Self-funded Participation in Clinical Trials

A Principle-Based Analysis of a Medical Ethical Dilemma

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Content

Preface

In the course of our professional endeavors as scientific medical researchers, we have occasionally confronted scenarios where the ethical frameworks governing the execution of clinical trials involving humans appear to be in conflict with the individual ethical standards of the participating patients. These discrepancies occur particularly when a patient is instructed not to contribute financially to the clinical trial in which he or she is participating, but at the same time wishes to participate in experimental interventions that have not yet completed the full spectrum of validation or received formal approval from regulatory authorities.

Ethical considerations merging strict adherence to clinical trial protocols with the imperative need for individual and compassionate patient care lead to a multifaceted discourse that embodies both scientific rigor and ethical profundity. This requires a wording based on a nuanced understanding of the dynamic interplay between the promotion of collective health interests and the protection of the inviolable rights of the individual patient.

Recognizing that clinical trials are foundational pillars in the evolution of evidence-based medicine, their design and execution necessitate strict adherence to established protocols to ensure the validity and reliability of results. However, this procedural rigor often stands in stark contrast to the individualized, empathetic care of patients, whose unique physiological, psychological, and socio-cultural contexts need to be considered. The ethical discourse thus pivots on an ethical conundrum: how to balance these seemingly divergent imperatives in a manner that preserves the scientific integrity of clinical research while respecting the intrinsic dignity and individuality of each patient.

In this context, it is essential to place ethical discussions within a wider social framework that is cognizant of the societal mandate to promote collective health equity while steadfastly upholding the ethos of individual patient autonomy. This comprises an empathetic engagement with patients' life experiences and the inclusion of their voices and perspectives in the decision-making processes for clinical trials. By doing so, we can strive to develop ethically robust frameworks that are not only scientifically sound but also in line with social justice principles.

To achieve a synthesis, it is crucial to foster a climate of interdisciplinary collaboration, drawing on the expertise of ethicists, clinicians, researchers, and patient advocates. Ethical scrutiny should not be considered a static checkpoint but rather as an ongoing, dynamic process that evolves in response to new scientific discoveries, emerging ethical paradigms, and the shifting landscapes of societal values.

Moreover, by integrating principles of shared decision-making, transparency, and accountability into the governance of clinical trials, we can create mechanisms that both respect patient autonomy and adhere to rigorous scientific standards. This integrative approach necessitates the use of innovative methods, including adaptive study designs that allow for a flexible response to individual patient needs, as well as the incorporation of real-world evidence to complement randomized controlled trials.

In conclusion, *the balancing act between strict adherence to clinical trial protocols and the need for individualized and compassionate care* demands a sustained and concerted effort towards ethical diligence and interdisciplinary synergy. Only through unwavering commitment can we strive for an equitable synthesis that honors both the integrity of clinical research and the dignity of patients. This venture *is not merely an academic or scientific challenge but a profound ethical undertaking that speaks to the core values of humanity and the collective pursuit of health and well-being for all.*

While it is generally accepted that a patient should not have to pay for his or her participation in a clinical trial, the Nuremberg Code, which for the first time established guidelines for medical experiments on humans, contains no such provision. Nowadays, we can observe that more and more patients with potentially untreatable or fatal diseases are given hope of cure or improvement by newly discovered drugs or procedures. Often these treatments are still in the early stages of clinical trials and are not freely available. Since 2014, the governments of nearly all US states have passed new laws known as “right-to-try” laws, which are intended to give terminally ill patients access to experimental therapies. At the same time, health insurance companies are being asked to cover the costs of these unapproved drugs and to pay for their clients’ participation in new clinical

trials. In this review, the authors use ethical principles and a real-life case study to analyze whether it is ethically acceptable for a patient to cover all or part of the costs for his or her participation in a clinical trial.

We would like to make it clear that, as physicians and surgeons, we support the Nuremberg Code and subsequent guidelines. We also adhere to fundamental principles such as the need to respect and protect human dignity. Human dignity is a complex and multi-layered concept, often discussed in the fields of ethics, philosophy, and human rights. It defines human dignity as the inherent, equal worth of every individual, simply by virtue of being human. The concept of human dignity is universally valid, inviolable and includes autonomy and respect. It therefore recognizes the autonomy of individuals and their ability to make decisions about their own life. Respecting these universal aspects of human dignity is one of the most noble and indispensable tasks of the physician.

The second most important aspect of the medical profession is set out in the principle: “primum non nocere, secundum cavere, tertium sanare” (first, do no harm, second, be careful, third, heal). This wisdom was established around the year 50 AD by the physician Scribonius Largus at the court of the Roman Emperor Tiberius Claudius. It states unequivocally that a physician must not harm anyone in his care and must heal. *If healing is only possible with new, not fully tested drugs or procedures, if there are no funds available for adequate medical trials, is it not the doctor’s duty to advise his patient to consider paying if this would allow him to enter a clinical trial that might cure him, prolong his life or alleviate his suffering?*

We regard the search for a balanced answer to this question based on an in-depth review not only as an academic exercise, but as a medical-ethical imperative with considerable practical benefits.

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1. Introduction

Since the end of World War II in 1945, a lasting and solid consensus has emerged among medical ethicists, legal scholars, philosophers, and practicing physicians that clinical trials involving humans must adhere to strict legal and medical-ethical safeguards [1–4]. These precautions are based on an interaction of fundamental ethical principles aimed at protecting vulnerable and dependent individuals. They include the imperative that test subjects must have the capacity for autonomous decision-making facilitated through informed consent, as well as the requirement of the necessary checks on the authoritative power exercised by experts over laypersons.

The ethical imperatives guiding these safeguards emanate from a rich historical context. The principle of protecting the weak and dependent ensures that individuals who may be frail, incapacitated, or otherwise vulnerable are shielded from coercion and exploitation. The autonomy of human research subjects, an essential principle in medical ethics, demands that individuals are fully informed and comprehend the nature, purpose, risks, and potential benefits of the clinical trial, thus enabling them to make enlightened decisions free from undue influence. Furthermore, the control mechanisms designed to limit the disproportionate influence of experts serve as crucial bulwarks against the potential abuse of power, ensuring that the interests and well-being of test subjects are paramount.

The need for such rigorous ethical standards is clearly illustrated by the outrageous historical precedents of human experimentation. Since ancient times, when rudimentary forms of human experimentation were documented, to the egregious transgressions of the 20th century, most notably under the Nazi regime during the so-called Third Reich, history is replete with examples where the absence of binding ethical safeguards led to abhorrent violations of human rights and dignity. The culmination of these unethical practices in the Third Reich has indelibly underscored the necessity for a sound ethical framework governing clinical trials, thus shaping contemporary standards and practices.

Overall, these ethical and legal constructs not only reflect an obligation to uphold the dignity and rights of human trial subjects but also signal a collective acknowledgment of the profound moral responsibilities inherent in conducting medical research. The safeguards established after 1945 serve as a testament to the lessons learned from historical atrocities and underline the unwavering dedication to ethical integrity in clinical experimentation.

1.1 Historical Background Emphasizing the Need of Ethical Standards

The "Aktion T4" program, an infamous aspect of Nazi Germany's racial policies, systematically exterminated approximately 72,000 individuals within Germany, primarily children and adolescents suffering from severe neurological and physical disabilities. These individuals were subjected to a variety of lethal methods, above all intracardiac phenol injections and, subsequently, gassing. These brutal killings took place within institutions that were euphemistically labeled as sanatoriums. Relatives of the victims were usually misinformed by standardized letters that falsely stated the cause of death as pneumonia and indicated that the funeral has already been held [5, 6].

From a historical perspective, it is essential to understand the meticulously orchestrated progression of the T4 program, which initially targeted life classified by the Nazi regime as "unworthy of life" ("lebensunwertes Leben"). This process entailed extensive identification, transportation, and extermination protocols facilitated by a network of medical professionals complicit in these crimes [7]. As the program progressed, its administrators planned to expand the scope to include individuals with severe cardiac conditions, who were derogatorily referred to as "useless eaters" [8]. However, this extension was ultimately aborted due to the anticipated public opposition.

Politically and psychologically, the decision not to further extend the T4 program underlines a significant social dynamic. Public resistance arose when the killings threatened a broader section of the population, which may

have included the relatives of many citizens. This is in sharp contrast with the scarce opposition encountered when the victims were predominantly persons with severe disabilities, a demographically and socially isolated group with whom the majority of the population had little direct interaction [9]. The divergent response emphasizes an unsettling utilitarian calculus at work in the population: widespread societal resistance—or the lack thereof—was strongly influenced by personal interests rather than principled stances against the inherent immorality of such actions.

From an ethical perspective, this disparity in the degree of resistance, based on the perceived social value of the victims, raises profound questions about moral responsibility and collective ethical behavior. It reveals a disturbing tendency towards moral complacency or selective empathy. The broad social acquiescence during the initial phases of the T4 program illustrates a failure to recognize and defend the intrinsic value of every human life, regardless of its perceived utility or social connection [10].

The ethical lapses evident in the relative silence surrounding the extermination of a marginalized minority highlight the importance of promoting inclusive ethical paradigms that recognize and protect the dignity and rights of all individuals, regardless of their physical, cognitive, or social status [11].

The history of medical experimentation involving humans extends far beyond the notorious examples from the Third Reich and the Japanese forces in Manchukuo during the Second World War. These incidents, while egregious, represent only a part of a broader, more complex narrative that encompasses various historical periods and ethical paradigms.

To comprehensively understand the ethical development and implications of human experimentation, one must look far back into the past of medical practices and philosophies. Ancient texts, such as the Hippocratic Corpus, already hinted at the moral concerns surrounding medical practices, advocating for principles like “do no harm.” These texts, however, were not always adhered to, and historical records from different cultures reveal instances where these principles were violated [12].

The practice of vivisection and ethically unacceptable medical

experimentation has marred the annals of history across various civilizations and periods. In ancient Persia, individuals condemned to death were often handed over to physicians for vivisection. This early form of human experimentation was based on the belief that direct examination of the living body was quintessential for the progress of medical knowledge. The rationale was that the suffering and eventual demise of a few individuals could potentially yield substantial benefits for the broader population.

The practice of vivisection is also well documented for the Alexandrian physicians Herophilus and Erasistratus during the era inaugurated by Attalus III of Pergamon in the 2nd century BCE. According to Celsus and Tertullian, these physicians performed vivisections on convicted criminals because they were convinced that the agony endured by these unfortunate individuals could advance the cause of medical science and lead to significant therapeutic breakthroughs [13–15].

This same line of reasoning persisted into the 20th century manifesting itself in the inhumane experiments conducted in the Nazi concentration camps during World War II. Here, countless victims were subjected to torturous and fatal experiments under the guise of medical research. Third Reich, for example, faced significant casualties among its pilots due to Soviet military operations on the Eastern Front and therefore sought to understand the physiological impacts of extreme cold. Consequently, prisoners were forced into pilot's gear and submerged in ice-cold water tanks to study the process of human hypothermia and potential rewarming techniques. These so-called medical experiments were carried out without any consent and led to the deaths of numerous prisoners [16].

Likewise, the Third Reich conducted altitude experiments on prisoners, exposing them to conditions that simulated high-altitude flights, which often led to their deaths. These experiments, like the hypothermia studies, were carried out with complete disregard for the lives and autonomy of the prisoners [16].

