# Unjustified Partiality or Impartial Bias? Reckoning with Age and Disability Discrimination in Cancer Clinical Trials

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**Abstract:** The exclusion of the elderly and people with disabilities from cancer clinical research without appropriate justification is discriminatory and is at odds with the ethos of EU principles, laws and research regulations. It further limits study generalizability. Several primary EU laws fronted by the European Charter prohibit engaging in disparate impact discrimination on the grounds of age and disability in all of EU tasks.

Elderly people and persons with disability have long faced a paucity of opportunities to enroll in innovative cancer clinical research due to exceedingly restrictive trial criteria and consequently raise ethical concerns about their rights as research candidates.[1] Recent systematic reviews of older adult participation in cancer clinical trials highlighted the multi-pronged complexities of their enrollment and retention in clinical trials[2] despite the disproportionately higher rate of cancer in this age group. People with disability also frequently face similar challenges as their disability is commonly used as an exclusion criterion.[3] Further, those with cognitive/intellectual disability or poor "performance scores," a measure of physical functionality, have often been an historic exclusion of most cancer trials.[4]

Clinical trials are considered the gold standard for evaluating the efficacy and safety of new medicinal therapies that eventually establish standards of care. Clinical trials, particularly in the field of cancer, have vastly expanded in recent decades, and their pivotal role in cancer care is reinforced by the plethora of emerging cutting-edge immunotherapy, cellular therapy, and biomarker-targeted therapies integrated with the broad use of innovative diagnostic and therapeutic techniques that defined precision medicine and which has burgeoned a previously inconceivable impressive development in the cancer therapy landscape[5] and improvement in cancer-related outcomes.[6] This is achieved through extensive investigation which includes a series of clinical trials; starting with determining the optimal dose of the anticancer intervention, how humans metabolize it, and any potentially harmful side effects (Phase I), then determining its initial efficacy in humans while continually monitoring for potential toxicities (Phase II) and finally determining its therapeutic efficacy in comparison to standard of care (Phase III). When successful, the European Medicines Agency (EMA) — the responsible body for the scientific evaluation, supervision and safety monitoring of medicines (i.e. pharmacovigilance)[7] and promotion of human health in the EU — can then use their results to approve new therapeutics and/or new indications for existing therapeutics. Phase IV studies are conducted after a therapy is provisionally approved by EMA and provide additional effectiveness or "real-world" data on the therapy. Despite the recognizable benefits of clinical trial participation, older adults and persons with disability have been

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systematically excluded from randomized clinical trials. Studies reported that less than 5% of all eligible adult patients with cancer, regardless of their background, actually enroll.[8] The recent COVID-19 pandemic exacerbated the pre-existing unequal access to healthcare services for older adults and persons with disabilities. It led to, amongst other emerging regional challenges, the reevaluation of the EU's laws and policies for human health agenda.[9] Blanket exclusions in some trials in the interest of preserving patient safety may be clinically necessary as it is at the heart of most such exclusions. But too-tight criteria end up keeping out the patients most in need and exacerbate existing cancer health disparities. Further, many exclusions are not well-justified. Pertinently, such exclusions limit the scientific reproducibility of data essential in evaluating the efficacy, dosage, and adverse effects of the treatments in older adults and people with disability and ultimately threaten equitable access to cancer therapies.

There are currently no legal provisions requiring investigators to justify exclusionary criteria. It can be argued that in the interest of patient safety such patients are excluded where "risks which may be incurred by that person are not disproportionate to the potential benefits of the research." This would be in line with the ethical principles of research subjects' protection and a tenet of the medical professional.

Legislative procedures are in place to ensure adequate standards of healthcare are exercised and maintained by healthcare providers and researchers alike. In the European Union (EU), EU Treaties represent the legal foundation for the adoption of any EU legislation, with the Treaty on European Union (TEU) as its backbone and the Treaty on the Functioning of the European Union (TFEU) outlining specific provisions to the policies and institutions. Article 3(3) and (5) of the former[10] encourage promotion of "scientific and technological advance" and "protection of human rights," respectively, with the latter[11] providing more explicit emphasis on public health matters. Article 19 (ex Article 13 TEC) of the TFEU, which aligns with Article 21(1) of the Charter of Fundamental Rights (CFR), empowers the EU with the competency to adopt legislative acts on prohibition of discrimination on several social grounds, including age and disability.[12] The CFR, which serves as a point of reference in EU law and is embedded into the EU constitution with the Lisbon Treaty, has the same legal value as the EU treaties as per Article 6(1) of the TEU,[13] such that the Court of Justice of the EU (CJEU) can draw upon it when adjudicating rights to health across the EU. Article 25 of the Charter articulates further the rights of the elderly.[14] The rights of persons with disability are protected under Article 26 of the same Charter[15] which prohibits against their discrimination on disability grounds and recognizes their rights to integration. The Revised European Social Charter of the Council of Europe through its treaty system guarantees, inter alia a range of human rights, the right to health with specific emphasis on protection of such rights of vulnerable persons including the elderly and those with disabilities.[16] It goes further in stipulating non-discrimination in its clause as enunciated in its article E.[17] Drawing on the core principles of the European Convention on Human Rights,[18] the Oviedo Convention[19] — the Council of Europe's legal regulation and the only international legal binding tool that sets provisions on protection of human rights in the field of biology and medicine — aims at protecting, without discrimination, the bio-rights, integrity, dignity, safety and identity of all human beings where biology and medicines is applied. It also aims at promoting scientific and biotechnology developments and whose principles are applicable to any medical act including biomedical research.[20] It upholds the concept of equitable access to health care as articulated in article 3 of its general provisions.[21] These rights are also protected under the 2006 United Nations (UN) Convention on the Rights of Persons with Disabilities,[22] which the EU endorsed in 2010 and reflected on with the core elements of European Disability Strategy 2010-20.[23] Specifically, this paper explores its preamble, which highlights provisions for undertaking particular protection to those who may be deemed vulnerable in the context of research.[24] Similarly, the Convention on the Rights of Persons with Disabilities, which stands as an integral part in the EU legal order[25] enshrines the equitable access to all human rights and dignity for all persons with disabilities.[26] By extension, the EU



