of trials are numerous and vary in kind and number. One of the most enduring pathways, which has earned wide consensus, is the obligation to not harm. This necessity can be both a start and an end in itself. The starting point may be located in the Hippocratic Oath but is more importantly enshrined in various ethical codes that govern human experimentation. A few decades later, the Declaration of Helsinki took that obligation to the next level by defining components of an ethical medical experiment, delving into realms such as the relationship with the scientific community through the trope of publish or perish, and the integrity of data collected as a requisite for respecting human dignity and the rights of the research subject. Lately, the principle of non-maleficence has also been regarded as the rule of thumb of ethical practice in clinical research.

Non-maleficence is the prohibition of any act or conduct that results in any form of unwelcome, postponed, or otherwise damaging effect upon any human being engaged in medical inquiry, either directly or indirectly, intentionally or with negligence. Non-maleficence prohibits acts of wrongful malice, recklessness, or ignorant inattention that might put lives in jeopardy or change their destiny for the worse. Embedded in that obligation are both consequences and likelihood of bad or harmful outcomes from the research, the intention of the researchers, and how avoidable those acts are. In that duty of care, research participants are entitled to the observation of rules that will minimize the occurrence of negative side effects, ranging from a mere inconvenience to lasting, possibly lethal, harm. Yet, this is not only the decision of researchers; their behavior and accountability directly determine and shape those rules.

11.3.4. Justice

Thus, the principle of justice is concerned with ensuring the fairness of the distribution of the benefits and burdens associated with participation in research. Justice also encompasses a wider societal justice, calling for social policies that create the structural conditions that make research possible. Consequently, some groups should not be unfairly over-represented simply because they are more easily available or lack the means to refuse participation, while others should not be under-represented in research simply because of injustice or entrenched power relations, particularly when funding is involved, and the results may benefit them. This means that vulnerable groups should be included among research populations in cases when research is likely to benefit them, such as in most research in the fields of health and medicine, otherwise, they could remain 'research orphans'.

Justice amounts to issuing a general call for the particular types of trial participants who are chosen to reflect the types of people diverse in the characteristics relevant to the purpose of the study. Moreover, particular characteristics that, instead of acting as exclusion criteria, should lead to inclusion within a study population should be rendered transparent in order for researchers to justify using those characteristics as recruitment criteria. Adherence to justice thereby ensures that trial populations truly serve some benefit for the wider society, who provide the funding to enable the development of the new treatments and preventive measures being investigated. In other words: Why should healthy people, who neither have the disease that is being investigated nor are predicted to suffer from the consequences of using the preventive therapeutic, carry the exclusive burden of health research?

11.4. Regulatory Frameworks Governing Medical Research

Regulatory considerations governing high-stakes medical research are grounded in standards designed to promote ethical research on human subjects. Meaningful progress in medical research is largely reliant on public trust that researchers are acting in the best interests of research participants, and more broadly, of society as a whole. When participants perceive that the risks of research are being undertaken to benefit already vulnerable populations with little chance of personal gain and that the likelihood of direct benefit is not proportionate to the risks, societal trust in research is at risk. At the same time, expectations of effective oversight at the institutional and federal levels are high. Regulatory frameworks governing medical research were created in response to some of the worst atrocities against human subjects, where unethical conduct was allowed to proceed unchecked.

Regulations governing research on human subjects apply ethically appropriate conduct in order to protect them from undue risk. A historical examination of regulatory safeguards elucidates how these legal frameworks operate to ensure ethical research

practices and the gaps and tensions that currently exist. The following sections of this chapter provide a summary of relevant international and national regulations, as well as the roles and responsibilities of institutional review boards. These regulations serve as guideposts for the ethical conduct of medical trialists, but there are questions regarding their efficacy in protecting subjects from undue risks in trials of unproven therapies with profiles similar to those of the poor outcomes being studied. In other words, oversight of risky trials need to be overseen by an IRB with expertise in either the specific disease process or population under study or the proposed experimental treatment in order to protect subjects from undue risk.