Similar atrocities were observed in Japanese-occupied Manchuria during the same period. Units such as the infamous Unit 731 performed vivisections without anesthesia on prisoners of war who had been deliberately infected

with pathogenic organisms. These ghastly experiments were intended to study the progression and impact of various diseases but led to unparalleled human suffering and death [17].

Even peacetime and democratic governments were not immune to ethically indefensible medical practices. The Tuskegee Syphilis Study, conducted over a staggering period of four decades between 1932 and 1972, is a notorious example. In this study, the United States Public Health Service observed the natural progression of untreated syphilis in African American men under the pretense of free medical care. Despite the availability of effective treatment in the form of penicillin, the participants were deliberately left untreated to provide data on the disease's natural history, leading to numerous preventable deaths and profound ethical violations [15, 18].

These historical examples demonstrate a recurrent theme of the subordination of individual human rights to a supposedly broader scientific or governmental benefit. The consistent use of morally reprehensible methods in both autocratic and democratic regimes serve as a vivid reminder of the perennial ethical challenges of medical research. The discourse on these issues continues to evolve, emphasizing the need for stringent ethical standards and rigorous monitoring to prevent the recurrence of such misconduct. The principle of informed consent and the respect for human dignity must remain paramount in all scientific endeavors to preserve the integrity of both medical practice and societal values.

[1] In July 2007 the public German TV-channel SWR claimed that Beecher was involved as scientific expert with CIA studies on human drug experiments in the 1950s and may have contributed with his work in the United States and in secret CIA prisons in Western Germany to the KUBARK Counterintelligence Interrogation document of 1963. According to these recent reports, and also according to US-historian Alfred W. McCoy, Beecher was scientifically responsible for human experiments with drugs (e.g. mescaline) conducted by the CIA in post-war Germany.

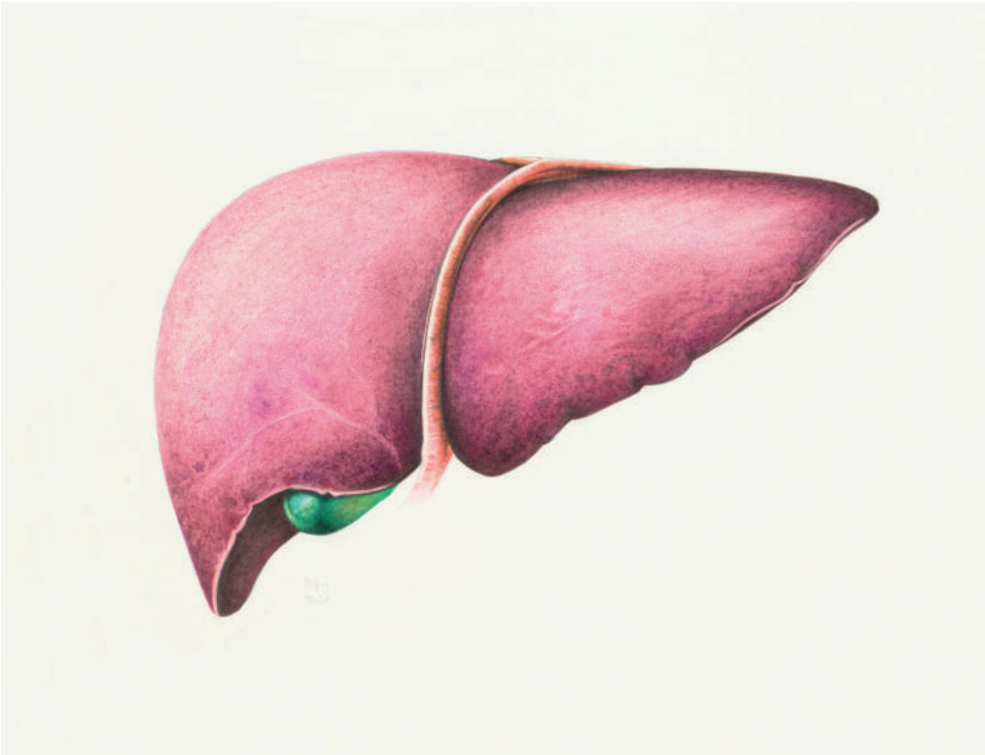

Fig. 1 Healthy liver

The liver is a major metabolic organ, which performs many essential biological functions such as detoxification of the organism, and the synthesis of proteins and biochemicals necessary for digestion and growth. Its other metabolic roles include carbohydrate metabolism, the production of hormones, conversion and storage of nutrients such as glucose and glycogen, and the decomposition of red blood cells. The liver is also an accessory digestive organ that produces bile, an alkaline fluid containing cholesterol and bile acids, which emulsifies and aids the breakdown of dietary fat.

Source: https://en.wikipedia.org/wiki/Liver (18.6.2024)

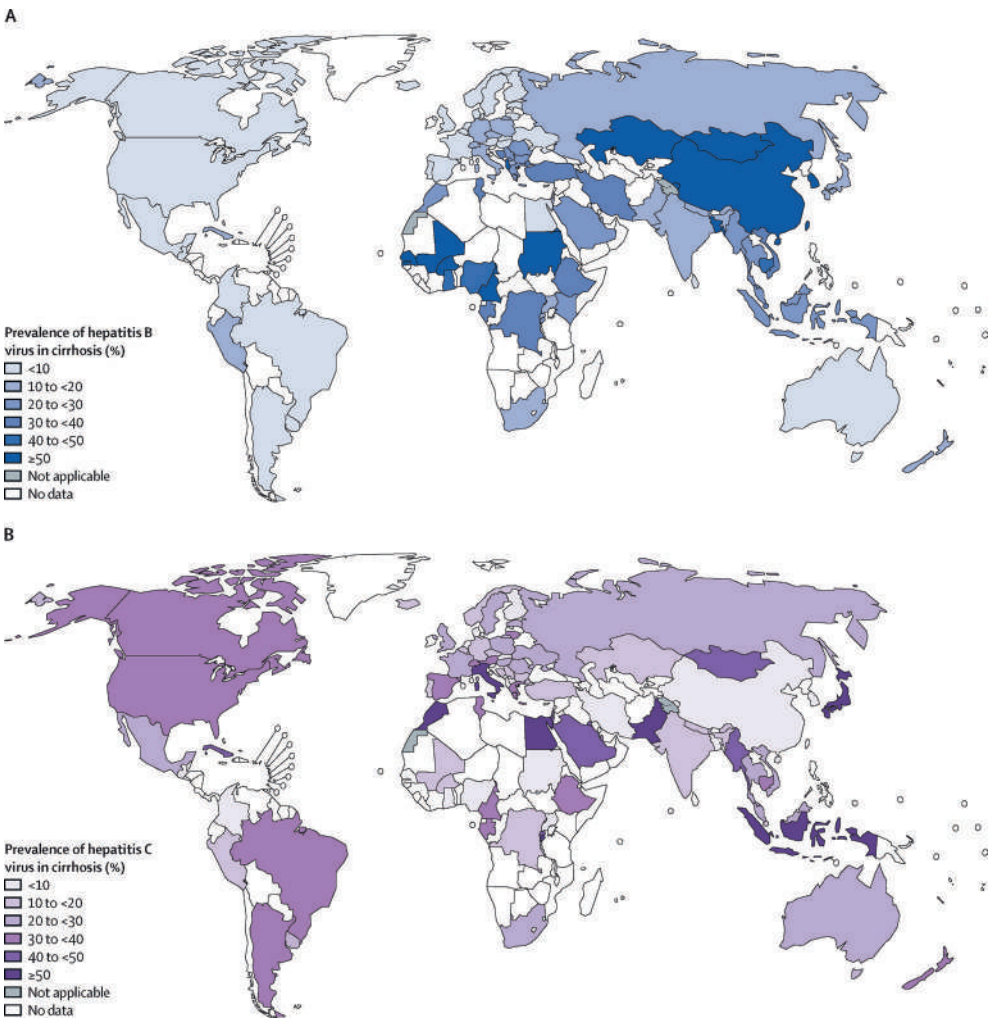

Fig. 2 Country-specific pooled prevalence of hepatitis B virus (A) and hepatitis C virus (B) infection among patients with cirrhosis

Source: **Catharina J Alberts, Gary M Clifford, Damien Georges, Francesco Negro, Olufunmilayo A Lesi, Yvan J-F Hutin, Catherine de Martel.** Worldwide Prevalence of Hepatitis B Virus and Hepatitis C Virus Among Patients With Cirrhosis at Country, Region, and Global Levels:
A Systematic Review. Lancet Gastroenterol Hepatol 2022; 7: 724–35.

Fig. 3 Viral infection with hepatitis B and C or “the tip of the iceberg”

When discussing hepatitis infections, the metaphor of the iceberg is an effective way of illustrating the clinical picture and epidemiology of the disease. It clearly shows that visible symptoms represent only a small part of the actual burden of the infection.

Fig. 4a-e Development of liver cirrhosis in microscopic view

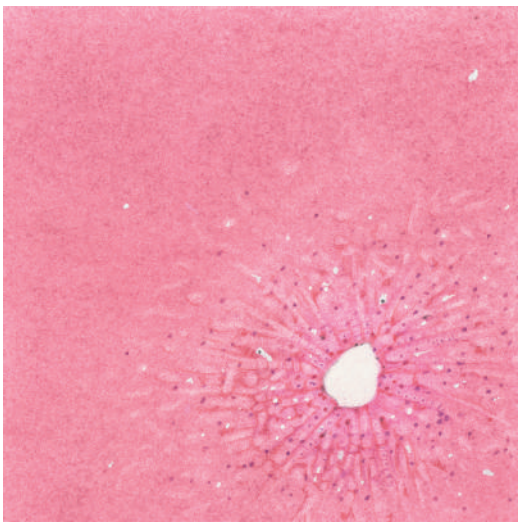

Fig. 4a Normal liver

Hepatocytes arranged in plates, typically one to two cells thick. Sinusoids between hepatocyte plates. Portal triads visible, containing branches of hepatic artery, portal vein, and bile duct. Central vein visible (white oval). Uniform nuclear size and cytoplasmic staining of hepatocytes.

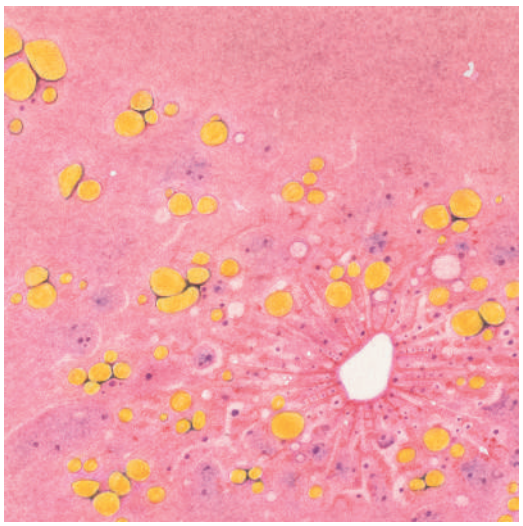

Fig. 4b Fatty liver (steatosis)

Hepatocytes with large, clear vacuoles (yellow spots). Displacement of the nuclei to the periphery of the cells. In some cases, small lipid droplets may be present. Generally preserved liver architecture.