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pharmaceutical legislation — the EU Regulation No. 536 of 2014,[27] hereinafter EU-CTR, which replaced the EU Clinical Trials Directive, enacted as of January 31st, 2022, contains provisions outlining the principles of the draft guidance on diversifying clinical trials through fairer representation of the traditionally underrepresented and underserved groups. It places emphasis on diversity as depicted in the following text: "Unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trial..."[28] It also contains additional prescriptive rules on the inclusion of vulnerable groups including "frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups.."[29] and "persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, and persons, who due to their age, disability or state of health are reliant on care and for that reason accommodated in residential care institutions, that is accommodations providing an uninterrupted assistance for persons who necessitate such assistance, are in a situation of subordination or factual dependency and therefore may require specific protective measures"[30] in clinical trials. The EU-CTR's deliberate and purposeful inclusion in clinical research serves as an added protection for such vulnerable groups and supports the validation of best management on a clinical trial.

The EU legislation under Article 179[31] and 182(1) TFEU provides measures to encourage research. This includes galvanizing pharmaceutical companies to develop medicines and technologies for rare conditions such as cancer through a system of obligations, rewards and incentives such as fee deductions when obtaining scientific advice from EMA to encourage manufacturers to research and develop medicines for specific patient groups. Additionally, the Commission's Europe 2020 strategy,[32] which is a "watered down" version of the 2000 European Council Lisbon Strategy[33] following the European financial crisis, maintains its initiatives to invigorate economic growth through research and innovation amongst other targets. Under EU law, the EMA, whose recommendations are what determines the legally binding decisions issued by the European Commission (EC), can publicize areas of unmet need for new medicines to encourage interested parties to research them. The EU-CTR obligates academic and pharmaceutical institutions that develop and host clinical research to provide equal access to participation in clinical trials for elderly patients and those with disability. Yet despite such obligations and provisions stipulated in EU legislations and directives and international laws, older adults and persons with disability remain starkly underrepresented in cancer clinical trials, an issue that has been long-standing, deeply entrenched and steadily increasing over time.[34] Further, the apparent incongruity of legislative calls for equity and implementation in cancer research highlights that there are still ongoing challenges in this area for law and regulation. There are currently no legal provisions requiring investigators to justify exclusionary criteria. It can be argued that in the interest of patient safety such patients are excluded where "risks which may be incurred by that person are not disproportionate to the potential benefits of the research."[35] This would be in line with the ethical principles of research subjects' protection[36] and a tenet of the medical professional.[37] Little attention has been focused on the role of clinical trial design in addressing equity of access to the underserved populations and whether easing, or better yet modernizing inclusion criteria to include these population. Broader questions are also raised about the ways in which a culture of implementation on one hand and respect for law and ethical obligations on the other plays a fundamental (and not necessarily always beneficial) role in shaping cancer healthcare research practice, as neither has used the full arsenal of legal and policy tools at its disposal to push for equal access. Further, concerns have been raised about the apparent lag but also challenges of regulating risks of a rapidly evolving field of techno-scientific research.[38] This leaves us with important questions regarding the extent to which EU laws, with its model for advanced and well conformed regional and constitutional order and where a right to research is well embedded in law and in policy, can and/or should shape the contours of cancer research and care. Additionally, whether its "Right to Research" has conceptualized inclusivity and diversity of clinical trial participants through impartial representation of the underrepresented patient groups.

In the first part of the paper, I have focused on the legally binding EU-CTR inclusivity provisions for older persons and persons with disability given their inter-relatability to evaluate the congruence of recently registered clinical trial protocols with these groups in cancer clinical trials through qualitative and quantitative analysis of eligibility criteria. I will next examine the implications of Charter and EU-CTR on cancer clinical trial protocols with particular interest centered on examining the eligibility criteria trends for



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EU-based cancer trials for older patients and patients with disabilities. I will then consider the prohibition on discrimination that EU legislation and by extension enunciated by EU-CTR and the unique challenges of applying Charter in cancer clinical research context. Finally, I will offer recommendations on what regulatory gaps need to be identified and how they can be filled. Consistent with this approach, this paper does not discuss non-EU laws, nor does it explore non-EU legal instruments for the purpose of EU law, which are beyond the scope of this paper.

## Methodology and Data

An advanced search function on beta.ClinicalTrials.gov was conducted on May 5th, 2023, using the following search filters: lymphoma; interventional studies; each individual EU member state (inclusive of Iceland, Norway and Liechtenstein as the EU-CTR is applicable in these countries); age groups of adults (18-65) and older adults (65+) and start date between January 31st, 2022 and May 5th, 2023 inclusive. Lymphoma was chosen as the representative category of cancer subtype for several reasons; it is a frequent cancer in older patients with 50% of cases occurring in patients aged 65 and older,[39] the author's specialist interest and author's access to full study protocols. Only interventional studies, irrespective of phase, were included as the EU-CTR only regulates this category of clinical trials. As the EU-CTR became effective as of January 31st, 2022, the search only included those trials registered on or after that date.

