

The medical experimentation on prisoners: a look back at an ethical debate dating back a century

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Background: Historically, prisoners have been exploited for the benefit of states and medical-pharmaceutical institutions under various justifications.

Objective: This review examines some facets of medical experimentation on prisoners (MEoPs), considering the historical course of events, the politico-economic factors that motivated these practices, and the evolution of the jurisdiction in place.

Methods: Narrative review.

Results: The analysis highlights the complicit role of Doctors who engaged in these practices as well as the involvement of states. The examples provided illustrate the extent of abuses that marked the Second-World-War and continued after its end. Despite legislative restrictions, countless ethical issues continue to fuel debates on the attributes of MEoPs, such as those related to scientific publication or inducement through remuneration.

Conclusion: Despite the implementation of various preventive measures in the form of laws and regulations, the exploitation of prisoners in medical research remains a major concern internationally because their multifactorial vulnerability makes them the preferred target of medical research investigators. Some practical implications and/or recommendations were suggested in this review.

Keywords: Human Rights, Medical research, Physician, Prisoners, Research Ethics, Second world war, Vulnerability

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1. INTRODUCTION

The issue of medical experimentation on prisoners (MEoPs) is thorny because it has always been associated with abuses and exploitation of human beings [1]. Indeed, some have stated that «*prisons represent the ideal place for research, the environment and population there are stable, the imposition of even strict rules of the experimental protocol is not a real obstacle, but above all, it is much cheaper*» [1].

The bibliography related to this theme is primarily linked to the Nazi experiments carried out in concentration camps [2-8]. These, due to their magnitude and atrocity, undoubtedly constituted the major event that shaped debates and legislation on an international scale [3-9]. However, historical reality teaches us that these practices tarnished several regimes during World War II and particularly flourished after the war ended. Several factors had shaped the laws in force to take



advantage of the 'vulnerability' of prisoners. This complicity involved Doctors, institutions, and even states [9].

The primary objectives of this narrative review were to recall the significant historical events surrounding the exploitation of prisoners in medical experimentation, and to analyze the roles of various stakeholders, considering the historical context and the evolution of ethical and legal concepts. The secondary objective was to recommend some actions and reforms to protect prisoners' rights in medical research.

2. The definition of a prisoner

A prisoner is «*any person who is involuntarily confined or detained in a penal institution*» [10].

3. Key historical events in MEOs

The exploitation of prisoners for medical research is an ancient phenomenon [1, 11]. The use of prisoners dates back to before the Persian era [1, 11]. In the Roman Empire, "physicians" used prisoners of war to concoct and test new poisons [1]. During the 18th century in Europe, war captives were destined to be inoculated with venereal diseases, typhoid, and any other type of fever and cancers with the objective of finding remedies to these diseases [1].

3.1 Early 20th century, before the start of the Second World War (American experimentation, on a small scale)

The following events will describe three examples of prisons where MEOs were documented before the start of World War II. First, during 1906, in the Manila Prison, Doctor Strong infected death row inmates with serum containing the Cholera bacterium [12]. Thirteen deaths were attributed to a "serum preparation error" [12]. Later, the aforementioned Doctor was promoted to Professor at Harvard, and the prisoners received cigars as compensation for their participation [12]. Second, during 1915, in the Mississippi Prison, Doctor Goldberger induced pellagra (*i.e.*; a severe nutritional deficiency that can lead to death) in a dozen of "consenting" prisoners (who were promised sentence reductions at the end of the study) to test the hypothesis of the potential occurrence of this disease in white men [13]. Third, in 1918, in the California prison, Doctor Stanley conducted testicular transplantations from death row inmates to elderly men [12]. In 1920, the

protocol expanded to include the injection of extracts from animal testicles into those of human recipients (specifically prisoners) [12]. The results were published in the ongoing, prestigious scientific journal, *Endocrinology* [12].

3.2. During the Second World War

Between the Allied forces and those of the Axis, prisoners were massively sacrificed in favor of military projects [14-22].

3.2.1. The Nazi Germany

The 'medical experiments' undertaken under the order of the Third Reich aimed to serve the interests of the state [14]. These objectives could be classified into the following three categories:

- i)* To improve the survival of military personnel of the Axis forces (optimize the survival of aviators at high altitudes as well as their resistance to extreme cold [14]). This included immersion in icy water and exposure to extreme cold [15], as well as endurance tests where prisoners were confined in low-atmospheric pressure chambers [15];
- ii)* To develop drugs and treatments for injuries and illnesses that German soldiers could contract in combat such as vaccine trials for contagious diseases, antidotes to toxic substances, as well as the beginning of the first tissue and organ transplant trials [14]; and
- iii)* To confirm the ideological dogmas of the Nazi worldview (*e.g.*; Mengele's experiments on twins, proving the racial inferiority of Jews, or the variability of disease resistance based on races) [23].

3.2.2. The Stateville penitentiary, Illinois, USA

Between 1944 and 1946, prisoners were deliberately infected with malaria in order to test the effectiveness of treatments under development [16]. It should be emphasized that during this period, finding an antidote for malaria was a strategic military objective for the USA, as they were involved in endemic areas in Asia and Japan [16]. The number of victims is uncertain, with around a thousand prisoners believed to have been affected [17]. These trials have been described as «*one of the worst crimes of the century, teenagers were kidnapped and murdered*» [16].