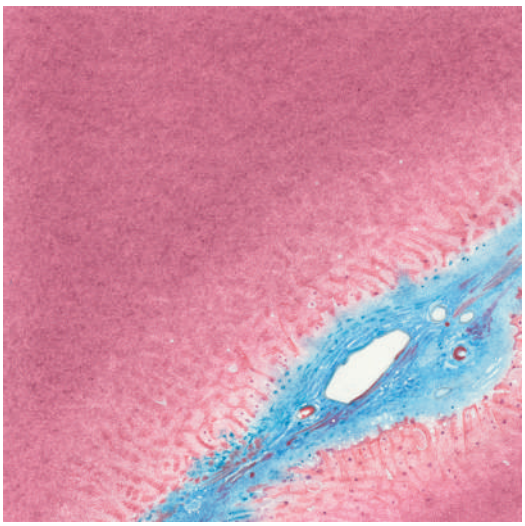

Fig. 4c Fibrotic liver

Increased deposition of collagen fibers, typically starting in periportal areas. Dilation of portal tracts (blue). Early formation of fibrous septa. Hepatocyte plates may appear distorted.

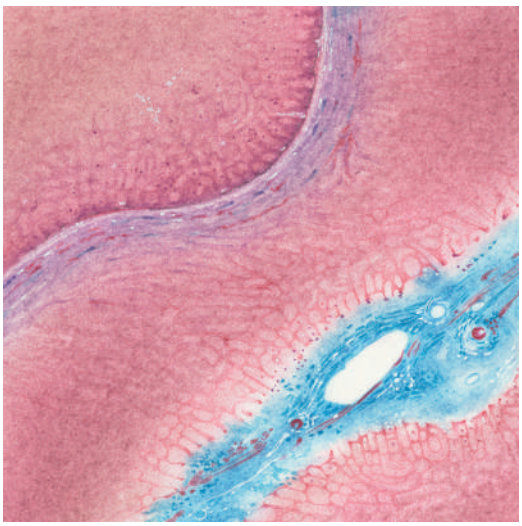

Fig. 4d Cirrhotic liver

Extensive fibrosis (blue) with formation of regenerative nodules (upper left semi-circle). Distortion of normal liver architecture. Thick fibrous septa surrounding the nodules. Variable size and appearance of hepatocyte within nodules.

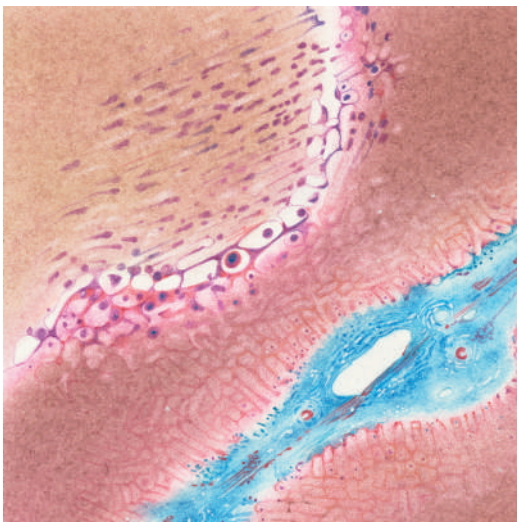

Fig. 4e Liver cancer

Loss of normal liver architecture (upper left corner). Absence of portal tracts within the tumor. Nuclear pleomorphism and hyperchromatism (changes in the nucleus). The surrounding liver tissue shows cirrhotic changes. Cancerous hepatocytes loose their structure and shape and infiltrate the cirrhotic environment. Trabecular or solid growth patterns.

Fig. 5a-e **Development of liver cirrhosis in macroscopic view (square illustration) based on microscopic changes (round illustration)**

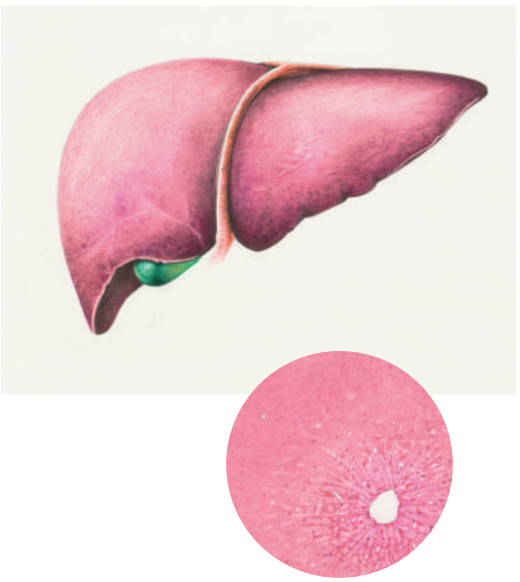

Fig. 5a Healthy liver tissue

The liver shows normal, well-organized hepatic cells with a typical lobular architecture and an adequate blood supply. The hepatocytes are uniform in size and shape, with healthy, functioning bile ducts and minimal connective tissue.

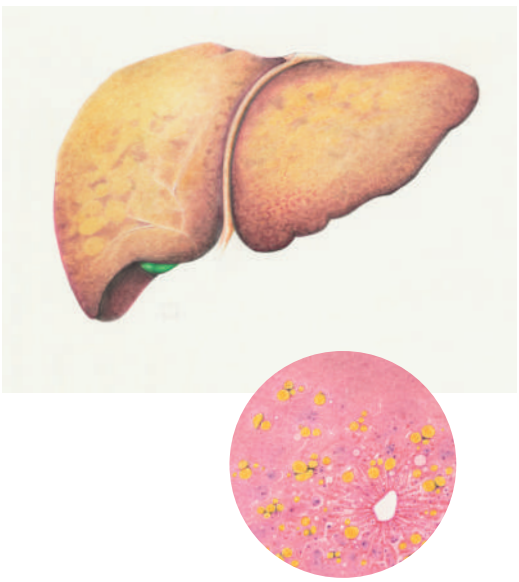

Fig. 5b Fatty liver/liver steatosis (early stage of liver damage)

The liver tissue shows an accumulation of fat within hepatocytes, making them appear swollen and distended. While liver architecture generally remains intact, the excessive fat deposits indicate the initial stage of liver degeneration.

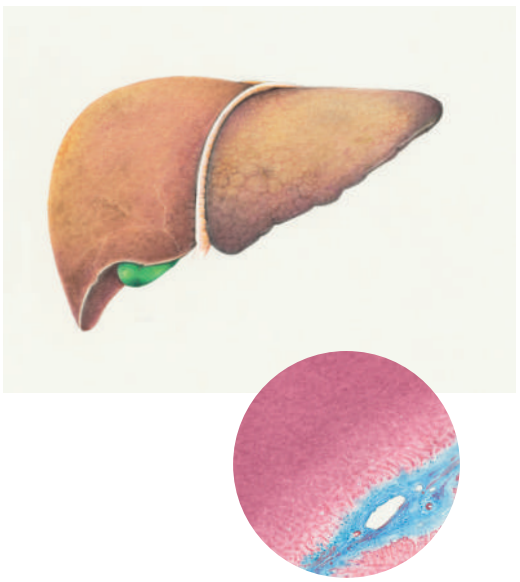

Fig. 5c Fibrosis liver (intermediate stage of liver damage)

The liver shows extensive formation of fibrous tissue (scar tissue) that disrupts the normal architecture and blood flow. This stage illustrates an intermediate phase in which collagen and extracellular matrix components accumulate, entangle the hepatocytes and begin to impair liver function.

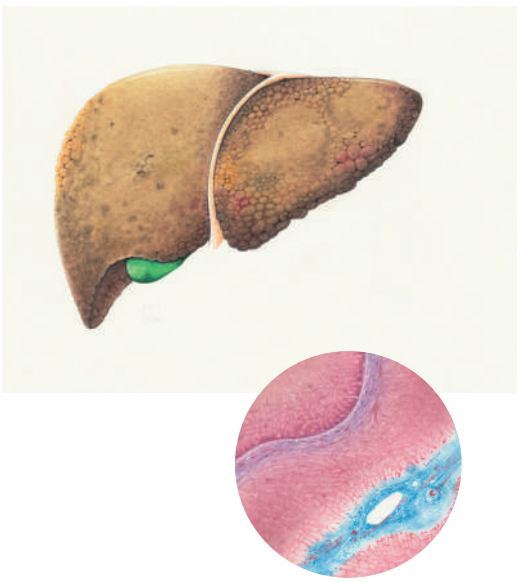

Fig. 5d Cirrhosis liver (advanced stage with irreversible damage)

The liver has developed advanced, widespread fibrosis with the formation of regenerative nodules throughout the tissue. There is significant architectural distortion, and normal liver function is markedly impaired. This stage is irreversible.

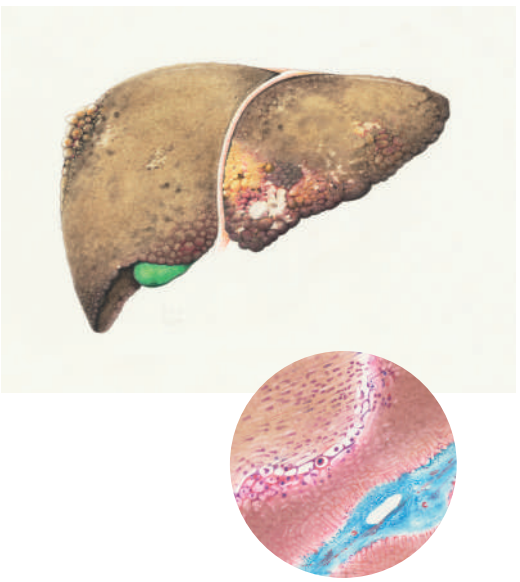

Fig. 5e Liver cancer (final malignant progression)

Malignant tumors are visible in the cirrhotic tissue. These hepatocellular carcinomas (HCC) appear as irregular, invasive masses, reflecting the aggressive nature of HCC development against a background of cirrhosis. Multiple lesions are often present, depicting the multicentric origin common in HCC.

Fig. 6 HEPADUA® Matrix Implant

Figure 6 shows the HEPADUA® Matrix before (left) and after (right) cell seeding. The red color is used to stain the cells. If they are reddish, this means that the cells are viable.

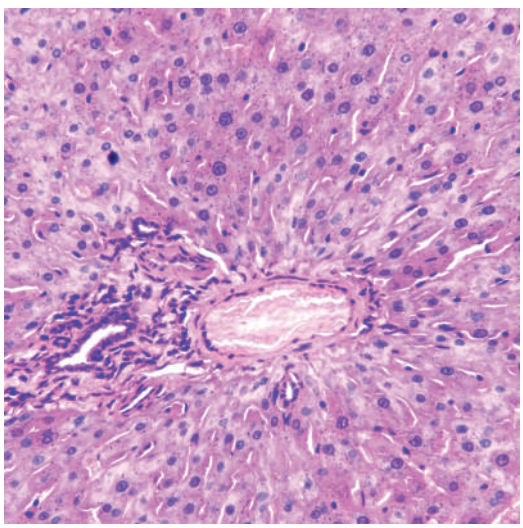

Fig. 7a Normal rat liver tissue in microscopic view

Hepatocytes arranged in trabeculae, typically one to two cells thick. Sinusoids between hepatocyte plates. Portal triads visible, containing branches of hepatic artery, portal vein, and bile duct. Central vein visible (white oval). Uniform nuclear size and cytoplasmic staining of hepatocytes.