Each trial protocol was evaluated for whether eligibility criteria stated an age limit and whether a pre-existing disability (unrelated to the lymphoma diagnosis) was an exclusion criterion. Age discrimination or ageism was determined as explicit where age cut-offs for clinical trial eligibility was noted or implicit where it limited access or created barriers to clinical trial eligibility. As for disability, there is no other harmonized definition, at least in the EU. In EU law, the concept of disability does not have a common definition and currently depends on the definition used by each member state's law. Nonetheless, both the EU and its member states refer to the definition conceptualized in Article 1 of the United Nations Convention on the Rights of Persons with Disabilities,[40] which is adopted by the CJEU and revised in 2013 and corollary, as interpreted in EU secondary legislation. It refers to "an impairment that is 'long term' and which, in the field of professional life, 'hinders an individual's access to, participation in, or advancement in employment.'"[41] For the purposes of this study and in line with the aforementioned definition for disability, any of the following categories were considered as disabilities; cognitive/intellectual, psychiatric, visual, hearing, speech, communication and/or mobility. Protocol evaluation also included whether the protocol provided justification for the exclusion and whether reasonable adjustments/measures to support disability were explicitly permitted for the given disability and/or investigator discretion through a review of wording of the protocol.

## Results

A total of two hundred nineteen clinical trial protocols were identified that met the search criteria and were analyzed. One hundred forty-two studies were excluded as they were duplicates. The final analysis included seventy-seven clinical trials. Upper age restriction enrollment criteria were identified in eleven (14%) trials. Only four (5%) of the trials were designed specifically to include older patients. People with mobility disability, determined by the study protocol as those who at best are "capable of only limited self-care; confined to bed or chair more than 50% of waking hours"[42] and/or "requires occasional assistance but is able to care for most of personal needs,"[43] were excluded in forty-six (59.7%) reviewed studies. Only six trials explicitly permitted their participation in the trial with a further one only if their performance status improved upon pre-phase treatment. Twenty (26%) protocols permitted investigators' discretion to include and/or exclude participants. Qualitative analysis revealed that some protocols provided this discretion based on concerns for participant safety or compliance with the investigational treatment, such as "concurrent severe and/or uncontrolled concomitant medical conditions (e.g., active or uncontrolled infection or renal disease) that could cause unacceptable safety risks or compromise compliance with the protocol." One protocol permitted discretion on the basis of investigator's opinion of expected survival beyond twenty-four weeks. Reasons for exclusions were noted as chronic illnesses in fifty-two (67.5%), psychiatric in twenty-three (30%) and cognitive or intellectual disability in thirteen (17%). Only six trials specified severity of the disability with "severe" deemed as an exclusion criterion. A very limited number of trials excluded participants on the basis of the patient's need for long-term care (3) and only one excluded participants with visual disability. None of the trials excluded participants with hearing or speech/communication-related disabilities. Relatively few study protocols included justifications for these disability-related exclusions. The total frequency of justifications for exclusions was forty-six (60%) and seventeen (22%) by disability. The justifications for exclusion of people with cognitive and intel-



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lectual disabilities typically concerned capacity to consent or "interfere with the participation or completion of the protocol." The justifications for exclusion in the psychiatric illnesses were primarily phrased in terms of safety or potentially "makes the patient unable to comply with study procedures and visits." Only twenty-six (34%) justifications were specific and appeared to be rooted in safety concerns.

## Discussion

These are just a few of the many cancer studies showing that, despite the EU-CTR recommendations, elderly patients and persons with disability are still underrepresented in cancer trials, and data on justification of exclusions are often missing in approval documents. A 2014 study which analyzed the participation of older people in preauthorization trials of recently approved medicines found that approximately a third of clinical trials excluded people purely on the basis of age.[44] The PREDICT stud,y which examined the professional views across nine European countries, found that older people and those with comorbidity continue to be excluded unjustifiably from clinical trials, with 87% agreeing that exclusion from clinical trials on age grounds alone was unjustified and 79% and 73% deemed under-representation of older people in trials caused difficulties for prescribers and patients, respectively.[45] Inflexible trial protocols that disproportionately penalize people from disadvantaged groups only serve to widen the disparity gap. Of course, the inclusion of patients with multi-morbidity — additional health conditions and polypharmacy — when people are prescribed multiple medications, can be seen as inconvenient since it increases variation in outcomes and challenges the principle of standardization. Further, the physiological effects of aging coupled with comorbidity and polypharmacy could alter the efficacy of a cancer drug. Additionally, older persons are renowned to be at a higher than expected increased risk of adverse drug reactions[46] and drug–drug and drug–disease interactions given the frequent polypharmacy and particularly in cancer care settings.[47] But considering that continuing to prescribe ineffective medicines is expensive, which would unnecessary drain resources of already-overstretched healthcare systems, a major overhaul of current practice to explore the roles and limits of the law and ethics in regulating cancer health-related research ought to be conceptualized.