These experiments were conducted under a personal order from President Roosevelt and carried out under the guidance of the US Committee on Medical Research

and the University of Chicago [16]. The objectives of this mission were to "provide 'adequate' provision for scientific research for reasons of national defense and security" [16]. This trial was conducted after approval from the American Medical Association, which deemed the protocol "compliant" with the rules of human experimentation [17]. The results of these experiments were published in the "still nowadays" prestigious scientific journal of the American Medical Association (known as JAMA) [17].

3.2.3. The 731 unit, imperial Japanese army

The 731 unit was a unit created between 1930 and 1940, and annexed to the Japanese army [18]. The main goal was to develop biological weapons for the ongoing war [18]. Bacteriological experiments were undertaken on Chinese children [19], experiments involving exposure to cold (*i.e.*; *frostbite experiments*) and point-blank shooting were conducted [19]. Undoubtedly, the most horrifying experiments conducted was vivisection, involving the extraction of organs from individuals while they were still alive [19]. The number of victims is believed to be over 1000, comprising mainly Chinese prisoners, comprising women, children, and elderly. Due to American interest in these experiments and the extreme brutality of the acts committed, no trials were held, and the archives pertaining to this episode of history remains secret to early 2024 (time of the present manuscript submission) [18].

3.3. After the end of the Second World War

The phenomenon of exploiting prisoners in medical experimentation had migrated to the USA after the end of the Second World War, with the country even recruiting Nazi Doctors through its intelligence services (*i.e.*; *Operation Paperclip*) [24]. Prisoners had then become the target of state institutions and pharmaceutical companies.

3.3.1. The Holmes burg prison, Philadelphia, USA, 1951-1974

Led by Doctor Kligman, a trained dermatologist, these experiments utilized prisoners [20]. Over 23 years, Doctor Kligman played the role of principal investigator on behalf of 33 pharmaceutical companies, developing both his knowledge and personal wealth [20]. The most 'famous' of these experiments was the one involving dioxin (*i.e.*; the most dangerous of poisons used as a

chemical weapon during the Vietnam War), conducted between 1965 and 1966 [21]. This study was funded by the Dow Chemical Company (*i.e.*; an American industrial giant and multinational specializing in the manufacture and marketing of chemical products), which paid Kligman over \$10,000 net to conduct this study [21]. Contrary to the established protocol, the prisoners were exposed to doses 486 times higher than the tolerated limits [21]. The records relating to this clinical trial were destroyed, and the exact number of 'participants' remains unknown to early 2024 [21]. Never prosecuted during his lifetime, Doctor Kligman even became a prominent figure for discovering and developing medications based on retinoid A [21].

3.3.2. The Oregon state experiments, USA, 1963-1973

The Oregon state experiments were done under the direction of Doctor Heller, a prominent endocrinologist [22]. The aim of the experiments was to study the effect of ionizing radiation on male fertility (a topical issue at the time): the testicles of 67 prisoners were exposed to increasing doses of X-rays (up to 600 rad) for varying durations [22]. These studies were generously funded by prestigious institutions including the National Aeronautics and Space Administration (*i.e.*; the NASA) [22]. The prisoners were termed "consenting" as they received 25 cents per day of radiation and \$25 for each biopsied testicle [22]. Additionally, the prisoners received a reduction in their sentence for their "service to society" [22].

3.3.3. The Hythian's drug-addiction treatment, USA, 2006-2008

Despite the restrictive laws in place in the USA, a pharmaceutical company named Hythian obtained permission to experiment with its treatments on incarcerated "criminals" in five American (USA) states [21]. Furthermore, the American state was able to compel anyone arrested for drug possession to undergo this withdrawal program called "Prometa" [21]. In return, the company was required to pay \$15,000 to the authorities for each new participant [21]. It should be noted that the withdrawal program lasted for 30 days, during which participants had to ingest three types of medications [21]. None of the experimented molecules had obtained the necessary prior approval from the Food and Drug Administration [21].

4. The 'complicity' of the Doctors

4.1 The historical case of Doctor Hallervorden

Doctor Hallervorden was an illustrious German psychiatrist and neuropathologist who conducted research on the brains of mentally handicapped individuals [25]. In order to obtain a sufficient number of "brains" for his research, Hallervorden collaborated with various investigators of the T-4 euthanasia program, going so far as to personally visit different extermination camps to collect "material" from freshly gassed corpses [25]. Hallervorden had published several works deemed of great scientific interest, which only reinforced his position as an academic researcher [25]. He was never prosecuted or charged [25]. In June 1945 (*i.e.*; at the end of the Second World War), Hallervorden was interrogated during the Nuremberg trials. Here is what he commented: «*There was wonderful material among those brains, beautiful mental-defectives, mal-formations and early infantile diseases. I accepted these brains of course. Where they came from and how they came to me was really none of my business*» [25].

4.2. The historical context and the distortion of ethical standards

The role of physicians under the Nazi regime continues to be a subject of much debate [26]. The physicians' ability to disregard the fundamental principle of the Hippocratic Oath of "Do no harm" and to commit such atrocities will always be surprising [26]. The impact of ideology seems to have played a determining role in these otherwise inexplicable behaviors [26]. Indeed, in the early 20th century, following the devastations of the First World War, a weary Germany became engulfed by the ideology of 'national socialism' [23]. Here, the fervent desire for the revitalization of the homeland became a paramount objective, even if it meant embracing radical policies [23]. In this ideological context of absolute totalitarianism, the notion of the 'individual' and the concept of bodily sanctity as we know them today did not exist [26]. At that time, the 'value' of an individual was determined solely by the nature of their contribution to the group [26].