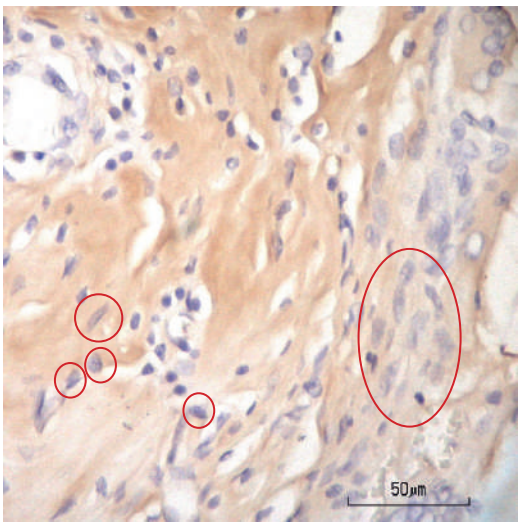

Fig. 7b HEPADUA® Matrix Implant in rat model in microscopic view (2 months after implantation)

The red circles show hepatocytes that are still round and beginning to take on oval shape. The oval red circle shows purple-colored hepatocytes that are already beginning to grow in clusters (at 2 months). At four months, liver-like structures with fully developed hepatic trabeculae appear.

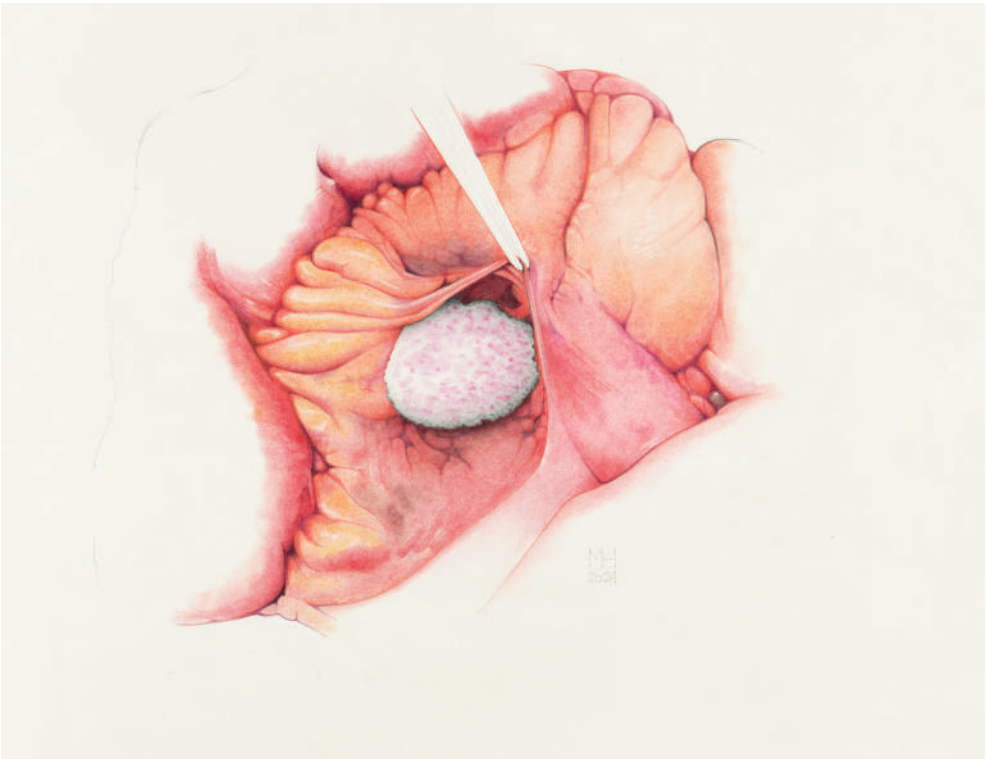

Fig. 8 HEPADUA® Matrix Implant in the mesentery of the small intestines

The figure shows the open pocket of the mesentery and the matrix being implanted. The reddish color indicates that the implanted cells are viable. From the pocket, all the venous blood enters vessels that lead to the portal vein and then to the liver parenchyma.

4. Medical Ethical Analysis

4.1 Introduction

Is it ethically permissible for participants in a clinical trial to bear all or part of the costs of their trial? As already mentioned, the investigation of this question is divided into three separate parts.

1. *The clinical trial is unethical because it imposes costs on the trial participants.*
2. *The clinical trial is conducted on vulnerable patients. As the volunteers suffer from severe liver disease with no other effective treatment option, they are unable to assess the consequences of participating.*
3. *The procedure of abdominal surgery with segmental liver resection and subsequent implantation of miniature liver pieces just two days later is a high-risk procedure.*

In the following text, the three theses will be analyzed using ethical methods. Based on biomedical principles and concepts, arguments are presented for the position that the participant-paid clinical trial is ethically justifiable. The ethical analysis will be guided primarily by the principles of Tom Beauchamp and James Childress [19, 26] and the values of William David Ross [105], as well as medical and surgical guidelines and ethical standards, and other research on the topic [38, 82]. The analysis will also take into consideration the potential risks and benefits to the individuals participating in the clinical trial, as well as the importance of informed consent and patient autonomy. The ethical implications of conducting such a high-risk procedure with the hope of advancing medical knowledge and potentially saving lives will be carefully examined. *Overall, the analysis will aim to provide a comprehensive understanding of the ethical considerations involved in this complex medical situation.*

In addition, in a comprehensive medical ethics analysis of a clinical trial, it is essential to thoroughly review the research objectives, methodology, and procedures as described in the investigator's brochure and trial protocol. By doing so, one can assess the potential risks and benefits to participants, evaluate the adequacy of the informed consent process, and ensure appropriate protection for vulnerable populations participating in the

study. To ensure that the clinical trial is conducted responsibly and ethically, it is crucial to understand the ethical principles and values underlying the design and conduct of the trial. By systematically considering all factors, researchers can ensure the integrity and safety of the clinical trial while adhering to the ethical standards in medical research.

4.2 Background

The principal investigator of the mini liver clinical trial being analyzed here, and one of the authors of this publication, is an experienced hepatobiliary surgeon working in a prestigious Swiss group of private hospitals, the Klinik Hirslanden, where he is duly accredited. During his formative years as an abdominal surgeon, he was involved in a large liver and kidney transplant program. He was often confronted with the problem of chronic liver cirrhosis, whether due to hepatitis, alcohol abuse, or non-alcoholic steatohepatitis (NASH). His deep concern that many patients with chronic or even decompensated liver cirrhosis would certainly die within a few months was the catalyst for the development and clinical trial of a novel treatment approach. He therefore established a long-term collaboration with a leading Asian university, Tarumanagara University (UNTAR) in Jakarta and a group of private hospitals, the private R.S. Gading Pluit Hospitals in Jakarta. He was also granted permission to teach hepatobiliary surgery by the country's surgical association.

The work in Indonesia raised awareness of the extent of untreated hepatobiliary problems in the country, particularly cirrhosis. Many patients suffered from chronic hepatitis, which eventually led to cirrhosis, impaired liver function, decompensated cirrhosis and ultimately death. In addition, Indonesia has very limited resources for organ transplants.

The collaboration with Tarumanagara University and the private R.S. Gading Pluit Hospitals in Jakarta proved to be a fruitful endeavour, as it provided access to state-of-the-art facilities and specific expertise. The partnership opened up opportunities for international collaboration and knowledge exchange in the field of regenerative medicine. Together, significant

progress was made in tissue engineering, particularly in the development of cell matrix implants for the treatment of liver diseases. Prior to this, the hepatobiliary surgeon had become aware of an innovative procedure that was still at an early stage of development. The novel method represented a promising treatment approach to alleviate or even improve the health of patients with chronic or decompensated liver cirrhosis by implanting the body's own hepatocytes.

Efforts to further develop the therapy were driven forward by the establishment of a certified laboratory with biosafety 2 level, good laboratory practice (GLP) and institutional good manufacturing practice. A grant from a private sponsor and the surgeon's/principal investigator's own financial resources made it possible to complete a Phase I clinical trial. Fifty patients were examined as part of the Phase I trial, eleven of whom were ultimately selected for implantation. All patient costs and the associated laboratory costs were covered during this phase.

Additional funding from the hepatobiliary surgeon has enabled the research laboratory to manufacture the matrix scaffolds in-house, ensuring quality standards, product freshness, and adaptation to local requirements and standards. The laboratory can now provide a product that is significantly better than the matrices used in the Phase I trial in terms of surface hydrophilicity, cell adhesion rates, cell viability, and cell survival rates. The next step on the way to approval by the responsible authorities would be a Phase II clinical trial to prove the efficacy and safety of the improved medical procedure.

As further financial support for the project exceeded the surgeon's/principal investigator's own resources, more than fifty potential sponsors in Asia and Europe were approached. However, they were reluctant to finance a medical treatment whose efficacy had not yet been proven in a Phase II clinical trial. Most investors indicated that they were interested in the new treatment approach, but that it would first have to be approved by a regulatory authority before financing (for which Phase II and III trials would have to be completed). Funding from the financial industry, banks, the private sector (including crowdfunding), government and other bodies (such as NGOs) is almost impossible until at least a Phase II trial has been completed. *This*

lack of funding in the early stages of development often leads to delays in bringing potentially life-saving medical treatments to market. Without the necessary resources to conduct Phase II trials, many promising products and procedures may never reach the patients who could benefit from them. To overcome this hurdle, it is imperative that researchers and developers find alternative sources of funding, such as partnerships with academic institutions or collaborations with established companies in the healthcare sector. Ultimately, the success of a new medical treatment depends on securing the financial support required for the complex and costly process of clinical trials and regulatory approval.

Patients have not yet been asked to contribute to the considerable costs. However, for the Phase II clinical trial, approval was requested from the Ethics Committee of the Ministry of Health in Indonesia to be able to demand a financial contribution from patients for their participation in the clinical trial. This procedure aimed to regulate the financial aspects of the clinical research while maintaining ethical standards and transparency throughout the process. Approval for cost sharing was not granted. The reasons for this decision by the Indonesian Ethics Committee of the Ministry of Health form the basis for our in-depth ethical analysis of self-funding by participants in clinical trials in the following sections 4.3 to 4.5.

The costs of conducting clinical trials are made up of various components such as accommodation, surgical fees, laboratory costs and disposable materials. These factors determine the expected cost of treatment. Since patients with advanced cirrhosis must be closely monitored to ensure best practice in current therapy, hepatologists need to consult the patients and carry out regular laboratory blood tests. In the proposed Phase II clinical trial, it is intended that these investigations will be carried out independently of enrolment in the clinical trial. To keep costs at a reasonable and minimal level, the clinical trial protocol will require a minimum of additional testing beyond standard care. The pre- and post-operative fees for hepatologists and laboratory tests will be equivalent to the patient's current out-of-pocket costs for the necessary follow-up as part of standard care.

In total, the principal investigator of the clinical trial has already invested USD 6 million for the entire costs of developing improved scaffolds, operating the laboratory, and conducting the Phase I clinical trial. The construction costs for setting up the laboratory and maintenance of around USD 3 million were borne by the university. For the further procedure, 15 patients would have to undergo surgery and at least 15 other suitable patients would have to be closely followed up under best conservative care as control group. The cost per patient operated amounts to around USD 20,000 and is sponsored by an unconditional grant from the Tarumanagara University (UNTAR). All costs for post-operative follow-up examinations over two years with laboratory tests, fibroscan and other examinations are covered by the principal investigator. The hospital would charge its costs of around USD 20,000 per patient for care in the intensive care unit as well as the doctors' costs to a minimal extent to cover its cost price.

