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Over or under-regulation of biomedical research: A comparative perspective and points to consider

Sivan Tamir

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EXECUTIVE SUMMARY

INTRODUCTION

Popular claims against over or under-regulation of biomedical research are often raised by researchers and sponsors, and ethicists and patients, respectively. We set out to examine the merit of such claims. First, by looking for meaningful comparative insights into inter-system commonalities and divergences, within clinical and health data research regulatory frameworks in Israel, the United States (US), the United Kingdom (UK), and the European Union (EU). Then, we questioned whether the grievance of over/under-regulation adequately captures the full complexity of the situation.

1. **Regulatory approval pathways for clinical trials**
   We first investigated regulatory review and approval pathways for clinical trials – mainly through Institutional Review Boards (IRBs)/Research Ethics Committees (RECs), in our jurisdictions of focus. We then looked into select features of each framework. For instance, **facilitating ethics review of multi-site trials**, by applying to a *single* IRB, to reduce burdensome bureaucratic procedures for researchers and eliminate variation in IRB decisions. We found that both the UK and the US require the use of a *single* IRB/REC for oversight of multi-site and cooperative research projects, whereas Israel introduced a rather limited pilot program in 2020, for reviewing "non-special" multi-site trials, through a designated National Committee for Multi-Site Trials. We also looked into the **availability of appeal mechanisms for ethics committees' decisions**, which reinforces the legitimacy and enhances justice and fairness of the review process in the eyes of researchers/sponsors. We found, that whereas the UK Clinical Trials Regulations establish an appeal mechanism for contesting unfavourable REC opinions, Israel and the US have no such appeal process for IRB decisions (although in the latter, institutions may *voluntarily* implement such mechanisms).

2. **Secondary use of health data in research**
   The onset of big data trends has led to a paradigm shift in research, recognising that big data research models require different review and approval pathways, thus prompting regulatory adaptations. In the paper, we provide a glimpse into the different regimes of secondary uses of health data for research.

3. **Over-regulation *vs.* under-regulation of biomedical research**
   The critique of over/under regulation of biomedical research questions, how much regulation is "sufficient" for public interests in safety, autonomy and transparency, to coexist with societal interests in promoting medical science. This is a highly subjective query, as **excessive/lacking regulation is in the eye of the beholder**. Researchers and sponsors typically complain of over-regulation, while ethicists and patient groups argue the area is under-regulated.

Excessive, cumbersome, over-regulation of research may turn out to be a *disservice* to society. As clinical trial applications become increasingly complex and time-consuming, researchers and sponsors are discouraged from pursuing investigative pathways, thereby hindering scientific progress. Some perceive it as an actual threat to clinical research. Over-regulation also renders clinical trials prohibitively expensive, driving out independent researchers without industry sponsorship, thus creating professional disparities.

Under-regulation is less costly for researchers and sponsors, entailing lighter scrutiny and speedier timelines, but may generate, in turn, poor-quality research, chaos, and uncertainty, leaving research subjects and societal interests inadequately protected. Moreover, past experience has shown that unethical research – due to lack of ethical guidelines and oversight – leads to mistrust in medical practitioners and health authorities.

4. **There is more to it than "over/under-regulation"**

   The grievance of "over/under-regulation" may be too simplistic a way to look at things. **A favorable regulatory climate for biomedical research is measured not only by the weight of regulation, or regulatory intelligibility, but also by *a*) its flexibility and adaptability; and *b*) its endorsement of scientific advances.**

   a) **Flexibility and adaptability** – as manifested in various revitalisation projects of clinical trials and health data research regulation, such as the 2018 US Common Rule revision; Israel's 2019 draft Patient Rights Regulations (Research Use of Health Information); the UK 2022 Medicines and Healthcare Products Regulatory Agency (MHRA) public consultation to improve and strengthen UK's clinical trials legislation; and the EU updated 2022 Clinical Trials Regulation.