## Age and Disability: Scope of the Problem, Ethical Relevance and EU Discourse

A fundamental determinant of health in the EU, age and disability continue to shape access to important healthcare resources, including cancer clinical trials. Health is a very expensive item in any EU member state and, as such, healthcare expenditures are of prime concern for the EU's budgetary and its member states' long-term economic viability which drive its fiscal governance. In 2021, the general government total expenditure on health alone in the EU amounted to €1,179 billion or 8.1% of GDP.[48] For the older patient, access to life-sustaining preventive care and treatments is often limited by explicit or implicit age-based criteria. In fact, access to virtually all types of healthcare, ranging from routine preventive cancer screenings such as mammography or colonoscopy to more expensive life-sustaining treatments is limited by ageist policies. A study of over 9,000 hospitalized patients predating COVID-19 noted that healthcare professionals were significantly more likely to withhold life-sustaining treatments for older persons, even after adjusting for patients' prognoses and preferences, a practice that persists to date.[49] This particularly features in countries with nationalized health insurance. In cancer trials, only 24% of participants are aged 70 years or older despite constituting 42% of the total cancer population.[50] Cancer is primarily a disease of aging. And with the world's population aging, so does the incidence of older people with cancer increase. The EU is no exception, as its demographic aging is likely to become of major significance in the coming decades, not just driven by rising life expectancy, but also superimposed by the consistent decline in birth rates. Based on the 2022 EU census, people aged 65 or older represented 21.1% of the population which is up by a 0.3 percentage points (pp) from the previous year and 3.1pp compared with 10 years earlier.[51] Therefore, the pervasive issue of aging requires fuller recognition in the health research context.

With the exception of Charter, the TFEU and the Revised European Social Charter, age is typically not included in international human rights laws' and treaties' provisions for non-discrimination and equality. Perhaps this stems from the notion that age does differ from other non-discrimination societal characteristics covered under EU law in certain valid circumstances, for instance, when it is deemed a rational and legitimate reason for distinguishing between different groups of individuals not applied to the other nondiscrimination grounds. As alluded to earlier, it may be grounded in rational considerations aimed at serving member states' finite resources and its individual respective social, fiscal and economic objectives, thereby it can be argued as not a "serious form" of discrimination.[52] Though age discrimination remains off the list of particularly suspect grounds that require "very weighty



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reasons" such as ethnic origin or gender, for instance, age may fall under the category of "other status" in the European Court of Human Rights (ECtHR).[53] Further, non-discrimination on grounds of age is accepted by the CJEU as a general principle of EU law.[54] Notwithstanding, these provisions advocate non-discrimination and equal treatment as part of their ethos and permit allowances for difference in access to health care facilities insofar as a proportionate, reasonable and objective justification and as has been epitomized in the UN Committee on Economic, Social and Cultural Rights; "In order to eliminate substantive discrimination, States parties may be, and in some cases are, under an obligation to adopt special measures to attenuate or suppress conditions that perpetuate discrimination." This has also been stipulated in the EU-CTR: "a justification for the gender and age allocation of subjects and, if a specific gender or age group is excluded from or underrepresented in the clinical trials, an explanation of the reasons and justification for these exclusion criteria."[55] Further, the UN Economic and Social Council declared that "such measures are legitimate to the extent that they represent reasonable, objective and proportional means to redress de facto discrimination and are discontinued when substantive equality has been sustainably achieved."[56] And whilst explicit age-based criteria have been removed, implicit age bias remains in effect, limiting access through referral patterns and other barriers. In healthcare, age-based rationing of critical, life-sustaining care has yet again become explicit during the time of COVID-19 as a solution by many healthcare systems worldwide to curb the challenges of critical shortages of ventilators and intensive care unit beds.[57] I take an exceptional view on this as these strictly age-based criteria clearly discriminate by age and do not allow consideration of differences in long-term prognosis, functional status, and patient preferences. The extant notion that "older adults are expendable"[58] reflects the disturbing and pervasive problem of ageism. Whilst they are often viewed as an economic strain on resources and frequently presenting various egregious challenges to labor markets, government tax, government spending and the wider economy, a recent economic analysis contradicted this. In the latter, it noted that adults in Europe and the US aged 60 and over were estimated to make contributions to the economy in the order of over $250 billion per year.[59]

Further, and on broaching the matter of persons of disability, the prevalence of physical disability rises as age increases, with more than 46% of persons aged 60 years and over having some form of disability.[60] The levels of people with disability inclusivity in cancer trials is illustrated by the outcome gaps between people with and without disabilities.[61] Over 1 billion people (15% of the global population) have a disability. There is no complete statistical assessment of disability in the EU, but based on data from the World Health Organization (WHO), there is an estimated 135 million people in Europe who live with disability and 6-10 percent of people are living with a disability in member states of the WHO European Region. Unlike age, the ground of disability has progressively become a separate yet complex and stratified sector of EU law.[62] Despite the many laws worldwide prohibiting disability discrimination, suboptimal cancer care because of late diagnoses and/or inadequate treatments that are not adapted for their specific needs and circumstances are commonplace. Much like older patients, understanding cancer treatment tolerance and outcomes for people with disability with underlying comorbidities that contribute to their disability is marred by their exclusion from clinical trials, thus limiting robust, scientific-based qualitative evidence that helps guide treatment decisions.[63] The dearth of data also limits access to the potential benefits of participation, jeopardizes the generalizability of research findings, and makes it harder to gauge the impact of cancer drug interventions on older people and people with disabilities and to study the effects of legal and policy interventions. Health funders/insurance programs may inappropriately limit access to needed drugs, therapies, or devices for people with disabilities based on health technology assessments of comparative product effectiveness and safety, cost-effectiveness, and societal benefit derived from study findings that excluded them from participation.[64] Whether their purported worse overall survival and/or progression-free survival rates is directly attributed to their underlying conditions remains unclear as a result.[65] In clinical trial settings, one confounding measure of physical (dis)ability is performance status (PS). It is one of the most common eligibility criterion in oncology trials with several trials excluding poor-functioning participants in favor of high-functioning ones on the basis of traditional and perhaps outdated scales that were designed to determine the ability of the patient to tolerate therapies in serious illness, specifically for chemotherapy. The underlying cause for poor PS, however, is not always articulated in their exclusion criteria, which is pertinent in oncology settings as disease burden can contribute to poor PS and the intervention under investigation as well as improve it. But also, PS is inherently subjective with interrater variability, thus opening potential for bias particularly for patients at the borderline between values.[66]