However, the two groups of 15 participants will not be sufficient for a reliable statistical comparison. *In the current situation, a clinical trial with enough patients to achieve statistically relevant results would only be possible if the participants are able to pay their share of the clinical trial costs.* The disclosure of past investments and future costs for a Phase II clinical trial and the modest cost recovery fees charged by the hospital demonstrate that trial participants would not be charged excessive or for-profit payments. All patients in the Phase II trial would be charged the same amount. The completed Phase I clinical trial has demonstrated that the new procedure is feasible and likely to have clinically relevant therapeutic value. Therefore, the research team believes that it would be justified to charge patients for their participation in the trial.

But even with equal costs for all participants, there would be an ethical dilemma in that wealthier patients would have access to a therapeutic procedure that would be denied to less affluent patients. *The question therefore arises as to whether the self-financing of clinical trial costs by participants is ethically correct under the given circumstances and whether further arguments can be put forward in favor of this position.*

So far, the following basic facts have been presented for an ethical review:

- Every effort has been made to find potential investors for a Phase II clinical trial.
- The potential trial participant suffers from chronic cirrhosis of the liver, which is beginning to decompensate and will eventually lead to death.
- The patient has no other treatment options as there is no transplant program of sufficient size in the country.
- The participating patient is asked to contribute to the costs of the clinical trial, which are kept as low as possible.
- Without the patient's contribution, the clinical trial cannot continue as scientifically demanded, and the patient is deprived of the opportunity to receive a potentially greater therapeutic benefit than with standard treatment.

4.3 Ethical Analysis Part 1: Self-funding by Participants

Thesis: The clinical trial is unethical because it imposes costs on the trial participants.

The ethics committee responsible for the proposed Phase II clinical trial classified the mini liver trial as unethical, as the participants would have to contribute to the trial costs. In the following, we examine this argument in detail on the basis of recognized ethical, philosophical, medical and legal principles and regulations.

Questions of biomedical ethics, at least in the Western world, are usually addressed by referring to the four principles developed by Tom Beauchamp and James Childress. They were first outlined in 1979 in the book "Principles of Biomedical Ethics" [19]. The authors base their medical ethical analyzes on the four moral principles of respect for autonomy, non-maleficence, beneficence, and justice. These principles are not structured hierarchically but are assessed and weighed up against and in relation to each other.

Analysis Based on Four Principles of T. Beauchamp and J. Childress

When considering the financial responsibilities of clinical trials, it is important to uphold these principles to ensure that the rights and well-being of trial subjects are protected. Balancing the financial aspects of a clinical trial with ethical considerations can help maintain the integrity and effectiveness of the research, ultimately leading to more reliable and trustworthy results. In this way, researchers and sponsors can uphold the trust of the public and the scientific community in the research process.

Autonomy: The patient is autonomous in his or her decision and has the right to refuse or choose a treatment (Voluntas aegroti suprema lex).

Beneficence: Physicians should act in the best interests of their patients (Salus aegroti suprema lex).

Non-maleficence: "First, do no harm" (primum non nocere).

Justice and equality: This principle concerns the distribution of scarce resources in healthcare and the decision as to who receives treatment (Justitia).

If the patient is autonomous in his decision and has the right to refuse or choose a treatment, and if we look at the Latin version of the principles, then the will of the patient is above the law. *This means that the autonomous patient, who could afford the medical procedure, also would have the right to decide autonomously that he wants to pay all or part of the costs of his health. The physician, who is supposed to act in the patient's best interest, would also have a duty to inform the patient that the procedure is available and that the patient can receive it if he or she wishes to pay for it.* Whether a doctor would harm patients by not informing them of this new therapy is questionable and an important consideration. It may be unethical to not inform a patient about a potential therapy, regardless of the cost. One could argue that insurance companies' restriction of certain medications for patients with public insurance could be perceived as unfair.

The term "beneficence" is most commonly translated as "good medical care" or "doing good" and is intended to mean "in the best interest of the patient". It includes additional aspects such as caring and humanity and

is also more than "doing the medical work correctly". For the analysis of the proposed Phase II clinical trial, beneficence would also mean helping patients to enroll in a trial to potentially benefit from new medical therapies.

In our view, the most important concept in applying Tom Beauchamp and James Childress' four principles to assess the ethical dilemma is the concept of justice. Justice plays a crucial role in the distribution of healthcare resources. This involves the balanced distribution of benefits and burdens within society, including access to medical care and participation in clinical trials. In the context of the proposed clinical trial, justice would mean ensuring fairness in the selection of participants and equitable distribution of potential benefits.

By considering beneficence and justice together, we can make ethical decisions that prioritize both the welfare of the individual patient and societal interests in the distribution of healthcare. *It can be argued that in a system where patients have universal access to standard care, the ability of wealthier patients to use their resources for alternative treatments should not be seen as unfair.* This is because the decision of wealthier individuals to choose other treatment options does not hinder the access of less affluent patients to standard care. In fact, allowing individuals to make their autonomous healthcare decisions can be seen as a positive aspect of a healthcare system that values individual choice and personal agency. While the lack of insurance coverage for certain medications may seem unfair at first glance, it is important to consider the broader context of access to healthcare and individual autonomy in which these decisions are made.

Can it be just and fair that wealthy patients can receive treatment while poorer patients cannot?

At first glance, it seems obvious that this is unjust and unfair, and that equality in the distribution of health care should be guaranteed for all patients—all citizens, all peoples. While many countries around the world uphold this principle, a closer examination reveals that despite egalitarian principles, a class system of healthcare often exists in industrialized nations. Patients who can afford it buy private insurance, which grants them many privileges in healthcare. In many cases, certain high-priced cancer drugs

are not covered by health insurance for patients with public insurance. Many would argue that this is unfair. But if patients have universal access to standard care, as is the case in many national health systems, is it unfair for wealthier patients to decide, based on the principles of autonomy, that they want to use their wealth to try something different? In this situation, the decision of the more affluent patient to try a different treatment at his or her own expense has no impact on the less affluent patient's access to the standard treatment—a crucial factor in balancing the principles of fairness and autonomy. However, the ethical implications of such decisions require further examination in the context of equity and justice in healthcare.

Allowing wealthier patients to use their own funds for alternative treatments may even benefit the healthcare system as a whole by reducing the burden on public funds. This could also lead to advances in medical research and alternative treatments that could ultimately benefit all patients. As long as universal access to standard care is guaranteed for all patients, it should not be seen as unfair for wealthier individuals to be able to access other treatments, but as a personal choice that does not affect the rights of others.

One therapeutic area that is closely related to the novel treatment is organ transplantation. Organ transplant programs around the world continue to struggle with a shortage of donor organs. Liver transplantation is no exception. Therefore, systems need to be introduced and implemented to ensure that the distribution of scarce organs is based on a set of rules that are not influenced by the social status, gender, age, wealth, religious beliefs, or race of the individual patient. While this is desirable and ensures equality in the population, it is also clear that some patients in urgent need of an organ will do virtually anything to gain access to a transplant. The numerous scandals in the Western and Eastern world involving corruption and manipulation of organ transplant lists and the provenance of transplantable organs in some parts of the world illustrate how difficult it is to ensure equality in this area.

In a country like Indonesia, where there is no significant liver transplant program, it is assumed that the situation is fair for all patients, as essentially no one has access to a liver transplant. This is only true if patients have no choice but to find a donor liver elsewhere and seek a transplant abroad.

The cost of a liver transplant depends on the country in which it is carried out. Typically, they amount to between USD 200,000 and USD 300,000. Wealthier patients have the opportunity to receive a liver transplant abroad, while patients who cannot afford this option are not accepted into a foreign transplant program. The argument of equality in the absence of a transplant program in the home country, while valid, is undermined by the fact that wealthy patients can and will use their resources to obtain organs elsewhere, while this option is not open to poorer patients.

Furthermore, unequal access to liver transplants highlights the ethical and socioeconomic challenges faced by patients in need of this life-saving procedure. The inequitable distribution of resources and opportunities for transplantation further exacerbates existing inequalities in the healthcare system. Additionally, the lack of regulatory supervision and enforcement mechanisms in foreign transplant programs raises concerns about the exploitation of vulnerable individuals who may be coerced into participating in organ trafficking schemes. Addressing these complex issues requires a comprehensive and coordinated approach that includes international collaboration, ethical guidelines, and equitable allocation mechanisms to ensure fair and equal access to liver transplants for all patients, regardless of their financial status.

These and many other examples of inequitable distribution of medical care give the principle of equality less weight than it might appear at first glance. *It may well be argued that the Beauchamp and Childress analysis in this context would not preclude a patient from paying at least part of the cost of the proposed mini liver implant procedure.*

Analysis Based on Utilitarianism

Another aspect in addition to Beauchamp and Childress' principles of justice and equality is fairness. Can it be fair that wealthy people have access to a treatment poorer people are unable to receive? This question of fairness is perhaps best assessed using a utilitarian approach. In this case, act utilitarianism may not be relevant, but rule utilitarianism [23, 37]. This ethical reasoning states that actions that benefit the greatest number of people are

morally right. The first conclusion would be that it is ethically questionable to give preferential access to a medical procedure to the rich and not to the poor. On second thought, this conclusion might be short-sighted, because if there is no new medical procedure at all, possible positive outcomes will never be proven. *If positive results are achieved by individuals paying for their own clinical trial, the results will later benefit the entire population.* The method that leads to positive results can then be implemented in such way that it is available at affordable prices to everyone who needs it. The utilitarian argument therefore supports the position that people who have the means should have access to the clinical mini liver trial.

There are other aspects to consider in terms of fairness. Even in a highly developed country like Switzerland, a patient undergoing in-patient treatment in a hospital pays part of the costs out of his or her own pocket. Nobody is concerned about this. An example: A Swiss citizen undergoes surgery that costs CHF 12,000. The hospital stay is six days. The patient has to pay the following amounts out of his own pocket: A fixed contribution (so-called "Franchise") of at least CHF 300, a deductible to be paid by the insured person (so-called "Selbstbehalt") of at least CHF 700 and an additional CHF 15 per day, i.e. CHF 90. This amounts to a total of CHF 1,090. If the minimum rates are applied, this corresponds to 9.08% of the total costs, i.e. approximately as much as the 10.8% cost share for the mini liver treatment. These rates, which can be much higher in percentage terms, also apply to new and experimental treatments, provided that they have been approved and monitored by a responsible ethics committee. This means that surgical procedures that are newly developed and not yet tested in Switzerland must also be paid for privately. Another example: If patients in the UK are switching to countries such as Sweden, Germany, and Switzerland due to enormous waiting times under the National Health Service (NHS) and pay the full treatment costs themselves—including for experimental therapies—despite having valid, paid-for NHS insurance, this can hardly be considered unethical.

Analysis Based on W. D. Ross' Prima Facie Duties

Another ethical system that can be used for review was developed by

William David Ross [105]. He combines elements from several earlier moral theories and philosophical traditions. In his philosophical reflections, he developed an important ethical theory that was new for the time, combining deontological pluralism and non-naturalism. The theory is based on several fundamental rules or principles, which represent duties. These "prima facie" duties are not hierarchically ordered and can conflict and collide with each other. The Latin term "prima facie" can be translated as "at first sight" and means so much as "as long as there is no evidence to the contrary". The author states that the prima facie duty is entirely real and self-evident, but always depends on the circumstances and is never absolute.

The seven different prima facie duties initially identified are:

1. **Fidelity:** We should endeavor to keep promises and be honest and truthful.

2. **Reparation:** We should make amends when we have wronged someone.

3. **Gratitude:** We should be grateful to others when they perform actions that are of benefit to us, and we should try to return the favor.