   b) **Endorsement of scientific advances** – over/under-regulation of research is also a subjective evaluation of substance. The regulation of novel scientific advances, and of the way to get there, namely, research – reflects a tension between two regulatory attitudes: enthusiasm (i.e., endorsement of scientific innovation); and skepticism – a precautionary approach towards scientific developments. **The attitude applied in practice will shape biomedical regulation in a way that profoundly impacts a country's research climate.** For instance, looking into human genome editing (HGE), we found that human germline gene editing (HGGE) for reproductive purposes is banned in Israel, while therapeutic, somatic gene editing seems to be permitted through broad interpretation of the law. HGGE is also prohibited in the UK. But, for specified purposes, the Human Fertilisation and Embryology Authority (HFEA) may grant licences for research (including HGE) in human embryos – outside the body. Somatic genome editing is permitted in the UK. In the US, HGE is a form of gene therapy, permitted upon FDA approval. HGGE is not outrightly banned (but limited through restrictions on federal funding).

CONCLUSIONS

After considering the biomedical research regulatory frameworks of several jurisdictions, and scrutinising the over/under-regulation critique, the following points should be considered:

- Regulatory efforts aim to balance between maintaining scientific rigor and robustness of experimental design to protect the rights and welfare of human research/data subjects, and having in place regulation that will not discourage research to the detriment of society. The results of such a delicate task, leave both sides dissatisfied to some degree.

- Inter-jurisdiction variations in biomedical research regulation are not mere technicalities. They echo tensions between interests of various stakeholders: sponsors; researchers; health maintenance organisations (HMOs), as data controllers; patient groups; and society at large. Consequently, the biomedical research policy reflects compromises between commercial and organisational interests, and competing public/private interests.

- Regulatory frameworks of biomedical research can also play a social function through commitment to social justice, ensuring equity and diversity by inclusion of underrepresented, marginalised populations (e.g., ethnic and racial minorities, women, etc.), in clinical trials and medical research databases.

INTRODUCTION

Biomedical research is a broad and rich area of practice, encompassing human and animal research, clinical trials, and epidemiological research. For the purposes of this analysis, we shall limit the scope of our discussion to human clinical trials and health data research, disregarding those other important domains.

The cross-jurisdictional nature of many clinical trials, particularly pharmaceutical trials, makes familiarity with the intricacies of national legal and ethical frameworks of biomedical research essential for researchers and sponsors alike. This paper comparatively examines regulatory review and approval pathways for clinical trials in several jurisdictions: Israel, the United States (US), the United Kingdom (UK), and the EU.

The challenging part of this endeavor is not identifying jurisdiction-specific biomedical research regulatory frameworks, but rather gaining meaningful comparative insights into inter-system commonalities and divergences. While we do not presume to provide a comprehensive comparative analysis here, we aim to highlight practical and ethically pertinent aspects of the regulatory regimes investigated.

We start by reviewing the regulatory approval pathways for clinical trials in our jurisdictions of focus. We then look into three significant features of each framework: facilitating ethics review of multi-site trials; genetic research and genetic exceptionalism in review pathways; and the availability of appeal mechanisms for ethics committees' decisions.

Keeping with the increasing trend in biomedical research shifting towards health data research, we also provide a glimpse into the different regimes of secondary uses of health data for research purposes.

After setting the stage with the comparative introduction to said frameworks, we delve into the question of the "appropriate" degree of regulation of biomedical research, then considering whether the over/under-regulation critique adequately captures the full complexity of the situation. We suggest that regulatory flexibility and adaptability, through revitalisation projects of existing regulatory frameworks, play a role here. Finally, acknowledging that whether biomedical research in a given jurisdiction is over/under-regulated is not merely an objective observation of measure, but also a subjective evaluation of substance, we look into these frameworks' endorsement of scientific advances.

1. Regulatory approval pathways for clinical trials

Clinical trial applications are typically reviewed by and require the approval of Institutional Review Boards (IRBs), or Research Ethics Committees (RECs) – independent, interdisciplinary committees, composed of scientific experts and lay public representatives. The statutory basis, setup, ethico-legal powers and operation of ethics committees vary across countries.[1] IRBs/RECs examine scientific quality standards and compliance with ethical principles, to ensure that the rights, safety and well-being of the trial participants are protected.[2] Core ethical principles include safety; respect for patient autonomy, as reflected in the informed consent process; scientific validity; social and clinical value; a favourable risk-benefit ratio; and fair/equitable subject selection. Approval pathways, and informed consent-related requirements, also vary between jurisdictions.