Furthermore, the Nazi ideology was bolstered by 'scientifically proven' foundations (*i.e.*; Social Darwinism) [27]. This logic, based on the supremacy of the pure race, aimed to preserve this superior race and to eradicate (regardless of the means) other inferior races considered as 'parasites' (*e.g.*; prisoners in the camps were classified among the most inferior races, but dangerous due to their numbers) [26]. To counter accusations of fascism, the Nazi Doctors were convinced that it was «*nothing but applied biology*» [28]. Operating on the premise that their role was to stop suffering, the disabled, the sick, the elderly, and the weak were exterminated [26]. The eugenics undertaken through mass extermination operations by gas or poison was perceived as sanitation operations or "pest control" [26]. The Nazi Doctors "were tasked with public health missions and ensured the well-being of the nation" [26]. Contrary to what we might think, the Nazi Doctors were highly esteemed and rewarded because they 'sacrificed' themselves through their science for the supreme reason of the state [26]. Despite irrefutable evidence of their crimes, all 23 Doctors tried by the Nuremberg tribunal (*see below*) pleaded not guilty [26].

4.3. The complicity of the state and its institutions

It would be 'simplistic' to attribute all the blame for the crimes committed in carceral settings solely to the Doctors. A review of history illustrates the clear and explicit involvement, generally implicit through complicity, of authorities in power. The case of the Nazi experiments remains striking due to the degree of involvement of the authority that adopted these atrocities as 'state policy' [29].

5. Evolution of legislation: The main milestones

The ethical concepts related to the regulation of medical experimentation in penitentiary settings have evolved significantly since the beginning of the century. The pace of revising regulations has been strongly influenced by scandals revealed either in Europe or in the USA [30] (Figure 1).

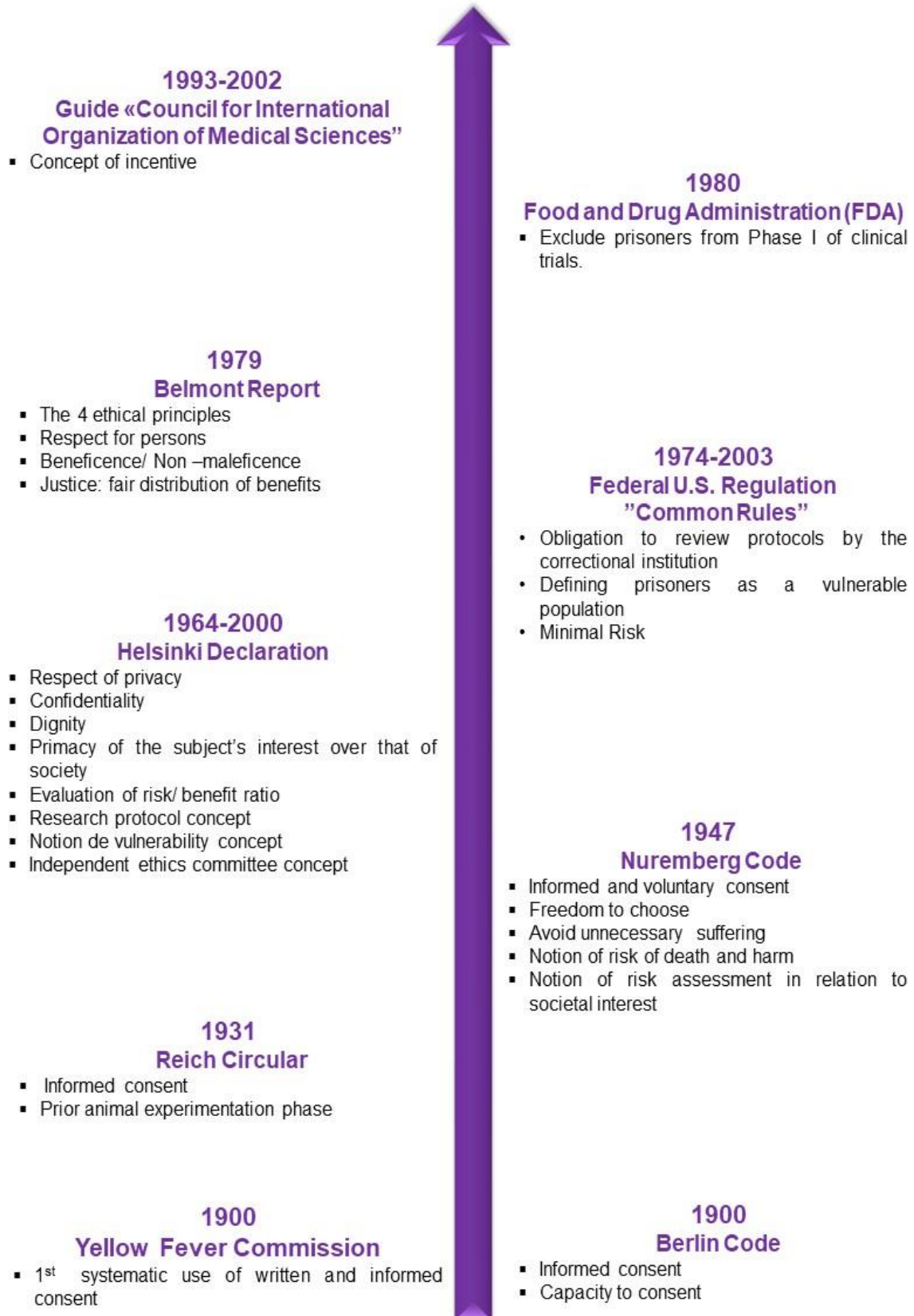


Figure 1. Chronological evolution of ethical concepts (partially adapted from Pont [30])