4. **Non-harm (or non-maleficence):** We should refrain from harming others, either physically or psychologically.

5. **Beneficence:** We should be kind to others and try to improve their health, wisdom, safety, happiness, and well-being.

6. **Self-improvement:** We should strive to improve our own health, wisdom, safety, happiness and well-being.

7. **Justice:** We should try to be fair and distribute benefits and burdens fairly and equitably.

As with the biomedical principles of Beauchamp and Childress, Ross does not establish a hierarchy of duties. He recognizes that the context and circumstances may be determinative, and the individual case must be

assessed accordingly. The prima facie duties 4 to 7 are particularly suitable for analyzing the thesis, as numbers 1 to 3 do not apply to the situation at hand.

The fourth prima facie duty "non-harm" corresponds to the non-maleficence of Beauchamp and Childress' four biomedical principles discussed earlier. It supports the idea that the physician should not harm his or her patients by withholding access to information about a possible treatment for their disease. The patient should therefore receive all necessary information about current and new developments in treatment. "Beneficence", the fifth prima facie duty, explicitly states that we should improve the health and well-being of others. This would place a special responsibility on the physician to do everything possible to enhance a patient's recovery and survival. Improving the wisdom and safety of the physician would also mean supporting anything that might bring new scientific insights to the preservation of health. *It can also be argued that the proposed clinical trial for the mini liver is based on fundamental new knowledge and proven early results and should be conducted to improve the wisdom of the public and their safety and well-being in the area of liver diseases.* Prima facie duty number six, "self-improvement", could be interpreted in the same way, that we should improve our knowledge and wisdom ourselves, which in the scientific field of medicine is only possible by conducting appropriate studies.

Prima facie duty number seven, "justice", corresponds to Beauchamp and Childress' principle of justice, which has already been used above in examining subjects' financial participation in the Phase II clinical trial costs. Another aspect in favor of contributing to the costs is that the Phase I clinical trial has already shown a certain therapeutic value. It would therefore be unfair to exclude a patient who meets all the criteria from the clinical trial simply because other potential subjects cannot be included in the trial due to lack of funds. Of course, the principle of justice also applies with regard to the equal treatment of the mini liver clinical trial compared to other trials approved by ethics committees in Indonesia and other countries worldwide. *Among these approved clinical trials, there are apparently also some in which exceptions to the rules were made and patients were allowed to pay part of the costs of trial.* This is further evidence that partial funding

by patients in a Phase II clinical trial is ethically possible under certain strict conditions.

Analysis Based on Further Fundamental Principles and Rules

a) Principles of Immanuel Kant

One of the most important thinkers in ethics, and therefore in medical ethics, is the Enlightenment philosopher Immanuel Kant. His contribution can be summarized in the modernized version of the "categorical imperative": "Man should act in such a way that his action may become an universal law". In the context of the "Golden Rule", this could also be understood as: "Do unto others as you would have them do unto you". One of his lesser-known principles is particularly important for medical research. It reads:

"A person may be an end, but never a means to an end."

If the patient, a person entrusted to the physician, is the end of the physician's actions, the physician is ethically on the right side. If he is concerned with the well-being of the patient, the preservation of his health and its long-term protection, and if the patient is respected as a person, there is little need to worry about the physician's ethics. However, if the other side prevails, if the patient is degraded to a means to an end, if the scientific publication in a peer-reviewed journal, the subsidization of a scientific fund and the surgical fee achieved are to become the guiding principles, then the realm of medical ethics has been abandoned. In the development of the mini liver, it can be assumed that the desire to help patients and at the same time create a new method that could save the lives of many people clearly and unreservedly dominates.

b) John Rawls' Theory of Justice

In "A Theory of Justice" [106] the ethicist John Rawls explores the question of justice in the distribution of medical goods. For Rawls, the purpose of society is cooperation with the aim of mutual benefit for the participants. This can

be clearly assumed in our example. On the one hand, the researchers strive to solve a medical problem together and to increase medical knowledge; on the other hand, the patients and later the population can benefit from a potential therapeutic benefit.

c) Jürgen Habermas' Discourse Ethics

Jürgen Habermas designs a discourse ethics [107] with a system that aims to do without transcendence. It is de facto a purely procedural ethics. Everyone is allowed to participate in a decision-making process and to make a demand. No one may be prevented from taking part in the discourse. Consensus here is congruent with "truth", as there is no superior truth. The problem with this way of thinking is that "consensus" does not automatically mean "right". Furthermore, everyone can never be considered to the same extent.

d) Compassionate Use Versus Clinical Trial

The distinction between the concept of an individualized treatment trial that does not require ethical approval and a clinical trial that must be approved by the responsible ethics committee sheds light on another aspect of justice. In 2009, A. Schwarz [108] published a paper reporting the medical results of a series of patients in whom a scaffold implant for hepatocytes was used—the same type of scaffold used in the Phase I clinical trial for the mini livers. These cell implants were placed clinically in 75 patients and the results of 50 patients were subsequently published. The patient group and the study were not submitted to an ethics committee as the German study group considered that they could operate on patients based on the concept of an individualized treatment trial. In our opinion, and in line with the opinion of many other medical professionals, an individualized treatment trial or compassionate use, is legal, but ethically and legally only possible in a "group of patients". The European Medicines Agency (EMA) stated in its 2007 "Evaluation of Medicines for Human Use" that the term "group of patients" can be interpreted as any group (i.e. more than one) of individual patients who would benefit from a treatment for a particular condition. In

our opinion, based on empirical considerations, such a group could comprise about 10, maximum 20 patients. If a series of more than 20 patients is treated, it is a full scientific clinical trial that must be approved by a decision of the relevant ethics committee. Compassionate use does not have to go through the ethics committee procedure and is at the discretion of the treating physician.

The mini liver research group adheres to ethical and legal principles. However, it appears that in the proposed Phase II trial, the same principles that are supposed to protect patients are now working against the potential benefit to patients and a well-functioning scientific group. Whether this can be considered justice is questionable.

e) Patient Information of Cedars-Sinai Hospital

Further evidence that patients can contribute to the costs of a clinical trial comes from Cedars-Sinai Hospital. In its patient information "Clinical Trials Frequently Asked Questions", under the heading "Will it cost me anything to participate in a research study?" it states: "In some cases, it will not cost you or your insurance company anything to participate. In other studies, the research team may bill your insurance company for the drugs, equipment, and services they provide. Your insurance company may not cover some or all of the costs, and you may receive a bill for these costs. The informed consent form for the trial will describe any costs to you in detail".[2]

Conclusion Ethical Analysis Part 1

In conclusion, the biomedical and deontological arguments based on Beauchamp and Childress' four principles and Ross' prima facie duties support our view that it is morally justifiable to impose a modest share of the costs of a life-sustaining procedure on the research participant.

This argument is valid if the Phase I clinical trial shows at least some clinical improvement in several patients. A Phase I trial, i.e. a feasibility trial, is necessary to prove that a particular procedure can be performed safely by

[2] The patient information was no longer published on the Cedars-Sinai Hospital website at the time of printing in July 2024.

the investigators. It cannot be the intention or aim of such a Phase I clinical trial to demonstrate and prove the efficacy of a treatment. However, the authors of the Phase I trial believe that clinically relevant improvements in liver function were observed in several patients. In addition, the deaths that occurred during the Phase I trial after completion of implantation were not related to the procedure. Significant improvements in physical performance were observed throughout the lifetime of the participating patients. As a result, a Phase II clinical trial was considered, and the protocol and application were prepared. Over the past two years, the research team has significantly improved the implantable scaffolds. It is therefore expected that the clinical results will be even better than in the first trial. It can be anticipated that participants in the Phase II clinical trial will derive a relevant therapeutic benefit.

4.4 Ethical Analysis Part 2: Vulnerability of Participants

Thesis: The clinical trial is conducted on vulnerable patients. As the volunteers suffer from severe liver disease with no other effective treatment option, they are unable to assess the consequences of participating in the trial.

The ethics committee responsible for the proposed Phase II mini liver trial classified the procedure as high-risk and assumed that it would be carried out on vulnerable people who would not be able to resist the desire for treatment despite the high risks. There is no doubt that the individuals enrolled in the Phase II clinical trial are vulnerable. Most of these participants will suffer from adverse effects of deteriorating liver function with symptoms such as fatigue, ascites, partial cerebral insufficiency or loss of consciousness and vitality. Patients know that there is no cure for their disease other than a liver transplant. They know that they will develop liver failure, which will eventually lead to an early death. As a result, they may be so desperate that they are willing to seek inadequate or even dangerous treatments. At this stage of cirrhosis, the level of vulnerability is certainly very high. This situation can be compared to that of patients

with metastatic cancer who have few treatment options left. Patients for whom modern medicine offers no further treatment options will not only seek advice from medicine but will also accept any other suggestion that offers help in this desperate situation—whether proven or unproven, myth or legend. Physicians are aware of many cases where untrained, unqualified, or dangerous practitioners have promised treatments and cures that have never produced positive results. Patients are often so desperate that they are willing to pay large sums of money to such practitioners for little hope of improvement or survival. Ethical physicians will always try to protect their patients from such unscrupulous charlatans.

Analysis Based on H. Jonas' Philosophical Reflections

One of the most influential philosophers who wrote a scientific essay on "Philosophical Reflections on Experimenting with Human Subjects" is the German American philosopher Hans Jonas [109]. His essay can be considered almost a classic, and Jonas' views are still recognized today. Arthur Schafer [110], a Canadian ethicist specializing, among others, in bioethics and social philosophy, re-analyzed and critically assessed Jonas' article in 1983. Schafer writes in his analysis of Jonas' paper: "The social misery of those potential victims of disease whose suffering would be avoided by continued medical experimentation is not in itself a sufficient justification for imposing risks on human subjects. The essentially melioristic aims of medical research must be subordinated to the sanctity of the individual [research subject]". Schafer concludes that Jonas' position would lead to a ban on all research on humans. However, Jonas' seemingly firm position undergoes several modifications throughout his essay. Thus, Jonas argues later in his paper that "if the research goal is worthy enough, it is defensible and right to accept certain types of volunteers". Furthermore, he writes: "As long as a doctor can say, even in his own mind: 'There is no known cure for your condition (or: you have not responded to any), but there is promise in a new treatment that is still under investigation, not yet fully tested for efficacy and safety. You will be taking a risk, but all things considered, I think it is in your best interest to let me try it on you'—as long as he can say this, he is speaking as the patient's doctor, and he may be wrong, but he is not turning the patient into an experimental subject". Introducing an untried therapy

when the tried therapies have failed is not “experimenting on the patient”. In this case, the doctor is “still in the process of treatment”.

For Hans Jonas, human experimentation represents a real conflict with higher ethical values. For him, the highest imperative is the fundamental rejection of human experimentation. The determination of the areas in which human experimentation is possible is secondary and requires a well-founded justification, the weight of which must correspond to the importance of the ethical values revealed in the experiment. One of the most important negative characteristics of human experimentation is the fact that it degrades the human being not only to a means to an end, but to a thing, to a passive object without the possibility of influencing what happens. Moreover, the action of which he is the object is artificially induced. Participation in medical experiments must therefore be voluntary [109].

It should be emphasized at this point that the development of the mini liver is not a pure experiment in the above sense, but rather a healing or therapeutic trial as defined above. The primary intention is to help the patients who volunteer to test a new method. At the same time, however, it is also about establishing a treatment method that not only will help other patients, but also will enable them to survive. It would be difficult to understand why patients should bear part of the costs of a pure experiment that does not benefit them personally, unless the sponsor is wealthy. The situation is different for patients who have a legitimate hope that this experimental treatment will improve their chances of survival. The reasons for this have been well documented.