Some states, like the US, Canada, and Argentina, allow for non-institutional, for-profit, *commercial* RECs to be established.[3] In fact, in these jurisdictions most industry-sponsored trials are reviewed by commercial RECs.[4] Critics question the independency and impartiality of such committees, given the inherent conflict of interest (being situated in a direct client-provider relationship with industry sponsors, who are already influencing research agendas to suit corporate interests[5]); as well as the potential non-accountability of non-institutional RECs.[6] The UK and Israel's regulatory frameworks do not allow for Commercial RECs.

In Israel, the Public Health Regulations (Clinical Trials in Human Subjects) – 1980 ("Clinical Trials Regulations"), channel research projects into two review pathways: *a*) Medicinal products, medical devices, and other clinical trials – defined as "special" trials – reviewed by IRBs.[7] ("Special" multi-site trials require *separate* submissions to an IRB at each site in which the trial is to be conducted); and *b*) a two-tier ethical review, consisting of both IRB and the Supreme Helsinki Committee, with final approval by the Director General (DG) of the Ministry of Health (MoH), is required for the following categories of research: (1) trials concerning a person's genetic makeup; (2) an experiment concerning fertilisation of women through artificial reproductive techniques; (3) a residual category – examining whether particular research-related issues are in compliance with the WMA Declaration of Helsinki – at the request of the MoH DG.[8] These seemingly more complex and sensitive trials are somewhat paradoxically defined as "non-special" trials.

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1 Research Ethics Committees (REC) - EUPATI Toolbox, https://toolbox.eupati.eu/resources/research-ethics-committees-rec/ (last visited July 20, 2022).

2 Won Oak Kim, *Institutional review board (IRB) and ethical issues in clinical research*, 62 Korean J. Anesthesiol. 3 (2012). at 8; doi:10.4097/kjae.2012.62.1.3.

3 UNESCO, *Establishing bioethics committees, Guide no. 1*, p. 51 (2005), https://unesdoc.unesco.org/ark:/48223/pf0000139309 (last visited July 20, 2022).

4 Trudo Lemmens and Carlos Herrera Vacaflor, *Clinical trial transparency in the Americas: the need to coordinate regulatory spheres*, Bmj k2493 (2018); doi: https://doi.org/10.1136/bmj.k2493.

5 Alice Fabbri et al., *The Influence of Industry Sponsorship on the Research Agenda: A Scoping Review*, 108 Am. J. Public Health e9-e16 (2018); doi: 10.2105/AJPH.2018.304677.

6 T. Lemmens and G. Ringkamp, *The Declaration of Helsinki and Transparency: When International Ethics Standards Face National Implementation Challenges*, *in* Ethical Research: The Declaration of Helsinki, and the Past, Present, and Future of Human Experimentation 51 (Ulf Schmidt, Andreas Frewer and Dominique Sprumont, eds., 2020); UNESCO, *supra* note 3.

7 Public Health Regulations (Clinical Trials in Human Subjects) – 1980, Fourth Schedule (IL). [in Hebrew]

8 *See* i*d*. s. 3b.

In the US, under Title 45 of the Code of Federal Regulations (CFR), part 46 (Protection of Human Subjects),[9] typically referred to as "the Common Rule," human subject research is subject to IRB approval (§ 46.111). The Common Rule, however, *exempts* some research categories from fully adhering to the requirements of its policy, where certain conditions are met (§ 46.104; e.g., secondary research for which *consent is not required*). Certain exemptions require a *limited* IRB review, i.e., the requirement for ethical review is satisfied by a determination that certain criteria are met (e.g., secondary research using *identifiable* private information or *identifiable* biospecimens, for which *broad* consent is required; § 46.104(d)(8)(iii)).

For research involving no more than minimal risk, and for which limited IRB review is a condition of exemption, a pathway of *expedited review* (i.e., by the chairperson or an experienced IRB member designated by the former) is available (§ 46.110). For example, in the case of storage/maintenance of identifiable private information/biospecimens for secondary research use, where the expedited review procedure is chiefly focused on evaluating the appropriateness of the broad consent obtained.

In the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004,[10] as amended by the Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019 (hereinafter: "UK Clinical Trials Regulations"),[11] establish RECs for reviewing research applications; stipulate pathways to authorisation for clinical trials and specify the considerations for REC's opinion; and set out conditions and principles of good clinical practice and for the protection of clinical trial subjects.