5.1. The Nuremberg code, 1947

After the end of the Second World War and in response to the atrocities committed in the extermination camps, the victorious Allied forces ensured to publicly condemn the Nazi Doctors by establishing the Nuremberg trials [31]. The Nuremberg Code that emerged from the Nuremberg trials is considered the "landmark" document that laid the ethical foundations for research involving humans [31]. This document specified for the first time the rights of participants and the responsibilities of investigators [31].

The Nuremberg Code established 10 mandatory rules for conducting any human experimentation [31]. The first amendment includes informed consent and voluntarism [31, 32]. Furthermore, the Nuremberg Code specifies the obligation for these experiments to be undertaken by 'qualified' researchers and the need to avoid procedures that could induce unnecessary physical or mental harm [31]. In other words, the 'risk incurred' should not exceed the 'expected benefit' [31].

The Nuremberg Code had an 'uncompromising' formulation regarding the requirement to obtain consent, "*the voluntary consent of the human subject is absolutely essential*" [1], which necessarily excluded all individuals unable to meet this criterion; however, these individuals were precisely the preferred target of medical experimentation investors due to their 'vulnerability' [1]. Due to its 'uncompromising' nature, the Nuremberg Code had a negative impact on research activity, earning it later the adjective of a "restrictive code" [1].

5.2. The declaration of Helsinki, 1964

The Helsinki Declaration was created by physicians to regulate the work of Doctors [1]. From its inception, this document was adopted by the World Medical Association [1]. The Helsinki Declaration is generally considered to be «*more lenient*» than the Nuremberg Code [1], with a formulation considered «*Complex and too vague*» [1].

Here is an illustrative example [30]: In 1964, *Article 5* of the Helsinki Declaration was presented as follows: «*Concern for the interest of the subject must always prevail over the interests of science and society*». Later, the text was 'rectified,' and the final version became less solemn, as the formulation was announced as: «*In medical research on human subjects, considerations*

related to the well-being of the human subjects should take precedence over the interests of science and society». This 'rectification' was largely explained by the pressures exerted by 'careerist' scientists and the financial profits of pharmaceutical companies [30]. It is notable that the Helsinki Declaration did not exclude incompetent individuals from giving their consent, such as those with mental disabilities [1]. On the contrary, the text provides "alternatives" to obtain their consent by allowing the agreement of the legal representative or that of the person concerned «*Where this is possible*» [1].

Although initially not intended to address the legislative framework of medical research in carceral settings, the text nonetheless alludes to «*Vulnerable persons requiring special protection*» and those who «*Might give consent under duress*» [1]. The obligation to submit the protocol to the prior approval of an ethics committee is a guarantee of respect for ethical principles and protection for future candidates [1].

The main 'legislative revolution' brought about by the Helsinki Declaration is that it 'imposed' the delivery of clear and, above all, complete information to any person volunteering for medical research. This information must necessarily include the objectives, the method, the sources of funding, possible conflicts of interest, and the institutional affiliations of the investigator [1]. Among the legal texts dealing with the subject, it is worth noting that the Helsinki Declaration is considered the most uncompromising regarding the obligation to clearly disclose all these details [1]. However, it is rare to observe this level of 'transparency' in medical research, and even rarer to see it for prisoners in particular [1]. In practice, some legislations may explicitly authorize the "deception of participants" [1] if the stakes were deemed 'significant' (*e.g.*; ethical principles of psychologists and code of conduct): «*Deception is warranted only if scientific, educational or applied value is significant*» [1]. The Helsinki Declaration is the only document that has addressed the issue of scientific publication in the context of human experimentation (33). Both the authors of the work and the publishing house have ethical obligations [33]. In case the work does not correspond to the principles of medical ethics, the publication should be prohibited [33]. Nevertheless, it is useful to recall that despite these restrictions dating back to 1964, there are still numerous violations, such as

research on transplants from executed prisoners continuing to be published [33].

6. The dilemma of Pros and Cons of MEoPs

6.1. The Pros

6.1.1. The historical argument

The scientific 'renaissance' could only occur through experiments on humans and on a large scale. The following paragraph will describe the German [12] and the USA [12, 13] examples.

During the Nazi era, and thanks to medical experiments on prisoners, German Doctors were international leaders in various fields: basic sciences, epidemiology, preventive medicine, various medical and surgical specialties [12]. This German leadership emerged decades before that of the USA [12]. For reference, since 1930, half of the Nobel Prizes have been awarded to Germans [12]. Before the end of the Second World War, medicine in the USA could in no way claim to rival German medicine [12, 13]. Experimental trials in the early 20th century were limited to rare studies conducted in prisons with an insignificant number of participants (*e.g.*; 2 for the Colorado prison experiment in 1934) [12, 13]. Without subsidies and without state policies encouraging these experiments, American research struggled to distinguish itself on the international stage [13]. After the conclusion of the war and a rekindled interest in the German experiments, Americans shifted their strategies, promoting the utilization of prisoners as research 'material' [13], while concurrently subsidizing these clinical trials for a multitude of reasons including defense and general interest [13, 34]. As a result (*i.e.*; setting aside ethical concerns and recurring scandals), the USA is now one of the global leaders in science.