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Further, clinicians often assign older patients higher numeric PS scores than younger ones, despite lack of objective difference in measured physical activity.[67] In addition, currently used PS scales are inadequate in patient aged 65 and over as it is less predictive of cancer-related outcomes in this population.[68] Restrictive PS eligibility criteria contribute to the pervasive age disparity between trial participants and the overall cancer population, raising concerns about whether PS is unjustly limiting older populations' ability to participate in trials. About one-third of the clinical trials have eligibility criteria that directly excludes individuals with intellectual disability or cognitive impairment based on their diagnosis or legal capacity to provide consent, and about two-thirds of clinical trials have eligibility criteria excluding individuals who might not be able to read or write, lack such functional skills as self-care skills or the ability to read and write, do not have access to technology, or who, in the view of the research team, are unable to complete study procedures, safely engage in the research, have the necessary health status or may otherwise confound study findings. These are exclusion criteria that adults with intellectual disability may be more impacted by due to systemic oppression and other social factors.[69] The ECtHR statutes require covered entities to take affirmative steps to facilitate the inclusion of people with disabilities, provide reasonable accommodations and make modifications to permit access. This obligation is not, however, unlimited; for instance, covered entities are not required to make modifications that would constitute a "fundamental alteration" of the program or service in question. However, they represent a set of responsibilities that go beyond what many investigators may be familiar with from other interpretations of nondiscrimination. More explicit justification of eligibility criteria would permit rational evaluation and review to determine whether accommodations or alternatives are possible.

## Exploring the Legal Scopes of CFR in Clinical Research and the Role of EU-CTR

Equality and non-discrimination are well grounded in the philosophical, political and constitutional traditions and fabric of the EU.[70] The CFR, which is regarded as the social constitution of Europe, enshrines these traditions into EU law as rights for EU citizens and residents. Following the entry into force of the Treaty of Lisbon in December 2009,[71] the CFR attained a legally binding status. Title III (Articles 20-26) of the Charter prohibits discrimination on any grounds and without prejudice to any of the associated treaties.[72] The Charter also stipulates that such prohibition extends to the right to access of all aspects of health care.[73] It calls for strengthening provisions that protect the fundamental rights within each member state in the face of socioeconomic progressions and scientific developments through making these rights more visible. It prohibits discrimination that may have a disparate impact on those that are most likely vulnerable as set out in its Article 21(1). Specifically, it recognizes the rights of the elderly in article 25 and persons with disability in article 26. However, the provision in Article 21(1) of the Charter "only addresses discriminations by EU institutions and bodies, when exercising powers conferred under the Treaties, and by Member States only when they are implementing Union law. It does not create any power to enact anti-discrimination laws in these areas of Member State or private action, nor does it lay down a sweeping ban of discrimination in such wide-ranging areas". Article 19 of the TFEU furnishes six grounds where appropriate action to combat discrimination is mandated and without prejudice to other provisions of the Treaties under special legislative procedure.[74] Age and disability are each one of these six grounds. It further establishes, as previously stated, that "the European Parliament and the Council, acting in accordance with the ordinary legislative procedure, may adopt the basic principles of Union incentive measures, excluding any harmonization of the laws and regulations of the Member States, to support action taken by the Member States…"[75] in support for achieving its primary objectives of non-discrimination. Unlike Article 21(1), this may cover actions of member state authorities and private individuals in any area within the scope of the EU's powers.

Though not as specifically defined as in the CFR, the EU-CTR laid out provisions for expansive promotions for equal access to participation in clinical trials established by sponsors in the EU member states. As the EU's pharmaceutical legislation, the EU-CTR effectively became directly applicable domestic law in all EU member states as of January 31st, 2022[76] and consequently, explicitly requires states to legislate on penalties for the infringement of the regulation.[77] Explicit discrimination can sometimes be difficult to prove but where it demonstrated, Title VI (Justice) of the Charter[78] permits institutions, bodies, offices and agencies of the Union to execute Title III provisions as part of the Charter's scope;[79] i.e. the right to an effective remedy — a condition sine qua non for the effective guarantee of the Charter's preamble. However, only the government of each member state and not an individual, and that generally through a parliamentary act, can decide how to act and what penalties it may enforce for when a clinical trial violates regulation. National medicines