Under the somewhat cumbersome current regulations, sponsors need to make two, separate, regulatory and ethics applications. A submission to the Medicines and Healthcare Products Regulatory Agency (MHRA) – the regulatory licensing authority responsible for clinical trial approvals, oversight, and inspection; and an ethics application for an REC opinion.[12]

Building on experience gathered through ethics review for COVID-19 research and following a short pilot, in January 2022 the NHS Health Research Authority (HRA) established a *fast-track* research ethics review to accelerate research. The fast-track review was initially conducted by a designated ethics committee, providing a combined review pathway (Clinical Trial Authorisation and REC opinion) through a single Clinical Trial of Investigational Medicinal Products (CTIMPs) application.[13] It was later integrated into the wider structure of (non-designated) RECs, to provide a larger pool of ethics committees.

The fast-track review entails a shorter time period between submission and REC meeting; a dedicated approval pathway; and an appealing turn-around time for correspondence with applicants.

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9 Code of Federal Regulations Title 45: Public Welfare, part 46 (Protection of Human Subjects), as amended by the *2018 Requirements* (2018 Common Rule) (effective date: July 2018; compliance date: January 2019); https://www.ecfr.gov/on/2018-07-19/title-45/subtitle-A/subchapter-A/part-46.

10 The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004 No. 1031; https://www.legislation.gov.uk/uksi/2004/1031/introduction/made.

11 The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019, SI 2019 No. 744; https://www.legislation.gov.uk/uksi/2019/744/made.

12 The Medicines for Human Use (Clinical Trials) Regulations 2004, *supra* note 10, §14 – "Application for ethics committee opinion"; and §17-20 – "Request for authorisation to conduct a clinical trial".

13 NHS Health Research Authority, *Fast-track research ethics review*, HRA.NHS.UK, https://www.hra.nhs.uk/approvals-amendments/what-approvals-do-i-need/research-ethics-committee-review/fast-track-research-ethics-review-pilot/ (last updated July 29, 2022).

Eligible for the fast-track review are urgent public health research (e.g., COVID-19 studies and more recently – Monkey Pox); and, seemingly somewhat different to the US risk-based *expedited review* pathway – global clinical trials phase I or phase I/II CTIMP, in healthy volunteers or patients.[14]

a. Facilitating ethics review of multi-site trials

A requirement for multi-site research to be approved by each site's IRB is not only cumbersome for researchers, but is also ground for significant inconsistency, due to variation in IRB decisions and conflicting requirements of separate IRBs. Such variation – attributed, inter alia, to institutional or professional culture – may "threaten the internal and external validity of the research."[15] Inconsistency could also lead to sentiments of inequality, unfairness, mistrust, and inaptness towards the IRB process. Satisfying the ethical oversight requirement in multi-site clinical trials, by applying to a *single* IRB/REC, does not only facilitate research by cutting through burdensome bureaucratic procedures, but is also key for averting such sentiments.

In the UK, according to the UK Clinical Trials Regulations, an application for an ethics committee opinion is to be made to a single REC, "regardless of the number of trial sites at which the trial is to be conducted."[16]

In the US, multi-site and cooperative [non-exempt] human subject research projects (involving more than one institution) require the use of a *single* IRB for oversight, according to the 2016 National Institutes of Health (NIH) Single IRB policy and/or the 2018 revised Common Rule (§ 46.114).[17]

Israel was rather late to follow suit, where in 2020, attempting to expedite the approval process for multi-site trials, and make it more efficient and uniform, the MoH Clinical Trials department launched a pilot program (Procedure 168) for "non-special" multi-site trials.[18] The Procedure instructs that drug and medical device trials in advanced stages of development, designed to be conducted at three or more sites, will require the approval of a designated National Committee for Multi-Site Trials. The National Committee's decision will be binding for all IRBs. It appears, however, that a parallel submission by the sponsor, to all relevant IRBs, is still required.

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14 This, however, may change with the adoption of a risk-proportionality approach, within the proposed legislative changes to the UK's clinical trials legislation (see below the section on *Revitalising regulatory frameworks of clinical trials and health data research*).