6.1.2. The economic argument

With the expansion of the pharmaceutical industry, the demand for clinical trials for new drugs had exploded [22]. For reference, it multiplied by seven times in a span of 10 years, between 1995 and 2005 [17]. It is also worth noting that until 1975, 90% of all new drugs developed in the USA had been tested on prisoners beforehand, and that Phase I clinical trials (*i.e.*; exploring toxicity and safety) were exclusively conducted in a prison setting [30].

6.1.3. The health argument

The prison population is particularly affected by diseases (*e.g.*; various addictions, infectious diseases with high levels of antibiotic resistance, psychiatric disorders), with a high prevalence of violence and suicide [30]. As a result, the prison environment poses a significant public health problem because prisoners are considered epidemiologically as vectors of diseases once they are released from prison [30]. Taking into account the limited financial resources of correctional institutions, medical research represents an opportunity to address these at-risk individuals and mitigate long-term health risks [30]. For prisoners, this represents an opportunity to access healthcare (*e.g.*; expensive medications) and benefit from quality medical care [35].

In 2020, amidst the coronavirus disease 2019 pandemic and the urgent need for clinical trials to validate new vaccines, the scientific community inevitably turned to prisoners who appeared to be 'legitimate' guinea pigs for research [36].

6.1.4. The argument of the supreme state interest

Indisputable and supreme, it justified all large-scale abuses [37-40].

6.2. The Cons

Prisoners are particularly vulnerable to risks of exploitation [37-40].

6.2.1. The abuses of the 'principle of the greater good'

During the first Gulf War (1990-1991), the U.S. Department of Defense ordered the prophylactic issuance of "pyridostigmine" to over 250,000 soldiers in the U.S. Army [34]. This molecule was presented as having protective properties against the deleterious effects of a hypothetical chemical or biological attack involving organophosphates or botulinum toxin [34]. However, these claims were theoretical and were never proven by clinical trials [34]. Furthermore, it was known that this molecule was toxic to the nervous system and could significantly impair performance during combat [34]. Having been administered without obtaining the soldiers' consent, one of them filed a complaint [34]. The plaintiff did not prevail because the Department of Defense cited "The supremacy of the public interest" and constitutionally argued «*The government's interest outweighed that of the individual*» [34].

6.2.2. The risks of coercion and undue influence

«Coercion occurs when an over threat of harm is intentionally presented by one person to another in order to obtain compliance» [39]. This definition requires the presence of the following two elements: The threat of harm and the origin of the threat being a third party (*i.e.*; other than the investigator) [39]. In a carceral environment, by definition, the freedom to exercise free choice is restricted [37]. At the same time, prisons are institutions particularly concerned with 'controlling' individuals' behavior through various disciplinary measures [38]. In this logic, medical experimentation should either be prohibited or restricted for fear that various pressures could coerce prisoners into participating against their will [40]. From a legal standpoint, there is little specificity on this matter: The common rule in the USA regarding the protection of human subjects simply states «An investigator should minimize the risks of coercion and undue influence» [39]. Induced incentives pose a problem concerning the boundaries that should not be crossed to avoid tipping into coercion [39]. The most common form of induced incentives is remuneration; as otherwise, the vast majority of candidates would withdraw if there were no financial incentive [39].

7. The ethical principles put to the test

7.1. The principle of 'free and informed' consent (autonomy and self-determination)

«No human being should be subjected to medical experiments without their free and informed consent» [10]. The principle of informed and voluntary consent should be respected for every individual undergoing medical experimentation [10]. This principle is one of the cornerstones of the Nuremberg Code [10, 32] and the Declaration of Helsinki [10]. It should be emphasized that the principle of "informed consent" should entail "full consent" ensuring the presence of the following three elements: *i)* Information, *ii)* Competence, and *iii)* Voluntariness [10]. The absence (or doubt) regarding any of these elements would call into question the credibility of the obtained consent [10].

The lack of information is a common situation where information is not fully disclosed to avoid deterring potential candidates [10]. The Nuremberg Code emphasizes that the information provided should be 'sufficiently comprehensive' to enable the candidate to

make an informed and voluntary decision «Sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision» [32]. The information provided should clearly outline the study's objective, its nature (*e.g.*; methods and means), as well as its duration [32]. The message should be clear and simplified so that the candidate (usually laypersons) can easily understand it [41]. Furthermore, the information should include the 'potential disadvantages' of the experimentation as well as its 'foreseeable risks' [32]. Legally, it is the duty of the investigator to demonstrate that they have clearly conveyed to their patient all the information, and that they have not omitted to mention any detail related to the experimentation [41].

The lack of competence refers to discussing the mental ability of the prospective candidate to give consent (*e.g.*; children, mentally disabled individuals, comatose patients) [10].

The defect of voluntariness and the question of vulnerability arise when, despite the assurance of complete information and mental capacity, there is doubt about the presence of any form of coercion forcing the candidate to participate in the experiment [10]. Due to their circumstances, prisoners cannot give consent entirely free from coercion [10]. The principle of voluntariness must be approached with caution in a prison environment where threats, harassment, and manipulation are common practices [10]. Indeed, the entire issue here is to assess the degree of vulnerability of the person to determine whether they can or cannot provide free consent in a hostile environment such as prison [10].