11.4.1. International Regulations

Most international regulations set minimum ethical and scientific standards; each country can interpret and decide which additional regulations are warranted to protect their citizens' welfare. At the same time, many countries are eager to attract in-country funding or other support that successful clinical trials may bring. Robust established ethical infrastructures capable of a careful review of subject risk allow speedier transitions through the review process and faster initiation of trials, leading to economic boosts for troubled countries.

The central tenet is that biomedical research involving human subjects is performed only to benefit those subjects; no greater than minimal risk can be incurred to such subjects, and only if their informed consent has been given. It is not clear how much legal footing this guidance has, beyond generating pressure to comply. Adverse events brought to light during clinical trials may lead to lawsuits levied against sponsor companies, investigators, and institutions involved, even when trials are conducted according to established practices. An informative event underscoring the practical value of this guidance was a major class action suit against a sponsor company for deaths resulting from a clinical trial conducted in Nigeria that was attempting to establish the effectiveness of an anti-malarial medication. The people of the Sava River delta had been informed of the trial and agreed to participate; however, the basic organizational structure of the application seemed unsound, with only the consideration of treatment groups for the infected with the plan of outfitting with insecticide-reserved nets those families who were not so infected to protect the surrounding population.

11.4.2. National Regulations

The first national regulatory framework was established in 1966 to require ethical standards for federally funded biomedical and behavioral research. The regulations, titled Protection of Human Subjects, are primarily enforced through the relevant

authorities. In 1974, the newly established Office for Protection from Research Risks promulgated its regulations, Basic Policy for Protection of Human Research Subjects. Revised in 1981, they are concurrent with other regulations mandating the establishment of IRBs in a variety of settings. Since then, additional provisions with specific provisions for pregnant women, fetuses, neonates; prisoners; and children, respectively, have been added for special populations. Various agencies maintain additional regulations to meet their mandates. Subsequent federal regulations have been informed by findings of relevant commissions and reports.

Most research is overseen at the local level by IRBs established in university and corporate settings and college review boards at affiliated teaching hospitals. Most IRBs operate under an assurance from the relevant office to conduct or supervise relevant research on behalf of the federal government. Separate IRB approvals are required for regulated research. Because institutional review/ethics boards respond to local concerns, their decisions often differ from institution to institution. Disparities in decision-making may be addressed by agreement of the institutions involved — usually through an IRB reliance agreement — or by the relevant authorities through their guidelines.

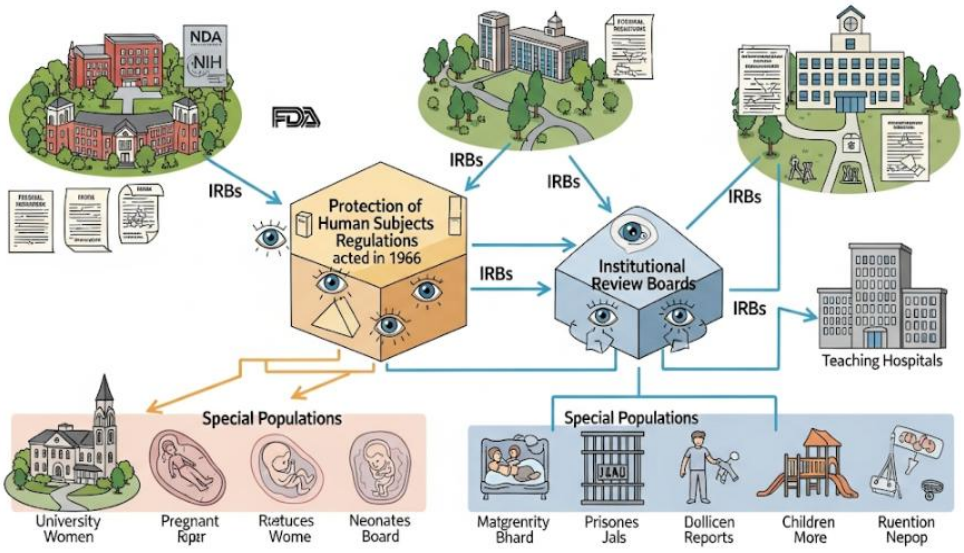

Fig 11 . 2 : The IRB Shield: Safeguarding Human Subjects in Research

11.4.3. Institutional Review Boards (IRBs)

Institutional Review Boards (IRBs) are regulatory bodies appointed by an institution to ensure the ethical conduct of research involving human subjects. IRBs serve a dual function. They fulfill the legal requirements outlined in regulations, and they ensure that an institution observes professional ethical standards of its choosing through