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regulators within each member state are empowered by the EU-CTR to oversee and enforce the regulation. They are specifically tasked to monitor the trial sponsors in their country[80] and enact corrective measures.[81] Therefore, the enactment of clinical trial conduct in each country will depend not only on their respective legal framework, but also on how proactive national regulators are. Further, it has been argued that the purpose of the changes introduced in EU-CTR serve to optimize the pharmaceutical market, ergo profit over key public health objectives of protectionism of research outcome and its participants.[82] In doing so, it bears the potential for skewing and/or even overlooking more pressing health conditions such as cancers in the already underrepresented patient groups, thereby exacerbating inequity rather than mitigating it. The EC has the overall duty to ensure the application of EU law in all member states [83] and supervises the enforcement of the regulation by the national medicines agencies. Where a member state does not comply with the law, the EC has the power to initiate an infringement procedure.[84] In this, the EC first notifies the infringing member state with a so-called "Reasoned Opinion," giving the member state the opportunity to reply and come into compliance. If the Commission is still unsatisfied, it can bring the infringing member state before the CJEU. If the court finds that the member state has indeed infringed the law, it can impose a fine for every day that infringement continues.[85] The EC has made it clear that the provisions of the Charter apply to all of the operations of the EU in all their actions and to member states when they are implementing EU law, and, thus, by extension, pharmaceutical industries of the EU that sponsor clinical trials and EU medical establishments that sponsor and/or conduct them are not exempt. One may argue that the Charter's obligation does not extend to extraterritorial third parties and could well amount to a regulatory insufficiency. That is, there is insufficiency within the relevant Charter's rules to recognize the rights of those protected under its scope of application beyond the EU and, in turn, this means that the regulatory domain in which Charter operates is itself fundamentally deficient. This deficiency, it is argued, is counterbalanced by a pro homine clause within its Article 53 scope on the non-restrictive level of protection of fundamental human rights being complemented by the ECtHR (as articulated by Article 52(3)), but also international human rights law embolden the EU's obligations within the normative precept to safeguard and preserve such rights beyond its borders where core substantive rights protected under the Charter are at stake.[86] It is through the ECtHR's inherent primacy in the EU's fundamental legal order, reinforced by the Charter's catalogue of rights, which prevails over EU secondary legislation and is directly applicable for the purpose of interpreting the fundamental rules of the Charter. And it is incumbent on the CJEU as the judicial body to safeguard those rights recognized by the ECtHR in the EU legal order when interpreting and implementing EU law and the Charter.

In sum, Title III of the CFR is designed to provide comprehensive protections and promotions that mandate fundamental rights to EU citizens in terms of equal access to the life and work within EU member states and European Economic Area (EEA) countries. It applies to all national authorities and EU institutions and bodies that implement EU law in all their actions. However, both researchers and sponsors have paid little attention to how the Charter applies in the research context. It is these implementation issues that I will address next.

## Limitations to Implementation of the CFR Specific to Clinical Trial Settings

Building on the above, the Charter's preamble embodies the EU's consensus on commitment to respecting fundamental rights inclusive and not limited to provisions of expansive protections that mandate equal access to all aspects of healthcare including clinical trial participation. It prohibits discrimination on several grounds with age and disability included. Title III addresses this where it specifies that "Everyone has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection shall be ensured in the definition and implementation of all the Union's policies and activities."[87] The phrase "high level of human health protection shall be ensured" represents certain normative responsibilities and provisions in clinical research settings including, but not restricted to, health promotion, care, and support. From a constitutional perspective, the Charter being a primary EU law lays down the general principles of EU law and aids interpretation and judicial review of secondary EU law, as well as national law implementing EU law. The Charter, however, does not empower the EC to intervene where fundamental rights are breached, nor does it render new remedies to effectuate human rights. Rather, where legal conflict in national or legislative measures arises and/or is incompatible with the Charter, EU law takes precedence over national laws of individual EU member states in accordance with the principle of primacy.[88] Primary law instruments do not, however, provide explicit descriptive



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policy measures on how to achieve compliance on the principle of equality in access to healthcare, nor is it enforced in clinical research context. Proscription of discrimination in healthcare on the grounds of age or disability is also not specifically addressed under EU secondary law, as it primarily depends on national regulations and their interpretation of the law. For instance, the EU-CTR does not specifically outline non-discrimination protection in access to clinical trials. It can be argued that clinical trial procedures can be arduous, overbearing and potentially deleterious for many older patients and those with disability such that it abrogates their clinical benefit to participants, but also the associated burden of treatment, and access difficulties, may form practical barriers. And given that clinical trials are precisely concerned with uncertainty in the applicability of an investigatory agent to produce new understandings, failing to provide equal access to clinical trials does not necessarily harm prospective participants. Further, and despite their primary status in EU law, the impact of Articles 21(1), 25 and 26 of the CFR in the development of case law pursuant to the horizontal clause of Article E of the Revised European Social Charter[89] is somewhat stifled. This, perhaps, may have curtailed the instigation of jurisprudence in light of the rules articulated in Title VII of the CFR regulating its interpretation and application, specifically Article 52(3) on the relationship between the Charter and ECtHR and Article 52(1) on justified limitations. In regards to the latter, the Charter stipulates possible limitations on the exercise of such rights as it addresses proportionality: "limitations may be made only if they are necessary and genuinely meet objectives of general interest recognized by the Union or the need to protect the rights and freedoms of others."[90] Insofar as limitations are concerned, these are justified if provided for by law, necessary and genuinely meet objectives of a general interest, are proportionate, and respect the essence of the right. This particularly resonates in utilitarian ethical views when justifying the use of age as a resource allocation criterion. But even then, the legal basis that permits such interference must be defined in terms of its scope and have a close relationship to the proportionality measure applied. Such incongruity, which is incompatible with the CJEU as the fundamental rights tribunal in upholding the rule of EU law, implores the reexamination of the Charter's rules on respect for individual rights in legal disputes where discrimination against the elderly and people with disability are concerned. It therefore highlights the need to develop the notion of reinforcement of the rigor with which Articles 21(1), 25 and 26 of the Charter are treated as principle provisions for the protection of fundamental rights articulated in its preamble and that requires the re-evaluation of the Charter's rules and its relationship with EU legislation, and its provisions designated more broadly to bolstering its enforcement to mitigate inconsistencies.