The vulnerability of prisoners is multifactorial, and there are numerous sources of abuse, making them undeniably the preferred target of experimental protocols [10]. As an indication, we cite [10]:

i) The high prevalence of illiteracy [30]. Moreover, mental disorders and psychiatric susceptibility are widespread among this group, frequently linked to drug abuse and illicit substances, primarily originating from an environment characterized by violence and criminal activities [30].

ii) The deprivation of liberty and the severed contact with the outside world. It should be noted that some legislations take advantage of this, offering sentence

reduction or commutation in exchange for participation in "community service" programs [10].

iii) The financial aspect, as the overwhelming majority of prisoners come from disadvantaged backgrounds, making them particularly susceptible to the "compensation" offered, no matter how meager or insignificant it may be [10].

Legally, the principle of voluntariness refers to that of "autonomy" and the capacity for "self-determination" of each individual (which is compromised in a carceral environment) [41].

7.2. The principle of beneficence and non-maleficence

This is one of the cornerstones of the Nuremberg Code [30], where it is imperative to avoid any "unnecessary" causes of suffering and physical or moral injury, and to ensure that the research subject is not exposed to serious risks that could result in death or other substantial harm [30, 32].

It is required that the research protocol be previously validated in animals and be based on the most recent knowledge incorporating the natural history of the disease under study [32]. It is the obligation of the investigators (who must be highly qualified) to ensure the proper preparation and safety of the administered "products" [32].

The issue regarding this aspect revolves around considering the "degree of risk incurred", which should be "proportionate" to the importance of the "sought-after benefit" [30]. This risk consideration is not a static element but an ongoing assessment throughout the experimentation process, where the investigator is obligated to stop the experiment if necessary when the degree of risk incurred becomes disproportionate to the benefit [30, 32]. Although the individual's interest should always prevail over that of society and science [30], in practice, the assessment of the "degree of risk incurred" is often conflicted with the communal benefit on one side and the academic ambition of the researcher on the other [30]. Similarly, current regulations require the researcher to assess in advance the risk incurred during

the implementation of their protocol (predictable risk) [30]. To optimize transparency assurance, it is now mandatory for every clinical trial project to be reviewed by recognized ethics committees that are stringent in adhering to regulations [30].

7.3. The principle of confidentiality

The Declaration of Helsinki of 1964 has been amended several times to ensure legal texts protecting confidentiality, privacy, and the integrity of individuals undergoing medical experimentation [32]. Indeed, although the prison environment restricts individuals' right to privacy, it is the duty of the investigator to protect it during the research process [42]. It is mandatory to keep patient (prisoner) data in protected and inaccessible locations [42]. It would be preferable to reserve a separate room for this storage (not the one where the Doctor receives visits from other inmates or staff members) [42]. Furthermore, it is strongly recommended to arrange the patient visit room (for questioning and clinical examination) to be separate from other rooms and to ensure maximum possible confidentiality during visits [42].

7.4. The principle of protection

Legislatively, the state has the duty to provide adequate protection because these are vulnerable individuals [30]. In its *Article 8*, the Declaration of Helsinki stipulates that [30]: «*Some research populations are vulnerable and need special protection. The particular needs of economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care*».

Regarding the protection of individuals undergoing medical research, particularly prisoners, it is important to note the presence of a dedicated text, that of the Office of Human Subjects Research, subsection C, established in 1979 (Box 1) [30].

Box 1. Office of Human Subjects Research, 1979, subsection C [30].

The general framework for research involving prisoners must adhere to the following strict conditions:

- ✓ Predictable risk should be minimized, with minimum defined as the probability and extent of physical or psychological harm that could result from routine medical examinations.
 - ✓ Research is only permitted if its purpose is related to:
 - i) The causes, effects, and processes of incarceration,
 - ii) Prisons as structures and prisoners as incarcerated individuals,
 - iii) Causes affecting prisoners as a social category,
 - iv) Practices that would reasonably improve the health and well-being of prisoners.
- Other points of subsection C stipulate that any incentive to participate should not influence the prisoner's free choice that the prison environment should not (due to its limited available options) influence the prisoner's decision, and that participant selection should be fair and random.

However, these regulations, deemed too restrictive, have been widely criticized for significantly limiting prisoners' access to 'the benefits of research' [30]. As a result, only a very limited number of American states has done the ratification of this text [30].

Given the prevalence of abuses against prisoners, it is somewhat surprising to note that this category is, until early 2024, rarely addressed in international treaties [30]. Indeed, regulations governing medical research on prisoners remain remarkably scarce [30]. Regarding the situation worldwide, the local legislation of very few countries prohibits the use of prisoners in medical research (*e.g.*; Germany, California Penal Code), or restricts their use (*e.g.*; Austria). While the absence of a clear legislative framework in the overwhelming majority of countries implies an implicit agreement from local authorities [30]. Furthermore, it is worth noting that there is no internationally recognized regulatory body to intervene in case of practices going astray [30]. An exception is "the Additional Protocol to the Convention on Human Rights and Biomedicine" (Council of Europe, 2007), which pertains to biomedical research and only binds the countries that have ratified it [30].