supplementary internal regulations governing the research that it sponsors. Fundamentally, IRBs serve to protect research subjects. The IRB assures itself that a research study is so designed to minimize risks, that benefits outweigh risks, and that subjects are adequately informed about the potential hazards of participation. To promote informed subject consent, the IRB reviews the information that will be provided to potential subjects for clarity, completeness, and accuracy. It also considers the proposed method for obtaining consent. If a research study's risk-benefit ratio is adverse, or if issues emerge concerning its informed consent process—for instance, if subjects are not provided adequate information or are coerced into participating—the IRB can require modifications to the study or deny approval altogether. IRBs pay close attention to issues regarding the relationship between researcher and subject as well as the subject's capacity for informed consent and therefore review the research plan to determine that subjects will be free of coercion or undue influence. When selection is equitable is another question of concern. IRBs also promote the protection of subjects from undue risks or exploitation. These issues led the federal government to require that researchers avoid subjecting vulnerable groups to research risks or inconveniences that may be considered undue. In particular, if a study may research doses of a study agent that are known to be toxic, subjects may not be classified as "healthy" because they are not at the full risk of the usual adverse effects of toxicity, the use of "healthy volunteers" is unacceptable.

11.5. Informed Consent in Medical Trials

Patients facing important medical decisions generally seek treatment to alleviate their immediate suffering. This retrospective focus may not allow them to grasp the important implications of their disease or treatment in some clinical trials. The sophisticated uncertainty surrounding the scientific purpose of the trial may impede their ability to understand its nature. These factors suggest that for Category 1 research, the focus ought to be on clinician-initiated therapeutic efforts to maximize patient welfare rather than truly informed consent.

Given the moral status of research as a form of social practice, Phase 3 RCTs have been criticized for being primarily concerned with the scientific righteousness of randomly assigning large populations in disregard of their moral agency. Enrolment in Phase 3 RCTs carries ethical charges producing tensions in the doctor-patient relationship. Doctors may both serve as an expert guide to their individual patient's medical future, while at the same time having an obligation to recruit for the device or procedure currently assigned to that cohort if it is believed to be the superior treatment option. Patients may struggle with making a choice when they know that the assignment may not be in their individual best interests, and feel the burden of Group Exemption to solve

the problem with clinical equipoise. They may worry that their decision impacts the process of reaching a scientific conclusion – that someone will go without the medicine, vaccine, device, or procedure that is of utmost importance to their health and well-being. These ethical issues suggest the need for a more robust approach to informed consent for Category 2 and 3 trials and especially Exempt Trials.

11.6. Vulnerable Populations in Research

Not all individuals in a society are equally positioned to resist exploitation, nor are they equally vulnerable to harm. As a consequence, Ethics and Regulatory Frameworks consider certain groups of individuals "vulnerable" concerning research and trials and hence accord them special protections from exploitation and maltreatment in the context of research and trials. Various individuals can belong to a shared vulnerable group of individuals, which then qualifies them for specific protections. When these groups participate in research and trials, ethics and regulatory issues not only concern the justice principle of fairness or lack of discrimination but also the beneficence principle of special care so that individuals do not suffer from high risks or burdens without possible gains. In this section, we want to explore the ethical principles and regulatory pathways concerning three vulnerable populations, which will be analyzed separately: children, the elderly, and pregnant women. These populations have been selected because they are represented in and have been excluded from research and trials in high numbers and with potentially grave adverse consequences not only for them as individuals but also for society at large that has an interest in gaining scientific knowledge concerning the development, aging, and reproduction by drawing clinical conclusions from such research and trial data. By studying these populations separately, we want to identify recurring patterns in vulnerable populations and their protection as well as specific features related to a specific population and its specific vulnerability. These similarities and differences help researchers, sponsors, funding agencies, organizers, and regulators to make better assessments concerning other special populations as well as the three specific populations when it comes to designing and conducting specific research and trials involving special individuals.