It follows that although the principle of equality is one of the basic values enshrined in EU laws, binding normative acts of the EU only marginally regulate the steadfast issue of equal access to healthcare when faced with the challenge of limited resources. It requires reflection on appropriate regulatory responses to equity in cancer research, including the re-examination of ethical concerns, and an examination of fair access to innovative research to the underserved populations.

Clinical trials provide mutual benefits to both the participant and the investigator/sponsor. For a cancer patient, it perhaps offers the only opportunity to receive innovative treatment not available otherwise outside a clinical trial setting, and may even be the only option where other treatments would be unsuccessful. For sponsors, their participation and inclusivity offers scientific knowledge and provides good evidential base that an intervention is effective for different groups without which systematic bias and underpowered analyses may be a consequence. This jeopardizes the efficacy of trials and equity of healthcare outcomes. Neither the EU-CTR nor the Charter provide the right to participate in any particular clinical trial. Further, private actors such the pharmaceutical companies are under no obligation to comply with the Charter where an EU task is not performed. Medical establishments that offer clinical trials must provide their patients with the opportunity to participate



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on equal terms to foster equitable access to participation in cancer clinical trials to improve health equity through access to care. It is likely that those responsible for research processes may not fully appreciate that CFR's strict interpretative approach mandates that eligible patients receive equal access to participate in clinical trials, even if their participation does guarantee direct clinical benefit. The vast majority of researchers do not intentionally discriminate on the basis of age or disability as they are directed by eligibility criteria and study protocols. Rather, it is the culmination of implicit, often unconscious biases and/or multiple barriers to research participation.[91]

It follows that, although the principle of equality is one of the basic values enshrined in EU laws, binding normative acts of the EU only marginally regulate the steadfast issue of equal access to healthcare when faced by the challenge of limited resources. It requires reflection on appropriate regulatory responses to equity in cancer research, including the reexamination of ethical concerns, and an examination of fair access to innovative research to the underserved populations.

## Recommendations

Promoting clinical trial access diversity for cancer patients creates participation opportunities for these marginalized groups that may otherwise have no viable access to innovative treatments. It will also afford reflections on real world evidence and improves generalizability of generated research results. Clinical trials must step up to the innovative drug developments through modernizing their designs. The key to achieving this is through congruence of the constitution of clinical trial subjects with the targeted treatment population. However, decisions around eligibility must be justified at each stage of the trial design and delivery, to determine which exclusions are necessary and which are not. Specifically, trial sponsors should justify exclusion of patients with disability and limit exclusions to those affecting patient safety and trial integrity. It is not uncommon that such protocol-driven barriers are due to a lack of awareness or enforcement of existing laws and regulations which could be reinforced through accountability to existing regulatory reviews. For instance, in the case for persons with disability, the UN Convention stipulates that parties to the convention should use statistical data to formulate and implement policies that "address the barriers faced by persons with disabilities in exercising their rights" and "with considerable detail, how the rights it proposes to protect are to be implemented and guaranteed."[92] Explicit chronological age-based cut-offs in cancer trials, for instance, have largely been rejected on the premise of age discrimination yet continue to be applied. Current approaches favor the allocation of resources based on allowances for the initial severity of disease (that is, likelihood of survival of the hospitalization) and long-term prognosis (that is, likelihood of survival for five years or more). Assuring equitable access to cutting edge cancer therapies to older patients, who are often disproportionately affected by cancer, is fundamental for an anti-ageist healthcare system. Promoting geroscience — the research into the basic mechanisms of aging, pathophysiology of age-related disorders and development of biological treatments to improve clinical interventions, is part of the solution. Designing elderly-specific trials that also include older adults, their family caregivers and geriatric experts helps older patients' access better-tailored care, although such stratification has raised concerns about discrimination, but then such approach is not dissimilar to pediatric-specific trials. Elderly-specific cancer trials recognize that older patients are not similarly situated to younger patients, and have genuinely different needs and ethical entitlements, but nonetheless have a claim to benefit from research. Their health is different. Their goals of therapy are different. Even their cancer is different with unique aspects of disease presentation. Strategies to enhance inclusion should include staff training, minimizing exclusions for stable conditions, involving geriatric experts in enrollment procedures, building flexible schedules and approaches for participation, and enlisting family cooperation and proxy consent. Age diversity is crucial to securing the evidence that older patients deserve, and supporting clinicians to prescribe medicines that are effective and provide value for money. To avoid age-based bias, consensus panels and involvement of ethics committees should utilize an interdisciplinary group for complex decision-making — including geriatric expertise and considering all evidence, along with the patient's and family's goals for care to address patient, provider and system factors and clinical barriers, including patient-level and provider-level barriers. Equally, trials need to be more accessible to patients.