7.5. The principle of Justice 'Equity / Equality'

Throughout the world, states are accused of failing to provide the necessary tools to prevent diseases and to cure individuals "crammed" into cramped spaces where they are victims of all kinds of violence, left to fend for themselves, and deprived of care [43]. According to the World Health Organization: «*Ill-health thrives in settings of poverty, conflict, discrimination and disinterest. Prison is an environment that concentrates precisely these issues*» [43].

Yet, governments have the obligation, through numerous national laws and international treaties, to remove barriers to healthcare for the prison population and to ensure adequate provision of materials and personnel to meet their needs [43]. Largely inspired by the story of the most famous prisoner, Nelson Mandela, the Mandela Rules (*points 24 to 35*), amended in several laws, aim to guarantee justice and equity regarding access to healthcare for every prisoner, regardless of the nature of their crime and the length of their sentence (Box 2) [43, 44].

Box 2. Some excerpts from the Mandela Rules (*points 24 to 32*) [43, 44].

- ✓ Prisoners should enjoy the same standards of healthcare quality as those applicable to the general community (*Rule No. 24*).
- ✓ Prisoners should have access to necessary healthcare free of charge and without any discrimination based on their legal status (*Rule No. 24*).
- ✓ Medical care in prisons should be organized in cooperation with that of the general population to ensure continuity of treatment and care (*Rule No. 24*).
- ✓ All necessary facilities for assessment, diagnosis, prevention, and treatment (including for mental health and drug addiction) should be available on-site to meet the needs of prisoners (*Rule No. 27*).
- ✓ Data (medical records) should be kept professionally (sealed and protected) (*Rule No. 27*).
- ✓ No medical decision should be overridden or removed by non-medical staff (medical autonomy in prisons relative to administration) (*Rule No. 27*).
- ✓ Medical ethics and patient (incarcerated) autonomy should be respected alongside the protection of confidentiality and informed consent (*Rule No. 32*).

7.6. Ethical considerations confronted with real-world challenges

Ethical considerations are universal and timeless. However, their applicability proves challenging in the face of multiple economic, political, and socio-cultural issues.

7.6.1. The disregard for human dignity, degradation, and inhumanity.

The history of the widespread exploitation of prisoners in medical research has been marked by cult phrases coined by investigators who have engaged in this practice. These expressions outrageously reflect the disdain that a large part of the scientific community holds towards this population: «*I saw no differences between guinea pigs and Jewish children*» [45] (Doctor Heissmeyer, experiments on Tuberculosis, 1964), «*Prisoners are fine experimental material...and much cheaper than chimpanzees*» [46] (Mitford, 1973), «*All I saw before me were acres of skin. It was like a farmer seeing a fertile field for the first time*» (Doctor Kligman) [21].

Until early 2024, the legislative lobby in the US that opposes the use of animals in research laboratories is much more powerful than the one opposing the use of prisoners [46].

7.6.2. The racial paradigm

The dehumanization of prisoners under the Nazi regime aimed to confirm their racial inferiority in order to justify their executions [2]. Beyond the Nazi ideology, this concept remains relevant until 2024 and is responsible for one of the main causes of societal segregation. These segregations can be religious, political, social, cultural, or racial. The 'superiority of the white race' was the origin of apartheid in South Africa [47], the genocide of Native Americans, and the enslavement of Black people in the USA, and continues to persist as the root cause of the most serious fractures in American society, as illustrated more recently by the 'Black Lives Matter' movement.

7.6.3. The ethical considerations of scientific publication

Scientific publication serves as recognition for researchers and lends credibility to their methodology and results [48, 49]. The issue of using data from experiments on prisoners is not new, but it remains a

scientific taboo [50]. There are several illustrative examples, such as:

i) Pernkopf's Atlas of Anatomy. Eduard Pernkopf, a German anatomopathologist affiliated with the prestigious University of Vienna, developed this document, deemed of «high scientific quality» during the Nazi regime [50]. It is well established that this document was created using cadavers of victims executed under the Nazi regime [50]. However, this reference is internationally distributed and has been translated into at least five languages since 1990 [50]. Additionally, this document is available on the Internet without mentioning its controversial origins [50].

ii) The contested legacy of Doctor Kligman (see above): Despite the controversies [51], his works continue to be accessible through scientific search engines. One can find experiments involving the inoculation of humans with viruses [52, 53], specifying that the patients were mentally deficient, prisoners, and children [53].

iii) The issue of organ transplants from death row inmates in China [49].

8. In developing countries

In comparison to developed countries, the overwhelming majority of the incarcerated population worldwide is found in developing countries [54]. It was estimated to be 7.58 million people in 2020, which represents 71% of all detainees [54]. It is acknowledged that prisoners in this part of the world live in appalling conditions and are subjected to all sorts of abuse and exploitation [54]. There are «*No comprehensive*» ethical guidelines governing medical experimentation in developing countries, and the lack of literature on this matter reflects more on the actual condition of detainees in these countries [54].

Several obstacles must be overcome to shed light on this issue: First, it should be noted that the prevailing logic in some of these countries is primarily repressive, focusing on maintaining order [54]. Prisoners are not considered citizens, and the question of human rights does not even arise [54]. Second, Human rights violations in prisons across different countries are systematic [55, 56]. Third, administrative coercion, closely linked to the executive power in place, exacerbates the opacity surrounding this issue, preventing information from leaking outside prison walls [54].