11.6.1. Children

As animals, children present formidable physiological and mental challenges, and their use in research and trials is ethically challenging. Children are necessarily involved in scientific research in a variety of disciplines that seek to understand a wide variety of aspects of child health and wellness, especially developmental biology, child

neuroscience, and pharmacotherapy. For all of the active research topics in the field of child health, the question remains, are we doing too much?

Child neuroscience research in children who are altered by congenital genetic diseases, injury, or infection can certainly help facilitate a better understanding of very abnormal neurodevelopmental pathways as they attempt to revert from gross abnormality to a more normative neurodevelopmental pathway. Neuroscience research using functional MRI or PET scans to assess brain function in children who are terminally ill or psychologically uncomfortable and are undergoing a life-ending procedure carries the questionable ethics of whether or not that knowledge gained carries significant benefit to the knowledge and understanding of – or optimization of treatments for – other children.

Due to the extended, gradual physical, emotional, and cognitive development of children, neurological and psychological aberrations, or terminal illnesses, child health issues are not easily generalizable to other healthy, older individuals, even adults who also experience the study of neurodegeneration and psychological aberrations in older individuals. Certainly, children along with other unique populations have been invaluable for the study of specific genetic aberrations and will continue to be part of genetic research and therapy studies.

11.6.2. Elderly

Older persons are often underrepresented in clinical trials, which may lead to the exclusion of the very individuals who may benefit the most from certain medical treatments. They experience more comorbidities, different pharmacokinetics, and drug interactions than younger patients. Guidelines ask for their inclusion and the population is usually over-represented in the recruited patients as the tested therapies are chronic, but there is still a discrepancy in the expected involvement and the real inclusion rate. Not all countries and age groups alike manage to achieve similar, worldwide representation. Funders should promote research on the older population and policies aiming to avoid health inequalities globally should be implemented. Failing to conduct research involving older persons could mean false extrapolation of the achieved results. Overall, the conduct of well-designed studies in older persons is desirable and could alleviate related challenges.

Pharmaceutical industry-sponsored clinical trials have historically been highly selective regarding eligibility criteria. The relatively small size and limited age range of participants have restricted the applicability of clinical trial findings to the general population. Therefore, data extrapolation from younger populations has been used to justify available therapies in older patients, even if healthcare professionals encounter

the latter more frequently in their medical practice. Exclusion criteria more likely featured age-related diseases and physiological age-related changes, but very importantly also clinical comorbidities and polypharmacy. Investigational therapeutic alternatives could therefore have undergone insufficient testing in individuals who would ultimately be prescribed such drugs. The wide criteria allowed in post-marketing research are not considered sufficient safeguards against such pitfalls, as in the long term, and most importantly with rare adverse events, possible complications may only be detected when drugs are marketed.

11.6.3. Pregnant Women

The inclusion of pregnant women in clinical research has long been controversial and problematic. Thus, even some groups support a more permissive environment for research on pregnant women than exists currently. Morality, they argue, suggests that a woman should be permitted to engage in research activities that may help her, which in turn may help the fetus, especially if there are no appropriate alternatives for the treatment of her conditions at stake and if there is no safety risk for the unborn child.

Informed consent documents have been criticized as the most impenetrable documents lawyers could devise. Even so, ease of understanding is particularly relevant in the case of pregnant women, as they may not only experience questions about a study from their perspective but also from the perspective of the fetus and of their role as the fetus' protector. Generally, in studies on pregnant women, controversy focuses on third-party risks. Yet, in some research, the fetus is an additional trial subject, with its potential seriousness for being associated with the risk of exposure to the investigational treatment, leading to ethical conflicts and disagreements.

These challenges raise the question of how such research should be adequately designed and conducted. Drawing on empirical evidence from an in-depth qualitative study with leading clinical researchers in the field, I explore central parameters constitutive of responsible clinical research on pregnant women, including the degree of necessity of the involvement of pregnant women, the inclusion of non-pregnant populations, the type of clinical study design, the specific interventions under investigation, the potential involvement of fetuses as trial subjects, the consent process, and other methodological and approval considerations. Moreover, I will point out lines of tension and difficulties that such research has to resolve as well as implications for future research policies. I argue that realistic and clinically relevant research questions must indeed be assessed via adequately designed clinical studies on pregnant women to advance scientific knowledge and to protect both mothers and future children in the long term.