Jonas is aware of these problems and argues that medical progress is only possible if research can be carried out under strict conditions. Jonas’ solution to the dilemma of human experiments is the “descending order of permissibility”. The first tests of potential drugs and procedures are carried out in the laboratory and, if the results are positive, further tests are carried out on animals. If positive results can be demonstrated and proven from the animal tests, the doctor himself or other volunteers are the first people to test the drug or procedure in an individual treatment trial. For a formal study in a Phase I, II or III clinical trial, the inclusion criteria for humans must be met in descending order. Jonas suggests that autonomous patients who

are exposed to social pressure should be included first. Patients who are not completely free should be included last, and with the utmost caution. Schafer [110] explicitly mentions this descending order of permissibility, starting with autonomous people and ending with people with limited personal autonomy, such as soldiers and prisoners. This category could also include patients with diseases that cause very dangerous conditions. Although these patients are in such a vulnerable state, Jonas supports the idea that they too could also be included in trials, as long as the necessary precautions are taken, and strict rules are followed.

The least vulnerable patients in the proposed Phase II clinical trial are those with advanced cirrhosis who are already showing signs of liver failure. And the patients most at risk would be those with end-stage cirrhosis. This end-stage was defined as a survival probability of less than six months. Based on the experience in the Phase I clinical trial, the inclusion criteria were narrowed to exclude patients with a survival probability of less than six months. Most importantly, the MELD (Model for End Stage Liver Disease) score [111, 112] is used, which predicts the survival of patients on the liver transplant waiting list. The MELD score should not exceed 10 in order to exclude as far as possible that patients eligible for the clinical trial are in an unduly vulnerable condition. Special consideration is therefore given to the protection of the clinical trial participants.

Analysis Based on Ethical and Legal Codices

Over the last century, ethical and legal rules have been developed to protect human subjects in medical trials from unreasonable demands and behavior by scientists. During World War II, prisoners in concentration camps were mistreated and subjected to cruel and inhumane pseudo-scientific examinations by physicians. After the war, the so-called Nuremberg Doctors' Trial was held to investigate these crimes. As part of this trial, a code was developed to ensure the safe conduct of research on human beings. The code was intended to protect human life and dignity, including of course, the life and dignity of prisoners. The so-called Nuremberg Code has been further developed and adapted by medical associations around the world, in particular by the Helsinki Code and the Tokyo Code. These

codes, which have been widely accepted by the medical profession as well as by individual professionals and their associations, guarantee that clinical trials involving human beings can only be conducted according to these very strict rules and regulations. These rules state that vulnerable phases in a person's life must not be exploited or taken advantage of. The newer codes also state that patients must not suffer any financial disadvantages as a result of participating in a medical trial. The entire procedure of the clinical trial and any necessary drugs or medical devices should be provided free of charge by the clinical trial sponsor. These guidelines are intended to protect patients from "evil", but can sometimes have the opposite effect, namely the exclusion of patients from a clinical trial if sufficient funds are not available for it.

Comprehensive Informed Consent Process

Given that the volunteers suffer from severe liver disease with no other effective treatment options, they may struggle to fully comprehend the implications of participating in the clinical trial. Therefore, it is crucial for physicians to communicate the situation in a manner that vulnerable patients can easily understand during the informed consent process. Mastering the art of communication in this context means presenting all necessary information transparently, without overpromising, and ensuring the patient grasps the situation. Including family members in these discussions can be beneficial, as they can provide additional counsel and support. Subsequent consultations with family practitioners can further reinforce understanding and decision-making. *In the Phase II mini liver trial, informed consent consultation is an ongoing dialogue, ensuring that patients and their families remain informed throughout the process. By fostering open communication and involving a support network, patients are empowered to make informed decisions about their participation.* Continuous engagement with both the medical team and family practitioners is essential for maintaining trust and clarity. It is through these comprehensive and compassionate consultation practices that we can honor the ethical standards of medical research and provide the best possible care for the most vulnerable patients. Ensuring that every patient has a clear understanding of what participation entails mitigates potential anxieties and promotes informed consent, thereby

improving the overall quality and ethical foundation of the trial.

Conclusion Ethical Analysis Part 2

The proposed Phase II clinical trial is complying with all relevant national and international laws and regulations as well as the ethical guidelines of medical associations for the protection of vulnerable participants. There is only one obstacle that could prevent patients from participating in the mini liver trial, which could be of great benefit to them: the lack of financial resources to conduct the clinical trial.

Participation in medical experiments must be voluntary. Ensuring that every patient knows exactly what their participation means will reduce potential fears and promote informed consent, allowing autonomous decision-making.

4.5 Ethical Analysis Part 3: Risks of Procedure

Thesis: The procedure of abdominal surgery with segmental liver resection and subsequent implantation of miniature liver pieces just two days later is a high-risk procedure.

The mini liver procedure was classified as high risk by the responsible ethical committee. The main risk factor in patients with chronic cirrhosis is the liver function itself. Liver function in cirrhosis is usually characterized by a slow deterioration. Sometimes liver function can improve again for no apparent reason, but such improvements are rare and seldom long-lasting. In the final stages of cirrhosis, the patient is no longer able to maintain a coordinated metabolism, which leads to death. This metabolic disorder is the real problem and a fundamental risk factor that complicates any surgery or intervention.

Expansion of Exclusion Criteria to Minimize Risk

For patients on the liver transplant list, the MELD (Model for End Stage Liver Disease) score has been developed as method of estimating survival time. In general, disease mortality correlates with a higher MELD score, even without surgery. This means that on the waiting list for a liver transplant, the patients with the higher MELD score are operated first if possible. At the same time, the MELD score is a reliable predictor of mortality in patients with liver cirrhosis who undergo surgery. It is therefore important that patients with a high MELD score are not included in the clinical trial. Since the completion of the Phase I clinical trial, the inclusion criteria have been revised and the increased risks associated with higher MELD scores have been assessed. These risks are now weighed against the possibility of the patient dying if the surgery is not performed. The shortage of liver organs available for transplant leads to patients dying while waiting for a transplant. However, most patients with cirrhosis do not make it onto the waiting lists. This fact must be weighed against a potential new treatment option, even if the risks of the procedures are not fully known and the prima vista seems high.

The inclusion and exclusion criteria from the Phase I clinical trial were adjusted to minimize the risk associated with liver surgery. It was also shown that the procedure itself is safe. However, the question remains as to what level of risk is acceptable for the volunteers and which risk is ethically justifiable. *The results of the Phase I clinical trial were therefore analyzed, the inclusion criteria narrowed down and the exclusion criteria expanded. This will improve the primary safety of patients.* However, this may lead to patients being reluctant to participate in this implantation program because they are still in an acceptable general condition even though their liver disease is terminal in the long-term prognosis. It will be the responsibility of participating hepatologists to counsel potentially eligible patients and explain to them the potential benefits and risks of the procedure. Without comprehensive information, it may otherwise be difficult for many patients to assess how their health will develop in the future. By expanding the exclusion criteria and carrying out a comprehensive risk assessment, every effort is made to ensure that patients are not exposed to unnecessary risks. The surgical procedure itself is relatively straightforward and involves a small resection of subsegmental liver tissue. This can be done quite simply by a partial resection of a lobe of the liver in the third segment at the

free margin. This margin is always very easily accessible and the surgical approach and procedure itself do not involve any major risks.

Depending on their MELD score, patients may be in a condition where surgery could further worsen their already impaired liver function. This could lead to acute liver failure. The inclusion and exclusion criteria adjusted after the Phase I clinical trial also minimize this risk.

Conclusion Ethical Analysis Part 3

In summary, it can be stated that the risks based on the serious health condition of the potential trial participants were minimized through expanded exclusion criteria and very strict inclusion criteria for the Phase II clinical trial. The two surgical procedures themselves are low risk if the MELD score is below 10. If it is above 10, the patient is excluded from the clinical trial. It can therefore be argued that the therapeutic benefit for trial participants is generally matched by an acceptable risk, which is again reviewed individually for each potential participant.

5. Discrepancies in Authorization of Self-funded Participation

The question to be examined was whether it is ethically justifiable and appropriate for subjects to pay their own participation in a clinical trial. *We were astounded to learn that in the case of conditioned medium, often referred to as secretome, the firm negative position has turned into the opposite, providing new arguments for our reasoning that it is acceptable for participants to pay for their own treatment in a clinical trial.*

5.1 Properties and Benefits of Mesenchymal Stem Cell Secretome

Mesenchymal stem cell (MSC) secretome or conditioned medium (CM) is a collection of molecules secreted by cells, including growth factors, cytokines, and other bioactive molecules. These secreted factors can have diverse biological activities and influence cell growth, differentiation, and communication.

Secretomes hardly meet the standards for commercial approval set by the US Food and Drug Administration (FDA) and the Indonesian Food and Drug Authority (BPOM). To assess this, it is essential to understand both the biochemical properties of secretomes and the regulatory requirements for biological drugs.

The complexity of the secretome makes it difficult to determine the exact mechanisms of action, which is essential for comprehensive regulatory documentation. Furthermore, the variability in concentrations of active components within the secretome challenges the standardization of dosing regimens [113]. Due to these characteristics, the FDA requires stringent quality assurance protocols to ensure each batch meets predefined specifications [114]. Rigorous clinical trials are necessary to demonstrate the safety and efficacy of new therapeutics. The complexity and variability of secretomes complicate the design and interpretation of these clinical trials, making it challenging to produce convincing and reproducible evidence of benefits that outweigh potential risks.

The difficulties of ensuring consistent formulation, standardizing dosing, thoroughly understanding mechanisms of action, maintaining quality control, and clearly demonstrating safety and efficacy are the primary reasons that secretomes struggle to pass the FDA's stringent regulatory requirements.

Mesenchymal stem cells, primarily derived from the Wharton's jelly of the umbilical cord, have long been recognized for their regenerative capabilities. When cultured, these cells release a variety of substances collectively known as the secretome. The therapeutic efficacy of the mesenchymal stem cell derived secretome can be attributed to the complex mixture of signalling molecules that play a critical role in modulating the immune response, promoting angiogenesis, and facilitating tissue repair.

Of note in this paradigm is the influence of CO_2 levels during the cultivation process. Under hypoxic conditions—characterized by a limited CO_2 concentration—mesenchymal stem cells tend to secrete higher levels of regenerative factors, thereby increasing the therapeutic potential of the secretome. This adaptation is consistent with the findings of studies highlighting the influence of hypoxia on the yield and functionality of mesenchymal stem cell derived secretomes.

Several publications of studies and clinical trials from the Tarumanagara Human Cell Technology Laboratory, led by Siufui Hendrawan and Hans U. Baer, have examined the properties and therapeutic potential of Wharton's jelly conditioned medium [115]. These and other publications provide in-depth analyzes and experimental data demonstrating its potential clinical applications. They prove that the conditioned medium derived from Wharton's jelly offers a promising therapeutic approach due to its rich composition of bioactive factors and its regenerative and immunomodulatory properties. The preparation involves precise cell culture and medium conditioning steps to ensure the recovery of a biologically active secretome. Continued research, particularly those from reputed laboratories like Tarumanagara Human Cell Technology, highlights the potential of the secretome and paves the way for future clinical applications.