The influx of pharmaceutical companies (from developed countries) into this part of the world, which has become their new preferred destination, raises concerns at multiple levels regarding the real applicability of ethical codes and international law [57, 58].

9. Perspectives

It appears that the issue of MEoPs remains one of the most illustrative ethical taboos of the ongoing exploitation of humans [9]. Despite numerous and evolving legislative efforts, in practice, the general observation is that the executive apparatus struggles to protect detainees in most prisons, particularly in those of the developing world [9]. This is certainly a pessimistic but unfortunately realistic observation, explained by the complexity of implementing measures on the ground to counter the persistence of abuses. Despite the commendable actions taken by certain international

organizations such as the International Committee of the Red Cross and Physicians for Human Rights) [59, 60], these actions remain insufficient. The authors of this work have previously explained the nature of the obstacles encountered and proposed potential solutions [9]. Box 3 outlines eight recommended actions and reforms to protect prisoners' rights in medical research. In the wake of successive and dramatic events that we are experiencing, we have the impression that the issue of MEoPs has been forgotten and pushed out of the collective interest, perpetuating this injustice in many prisons around the world in silence. Through this work, we hope to contribute to a general reawakening of consciousness leading in the not-too-distant future to the establishment of a consensual international action with effective and enforceable executive tools (*e.g.*; financial sanctions and risks of criminal prosecution) against the countries and actors of these abuses.

Box 3. Suggested actions and reforms for protecting prisoners' rights in essential medical research (modified from the reference [9]).		
N°	Area	Recommendation
1.	Informed consent	<ul style="list-style-type: none"> ✓ Clear guidelines: <ul style="list-style-type: none"> • Develop comprehensive and clear guidelines for obtaining informed consent from prisoners • Ensure the information is easily understandable, using visual aids or educational sessions to improve comprehension ✓ Independent review: <ul style="list-style-type: none"> • Implement an independent review process for informed consent to verify its authenticity and voluntary nature
2.	Ethics review board	<ul style="list-style-type: none"> ✓ Prison-specific review boards: <ul style="list-style-type: none"> • Create ethics review boards dedicated to research involving prisoners, including members knowledgeable about the unique challenges and ethical issues in prison research. ✓ External oversight: <ul style="list-style-type: none"> • Involve external experts in the review process to add impartiality and specialized expertise.
3.	Community involvement	<ul style="list-style-type: none"> ✓ Community representation: <ul style="list-style-type: none"> • Include representatives from the prisoner population or their advocates on ethics review boards to ensure their perspectives are considered ✓ Community consultation: <ul style="list-style-type: none"> • Engage in ongoing consultation with the prison community to understand their concerns and gather feedback on research proposals
4.	Benefit and risk assessment	<ul style="list-style-type: none"> ✓ Balanced approach: <ul style="list-style-type: none"> • Assess the potential benefits and risks of research, ensuring significant benefits and minimized risks, with consideration for the direct benefits to prisoners and society. ✓ Risk mitigation: <ul style="list-style-type: none"> • Establish measures to reduce potential physical and psychological harms, regularly evaluating and adjusting these measures as needed.
5.	Transparency and accountability	<ul style="list-style-type: none"> ✓ Public reporting: <ul style="list-style-type: none"> • Foster transparency by requiring researchers to publish findings, including unexpected outcomes or adverse effects, in accessible formats. ✓ Accountability mechanisms: <ul style="list-style-type: none"> • Implement mechanisms to hold researchers accountable and ensure compliance with ethical guidelines, which may include regular audits and reviews.

6.	Education and training	<ul style="list-style-type: none"> ✓ Training programs: <ul style="list-style-type: none"> • Create training programs for researchers, prison staff, and ethics review board members to improve their understanding of the unique ethical considerations in prison research. ✓ Communication skills: <ul style="list-style-type: none"> • Stress the importance of effective communication with prisoners to ensure they are well-informed about the research process and their rights
7.	Alternative research models	<ul style="list-style-type: none"> ✓ Non-invasive research: <ul style="list-style-type: none"> • Promote the use of non-invasive research methods to minimize physical and psychological impact on participants. ✓ Community-based research: <ul style="list-style-type: none"> • Encourage community-based participatory research models that involve the incarcerated community throughout the research process, from planning to dissemination.
8.	Legal safeguards/protections	<ul style="list-style-type: none"> • Advocate for and ensure legal protections for prisoners participating in research, ensuring voluntary participation and protection from coercion or undue influence.

Conclusion

Despite the extensive history of exploitation and the protective measures that have been implemented, prisoners are still viewed as an ideal "prey" for medical and pharmaceutical research due to their vulnerability and precariousness. The applicability of regulations depends on the executive powers in place, which are accused of either laxity or complicity. The authors urge international organizations, such as the World Health Organization, to organize a dedicated consensus on medical experimentation involving prisoners.

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Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

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COMPETING INTERESTS

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AUTHORS' CONTRIBUTIONS

MG: conceptualized and designed the study, drafted and revised the initial manuscript, critically reviewed the manuscript for important intellectual content.

HBS: drafted and revised the initial manuscript, and critically reviewed the manuscript for important intellectual content.

Both authors approved the final manuscript as submitted. They agree to be accountable for all the aspects of the work.

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DECLARATION

To enhance the academic writing of our paper, we employed the language model ChatGPT 3.5 [61]

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