In February 2021, the EC presented its roadmap to achieving this through its Europe's Beating Cancer Plan and its flagship cancer equity initiatives[93], which has worked to address the underrepresentation of diverse populations in the cancer research field. The EMA, EU-CTR and relevant oversight bodies should follow through this vision and promote compliance with EU laws on equality as part of its remit, by providing additional clarity for investigators and institutional review boards (IRB) on legal obligations on how



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CFR applies to the clinical research context and best practices with respect to the inclusion of under-represented populations, including contemporary examples of concepts such as reasonable accommodation, fundamental alteration, supported decision-making, and similar legal constructs. Further, the EMA can play critical roles in achieving such outcomes by supporting policies that require representation and providing funding levels and capacity-building opportunities that provide researchers the necessary resources and skills to flexibly include adults with intellectual disability in clinical trials.

The pharmaceutical industry, which sponsors 60% of clinical trials, is uniquely positioned to drive forward inclusivity. More effective biomarker-driven therapies warrant reconsideration of the traditional approaches. Broadening eligibility criteria to be more inclusive can increase the number and diversity of trial participants. One way of doing so involves augmenting consent capacity through environmental modifications to increase the understandability of consent materials; this emphasis on accommodations to enable equal access is consistent with EU laws. Another piece involves meaningful assent procedures when someone does have a legally appointed guardian. A third piece requires rigorous scrutiny of eligibility criteria and their assessment so that criteria are appropriately justified and assessed via standardized processes. A fourth piece involves harnessing the concept of "inclusive citizen science" defined by the EC as "any activity that involves the public in scientific research and thus has the potential to bring together science, policy makers, and society as a whole in an impactful way"[94] to promote inclusivity and address the unmet needs in biomedical research; i.e. democratizing science.[95] Not only does this align with one of the principles of EC's work ethos, but it is also embedded in several EU projects and initiatives.[96] Flear had argued that although citizen science can be perceived as empowering citizens through their participation in the governance of research, it has been "institutionalized as part of the production and legitimation of sociotechnical order" in EU law and policy that supports market-oriented priorities.[97] As citizen science garners increasing interests in the EC agenda and its stakeholders, it is important that EU law and policy respond to the nuances that arise from regulating this field of biomedical research. As a prerequisite to an adequate regulatory response, any iterations must take a broader view of what is at stake and foreseeable risks. Flear's "key agendas for further work" would be a start.

Further, implementation of these recommendations will require greater collaboration, and even co-production, of research regulation by various stakeholders in cancer research for a more adaptive, flexible and proportionate response to equity challenges. This can result not only in delivering good medical research for the public good but also incentives following EMA market approval. Further, I posit that regulatory stewardship requires fuller recognition and better integration of the approach into the effective functioning of law and regulation in the health research context to ground more robustly the moral legitimacy for equity in cancer research.

## Conclusion

Cancer trials have largely been driven by the constant need for drug development in the realm of precision medicine. They are the gateway to the development of any efficacious and safe treatment. The benefits of each trial must be balanced against the burden it places on participants. While the EU-CTR has undoubtedly provided an initial step in driving diversity, if it is to remain "effective and relevant" but also adaptive to emerging challenges, it must be open to revisiting and reconfiguring EU laws and policies,[98] with proper deliberation and public involvement, with openness and transparency. As Hervey et al. argues, for the EU to realize its professed values of respect and protection of human rights and equality, it must harness the "dynamic potential" of EU health law whilst ensuring legitimacy measures are under check.[99] Not only that, but when doing so, and if law is to adapt to contemporary research, deliberation and revalidation and not necessarily revision of the law must take a wider view in recognizing the rights of the underserved populations within the current cancer research landscape. Synthesis of regulatory tools is needed regarding the application of elderly and persons with disability rights law to clinical research, giving particular emphasis to participants' decision-making autonomy, the need for individualized assessments of needs, and reasonable adjustments to enable participation in order to ensure that clinical trial inclusivity and diversity are being met and monitored. Policies, law and indeed guidance can play a valuable role in promoting the ethics of cancer research. Investigators and sponsors should limit, and RECs, IRBs and funders should scrutinize, proposed trial exclusion and broaden inclusion criteria, with special attention to the terminology and language used in study protocols. Scientific or ethical justification for exclusions should be a requirement and critically reviewed. Study protocols should be planned, and research procedures and outcome assessment built and/or modified so that they can be used by and accessible to older persons



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and people with disabilities. Further, I contend that in addressing the barriers to inclusivity of the underrepresented populations through disseminating understanding of their nature and through multiple stakeholders working together to overcome them, provide an ideal opportunity to make cancer trials much more inclusive. Whilst cancer research has become increasingly advanced, it is more important than ever to harness legal orders of the EU and ethical frameworks that safeguard the rights of the underrepresented from undue institutional bias or influence. While making full use of the range of medical technologies and therapeutic research modalities, we must strive towards providing truly personalized research that responds to the individual cancer needs of every patient-person over more commercially profitable research. Only if we achieve this will the EC's vision of equity be realized. As the Nobel Prize-winning New Keynesian economist Joseph Stiglitz wrote in his book *The Great Divide: Unequal Societies and What We Can Do about Them* — "Inequality is a choice." After all, it is not the patient who is the issue — rather the system that creates "epistemic injustice" as Flear argues.[100]

## Note

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