11.7. Risk-Benefit Analysis in Clinical Trials

Overall, the goal of research is to demonstrate that a significant benefit can be gained from the implementation of a novel therapy or diagnostic tool. In conducting a specific study, researchers seek to demonstrate that the benefit of new knowledge outweighs potential risks and harms to study participants. If they do not, such an endeavor would not merit conducting the research. In such a manner, the probabilistic structure associated with research in humans contrasts with that of routine clinical practice, where the individual may bear all of the risk, while the physician may receive the entire benefit. Even within the different contexts of clinical research, however, this proposition is not consistently recognized. The ethical maxim of beneficence - that we should act in ways that lead to a good result - has traditionally been focused on minimizing risk. The belief is that as precautionary measures are taken to protect against evident and possible harm to study subjects, investing in a potentially unwarranted level of protection would not seem a violation of the ethical principle of beneficence. Following this rationale across fields of research may become overly strict and lead to diminished availability of research targeted at those whose disease process suggests they are not likely to benefit from the research itself. Reciprocity presents yet another angle from which the analysis of risk and benefit can be approached. Individuals who are engaged in research must participate in a process in which the larger community has a stake, even when they may not realize benefits from doing so. In this sense, individuals are a means to an end that somewhat extends beyond each one of their contributions. On some accounts, they are more than simple porters of risk, and perhaps less than simple conveyers of benefit - unsure agents whose every horizon is shorter than the time frame of the research. Rather, they help the research progress toward a desired product, and in doing so, they help the public advance to a larger goal. Noncelebratory urge that it is the very offering of "garnering generalizable knowledge" that authorizes not only reciprocal obligations toward research participants but also differential consideration of potential risk and potential benefit.

11.7.1. Evaluating Risks and Benefits in Clinical Research

Although the main focus in undertaking a clinical study is to document objective information about the effects of a drug or medical device in a given patient population, it also, and perhaps more importantly, aims at clearly establishing the risk-benefit balance that circumscribes the clinical indication(s) for the investigational product. Indeed, one of the main functions of regulatory review of industry-sponsored clinical trials is to review the potential risks and benefits associated with having a patient participate in the conduct of the study, to draw a conclusion as to whether the risks are reasonable about potential benefits and to protect the study participant in case of

unacceptable risk. In essence, the sole basis for regulatory approval of an otherwise unapproved drug or device is to be able to show that the intervention will provide a sufficient advantage over what the population could achieve untreated or treated with a placebo (benefit), that the risk of the intervention is acceptable compared to the increase in the likelihood of benefit (risk). If risks are greater than those posed by the disease and associated with treatment with these agents, the study may not be a valid endeavor.

This balance of risks and benefits is inherently subjective. Indeed, it is the view that the risk-benefit analysis is a matter of individual moral or ethical choice. Risk is only defined in proportion to benefit. A drug that has severe known risks that are outweighed by the patient's severe unresponsive underlying medical condition who will possibly die very soon if the drug is not taken may be thought acceptable for individual use. However, this is not the same as drug use to recruit individuals for a clinical trial in search of a compound that shows potential activity whose results might favorably influence the health of thousands of others around the globe. While the moral rationale for mandatory clinical trials before drug registration is based on a utilitarian principle, which focuses on the consequences to the overall population rather than to the trial participants, it is argued that the organization and conduct should nevertheless be such that individuals involved would hold a "moral status" equivalent to that accorded to persons outside the study.