The milestone in the use of stem cell biology for therapeutic purposes heralds a future in which advanced biotechnological interventions can provide solutions to some of the most challenging medical problems.

Regulatory approval of the conditioned medium would be particularly important due to its significance for regenerative medicine. Its application covers a wide range of diseases, from chronic wound healing to neurodegenerative diseases. Research has repeatedly shown that the secretome can accelerate tissue repair and alleviate inflammation, which is crucial in clinical scenarios.

5.2 Self-funded Participation in Clinical Secretome Trials

Clinical trials are essential to prove the safety and efficacy of new treatments. However, the high development costs associated with novel therapies such as the secretome pose a significant funding problem. Costs include producing the secretome, conducting the trials, paying research staff and monitoring patient outcomes. For emerging therapies without substantial financial support, it is difficult to cover these costs. Conventional funding is not always available, prompting researchers to explore alternative funding models. Funding for such clinical trials can come from a variety of sources, including government grants, pharmaceutical companies and sometimes directly from patients. In scenarios where existing treatments are limited or ineffective, patients may choose to self-fund the cost of their trials.

When patients self-fund their participation in clinical trials, ethical concerns arise. To ensure ethical integrity, these trials should involve informed consent where patients must be clearly informed about the nature of the clinical trial, the costs involved, and the possible outcomes. Measures should be taken to prevent exploitation, possibly including subsidy programs or sliding scale payments based on economic need [116]. Regulatory authorities must closely monitor such clinical trials to ensure they comply with ethical guidelines and that patient welfare is prioritized.

As the healthcare market evolves, models where patients make a financial contribution may become more prevalent, particularly in areas of high unmet demand. This is especially true where there is a demonstrated benefit and a belief that participation in the clinical trial will provide access to life-changing therapies. Each of these factors contributes to a scenario where this funding model, while controversial, can be rationalized under stringent ethical and regulatory control.

5.3 Discrepancies in Authorities' Responses to Self-funded Participation

In Indonesia, at least the Ministry of Health has agreed that secretome can be sold to patients and paid for in full, provided that it is produced in a laboratory with good manufacturing practice and under the premises of clinical trials. We have seen such protocols consisting of a few pages of information, which leads us to the conclusion that these trials are just a pretext to sell the secretome.

A startling discrepancy emerges when one examines the responses of various health regulatory organizations such as the FDA (Food and Drug Administration), EMA (European Medicines Agency), and BPOM (Indonesian Food and Drug Authority) to the ethical question of whether patients can fund their own clinical trial.

In particular, the response from the Indonesian Ministry of Health's ethical committee has been remarkably rejecting. When queried as to whether it is permissible for patients to fund their own trials, the committee responded with disbelief and vigorous objections. This stands in stark contrast to the Ministry's approach to new treatments involving conditionally approved medicinal products, such as secretomes. Here, despite the ethical uniformity required by international guidelines, a different and possibly more lenient stance can be observed.

5.4 Ethical Concerns Related to Discrepancies in Authorities' Approval

These discrepancies raise complex ethical questions. First and foremost, the principle of justice in research ethics requires that all participants be treated equally. The observed disparity in the attitudes of authorities raises questions of whether patients are treated fairly and consistently in different contexts. The inconsistencies could promote inequalities in access to experimental treatments and clinical trial opportunities.

Moreover, the principle of beneficence, which states that researchers must act in a way that benefits participants and prevents harm, must be scrutinized. Allowing patients to self-fund their participation in clinical trials could be argued to give those with the financial means faster access to novel treatments, with potentially significant therapeutic benefits. However, it also carries risks related to undue influence and coercion, as patients may feel pressured to participate in clinical trials due to their financial investment, which could jeopardize their genuine informed consent.

The principle of autonomy may also be at stake. Patients who self-fund their participation in clinical trials can indeed exercise their autonomy by choosing to invest in their health. Yet, the relationship between financial investment and voluntariness needs careful examination to ensure that patients' decisions are made free from coercion and that they fully understand the implications of their financial commitment.

To elaborate, one could refer to the Declaration of Helsinki, which emphasizes transparency, informed consent, and the protection of vulnerable populations in the ethical conduct of medical research [117]. The issues raised require thorough dialogue and reflection within the research community to harmonize ethical frameworks that support both scientific advancement and the protection of participant rights [118].

In conclusion, the ethical permissibility of subjects financially contributing to their clinical trial requires a careful understanding and application of ethical principles. Our analysis shows that under strict guidelines and oversight, we can create a framework that preserves the research integrity while protecting the autonomy and well-being of participants. This discussion not only broadens the discussion on self-funded clinical trials but also challenges traditional models of research funding and promotes a more participant-centred approach. *The ethical guidelines we refer to emphasize the need for transparency, informed consent, and the avoidance of coercion. If these ethical principles are adhered to, self-funding a clinical trial by the participants can be seen as empowering the individual in research, rather than an ethical dilemma.*

The authorities' apparent dual standards in relation to self-funded participation in clinical trials and conditionally approved treatments raise significant ethical concerns. These concerns must be addressed through collective, transparent efforts and ethical guardrails. This will ensure that progress in medical research is not achieved at the expense of ethical integrity and fair, equitable treatment of all research participants.

6. Conclusions of Principle-Based Analysis

The German saying “Wenn zwei das Gleiche tun, dann ist es noch lange nicht dasselbe” could be translated into English as follows: “If two people do the same thing, is never quite the same thing”. In variation of an English proverb, this could also be paraphrased as “What’s good for the goose is not necessarily good for the gander”. These sayings express the idea that the same actions or circumstances do not necessarily have the same effects or implications for different people.

The ethical committee in Indonesia has described the thoroughly documented Phase II clinical trial as unethical due to the intended cost sharing by participants. In the case of secretomes, which are sold by large pharmaceutical companies without serious studies, these ethical concerns obviously do not apply. Most known trial protocols on secretomes contain only a few pages of information and clearly show that they were written for sales purposes and not to gain scientific knowledge. In Indonesia, but also in other countries, dermatologists are now freely selling secretomes and gels containing secretomes on the market.

The recent semi-approval of secretomes to be sold to patients without prior proper clinical trials by the Indonesian Ministry of Health, and similarly by other nations such as the US, marks a significant inequity in the medical ethical field of clinical trials and certification. Furthermore, a comparison of the rigorously documented Phase II mini liver trial with the far less stringent requirements for secretome treatments, which in Indonesia only demand a GMP-certified production facility and minimal documentation, shows that the required standards are not consistent.

This inconsistency in the approval and protocols of clinical research involving humans appears to be due to external pressures from commercial entities or patient organizations rather than purely ethical deliberation. This observation underscores the need for a standardized and transparent ethical oversight process and an unbiased, principled decision-making that upholds the integrity of clinical research while safeguarding the rights and welfare of participants.

In this discourse, we have undertaken a comprehensive examination of the ethical implications of patient self-funding of clinical trials. In our detailed analysis, we have explored key ethical principles such as justice, beneficence, and autonomy, and applied them to the specific context of patient-funded research. *Our findings suggest that, under stringent guidelines that ensure transparency, informed consent, and protection against coercion, it is ethically permissible for patients to finance their participation in clinical trials. However, this statement is nuanced and contingent upon several critical conditions being met.*

While the Nuremberg Code and its successors set out the basic ethical guidelines for research involving humans, the evolving landscape of medical research introduces new challenges and debates that require ongoing ethical review. The issues of subjects' financial participation in their clinical trials shows that, despite historical progress in research ethics, there are still areas that require further ethical evaluation and consensus.

In summary, our arguments support the ethical plausibility of patient-funded trials within a sound framework of oversight and ethical safeguards. Moreover, the inconsistencies observed in regulatory responses warrant continued dialogue and further investigations in this area. We hope that this treatise will stimulate thoughtful discussion and inspire future research as well as ethical reflections to address these emerging issues. Through open and honest discussions, we can work towards a more transparent and fair research environment that upholds the values of autonomy and respect for the individual. Through collaboration and ethical reflection, research can evolve and progress responsibly.

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Dr. Hans U. Baer, an esteemed retired academic surgeon, has built a notable career specializing in hepatobiliary and pancreatic surgery. He currently leads the Baermed Group and maintains a practice at the Klinik Hirslanden in Zürich. Throughout his career, Dr. Baer has advised and treated numerous patients with liver disease, particularly those suffering from cirrhosis. The challenges associated with the development and progression of liver cirrhosis have sparked his interest in innovative approaches to improve liver function.

In an effort to achieve concrete progress, Dr. Baer co-founded the Tarumanagara Human Cell Technology Laboratory in collaboration with Tarumanagara University in Jakarta and serves as its International Director. The research facility focuses on liver cell matrix implants and tissue engineering and has developed groundbreaking products such as Hepadua®, a mini liver implant.

Dr. Baer holds a Master of Applied Ethics from the University of Zürich, adding a valuable dimension to his medical practice and research. He serves as Associate Professor of Surgery at the University of Bern (emeritus) and Tarumanagara University in Jakarta (active). Dr. Baer is also Chairman of the Board of Directors and a co-owner of vivévis, a company for abdominal and robotic surgery based in Zürich. As Chairman of the Board of Directors of the Swiss Company Medicalculis GmbH, he is committed to the development of calculation systems for determining benefits in supplementary hospital insurance.

Dr. Baer is married to Christina and has two children with her. His dedication to the progress of medical science is reflected not only in his professional achievements, but also in his constant pursuit of knowledge and innovation.

Prof. Siufui Hendrawan, MD, PhD, M. Biomed

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Dr. Siufui Hendrawan, Master of Biomedical Sciences, is an avid researcher specializing in tissue engineering, stem cell biology, and biomaterial science. She is an active lecturer at Tarumanagara University Faculty of Medicine, particularly in the Department of Biochemistry and Molecular Biology, and holds a title of Associate Professor.

In 2011, the university, together with Baermed Group, established a research laboratory called Tarumanagara Human Cell Technology Laboratory (THCT), headed by Dr. Siufui. At this iGMP-certified research facility, she has led numerous preclinical studies and, together with Dr. Hans U. Baer, has successfully conducted clinical trials in liver cirrhosis patients, pioneering the development of mini liver organs and hepatocyte matrix implants.

Another major research project Dr. Siufui has developed, is the derivation of secretomes from mesenchymal stem cells (MSC) and their therapeutic applications for various diseases, e.g., chronic wounds, diabetes, hernias, epilepsy, and degenerative diseases such as osteoarthritis. She is planning further collaborations with clinicians and academics in the future to advance the use of secretomes and expand their therapeutic applications.

In addition to her research work, Dr. Siufui is an active member of the Universitas Tarumanagara Human Research Ethics Committee (UTHREC) and the Institutional Animal Care and Use Committee (IACUC) to assess the ethical aspects of clinical trials involving humans and the use of animals in research, respectively. As laboratory coordinator for the Faculty of Medicine, she is also responsible for the development of laboratories for education and research purposes.

Dr. Siufui lives in Jakarta with her spouse and two children. She is passionate in seeking for breakthrough to alleviate degenerative diseases and will continue to contribute through her constant research work.

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He is co-author of the Swiss Code of Deontology FMH and acted in several committees, as in the Ethics Committee of the Canton of Zürich. Currently he serves in the General Ethics Board of the private clinic group Hirslanden AG as an advisor and as a member of the Council of Honor of the Medical Association of Zürich AGZ. In 1989, Dr. Knessl wrote the first book on general medical ethics in the German-speaking countries. Until now, he is an author of a total of seven books.