11.8. Conclusion

Over the past two decades, we have witnessed the remarkable promise of human genetic and neural research and a set of fundamental ethical paradigms framed on principles of respect for individuals, and justice that protect our most vulnerable citizens. In reviewing the ethical and regulatory landscape for high-stakes research, we see significant gaps for consideration in moving this space forward. Such promising research on public benefit, cultural horizons to decenter Eurocentrism, and the need to provide greater consideration for group harms and representational justice beyond respect are necessary steps in the pursuit of possible decentering strategies and reconceptualizations for the major ethical principles. Looking into the future, we also argue that technologies that evolve from basic scientific discovery warrant a review of research oversight and regulation at a national and global level. Such regulatory efforts should not only consider the increasing number of actors, but also the need for enforcement mechanisms, as the work of monitoring the research environment is fundamentally the work of protecting human research subjects and their communities.

Thus, even as research and discovery lend us more capabilities, it may be necessary to increase the burden of expectation on the research community to ensure that the public interest and the benefits of mitigating group harms are at the forefront of invention and

innovation, especially at a time of global uncertainty and need. The call for improvement in scientific integrity, transparency, and honesty are themes echoed throughout this text that can only serve to strengthen the social fabric within which science evolves, as every researcher knows that research exists not in a vacuum, but in human communities that expect that greater goods emerge, in return for the privileges accorded to scientific inquiry.

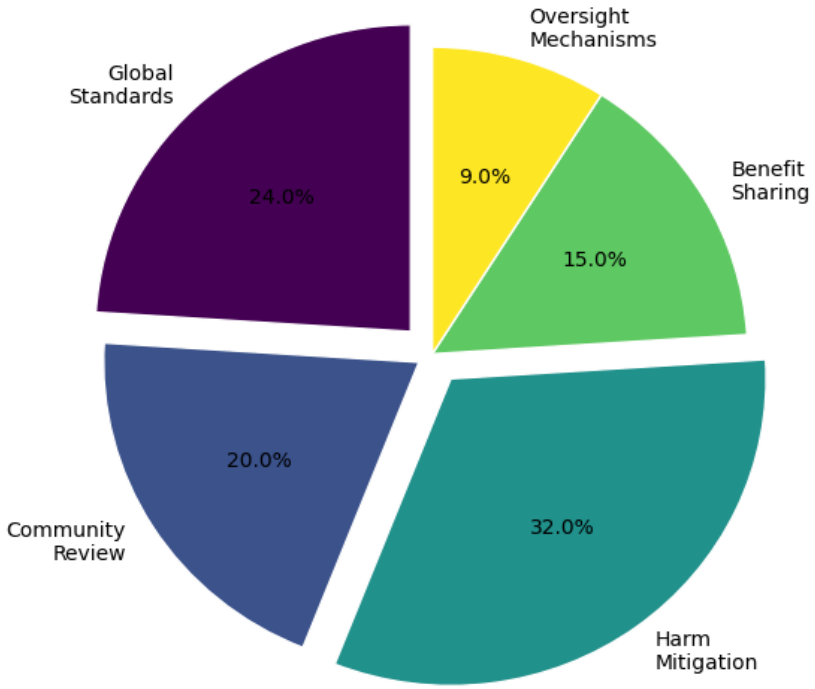

Fig 11 . 3 : Future Regulatory Priorities

11.8.1. Summary and Implications for Future Research

Conventional ethical guidance fails to resolve significant definitional ambiguity about what constitutes high-stakes medical research, as does the race and disability focus of regulations surrounding the inclusion of marginalized groups in research. Health inequities uniquely characterize some medical research, but not others, and we are skeptical that an ethic of care will resolve questions about which medical research is ethical or whether it is of sufficient import to the advancement of health that it be approved by an IRB. The conventional emphasis on the risk for research participants, however, is unwarranted for some high-stakes medical projects, and while health equity is not the only aspect that needs to be weighed in favor of approval, it is an important consideration due to the contextually defined asymmetry of interests. Furthermore, while

non-relational principles place minimal conditions of justification, we argue that the Justifying Conditions Model best captures the approval demands for projects trying to achieve a health-equity focus in high-stakes research. We end by briefly discussing two potential implications of our analysis: the creation of ethical committees focused on medical research targeting the health inequities of marginalized communities and the creation of a premium for studies that support and fund the capacity of the health systems of marginalized communities. The former would make explicit a condition of justified intrusion into the social fabric of these communities, while the latter would ensure minimal translation gaps in the uptake of the results back into those communities.

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