15 Changing the Common Rule to Facilitate Multisite Research and Establish an Appeals Process, APHA.ORG, Policy Number: 20129 (2012), https://apha.org/policies-and-advocacy/public-health-policy-statements/policy-database/2014/07/21/10/52/changing-the-common-rule-to-facilitate-multisite-research-and-establish-an-appeals-process (last visited July 20, 2022).

16 The Medicines for Human Use (Clinical Trials) Regulations 2004, *supra* note 10, § 14(2).

17 Single IRB for Multi-Site or Cooperative Research, GRANTS.NIH.GOV, https://grants.nih.gov/policy/humansubjects/single-irb-policy-multi-site-research.htm (last updated Mar. 29, 2022).

18 Pilot for studies classified as non-special [Procedure 168], MoH Clinical Trials Department (5.1.20) [in Hebrew], chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fwww.gov.il%2FBlobFolder%2Fpolicy%2Fdr-168%2Fhe%2Ffiles_circulars_dr_DR_168.pdf&clen=750953&chunk=true.

b. Genetic research and genetic exceptionalism in review pathways

In adherence with a genetic exceptionalism[19] approach, all the regulatory frameworks examined have in place a designated ethical review pathway for gene therapy trials, albeit not all of them maintain an exceptionalistic approach for more "standard" genetic samples and data research.

In Israel, as mentioned above, genetic research requires a *two-tiered* ethical review, consisting of both IRB and the Supreme Helsinki Committee, for a final regulatory approval by the MoH DG. A two-tiered ethical evaluation and approval, by an IRB and a designated MoH central Committee for Advanced Therapies, is similarly required for gene therapies (and other above-minimal risk clinical trials[20]). Furthermore, genetic research involving DNA sampling and testing, is specifically regulated by the Genetic Information Act 2000.[21] The Act and the MoH Guidelines for Clinical Trials in Human Subjects[22] stipulate a waiver of informed consent for research conducted on previously collected genetic samples (retrospective research) – provided anonymisation is guaranteed. For example, where only *unidentified DNA samples*, or *existing* DNA samples stripped of all identifying information, are being used.

In the UK, under the Human Tissue Act,[23] research involving DNA analysis only requires ethical approval from an NHS (The National Health Service) REC, where bodily material (such as blood; including gametes) from the living is stored with the intention of conducting DNA analysis *without consent* from the person who is the DNA source. In such case, the material must be *non-identifiable* to the researcher. Interestingly, there is no requirement for ethical approval where consent is in place for DNA analysis.[24] However, where the original consent for DNA analysis is narrow (i.e., specific to a particular study or studies) rather than broad, further ethical approval should be sought to analyse DNA within non-consented-to projects.

For research involving *anonymised* extracted DNA, no ethical approval is required as the research involves neither tissue nor data of NHS patients, under NHS research governance schemes. Ethical approval would only be required where the DNA sample is stored with identifying information. Notwithstanding this, ethical review could be *voluntarily* sought by researchers using anonymised DNA, where the research involves ethical complexities.[25]

As for clinical trials involving medicinal products for gene therapy, an application for an ethics committee opinion, should be made to the Gene Therapy Advisory Committee (GTAC). CTIMPs involving a gene therapy medicinal product are excluded from the fast-track ethics review.[26] As will

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19 *Genetic exceptionalism* is the notion that genetic information is meaningfully distinct from other types of health information, in medical, social (familial and community), and ethical contexts, therefore meriting different treatment and special medico-legal status.

20 This two-tiered review (IRB plus central professional committee) is also required for medical products containing cells or tissues, trials involving drugs, and medical devices (novel medical technologies).

21 Genetic Information Law of 5761-2000. https://www.gov.il/he/departments/guides/protocol-of-medical-research-involving-human-subjects. [in Hebrew].

22 Guidelines for Clinical Trials in Human Subjects (No. 14), MoH (2020). https://www.gov.il/he/departments/guides/protocol-of-medical-research-involving-human-subjects. [in Hebrew].

23 Human Tissue Act, UK Public General Acts c. 30 (2004).

24 NHS Health Research Authority, *Use of human tissue in research*, HRA.NHS.UK, https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/use-tissue-research/ (last updated Nov. 16, 2021).

25 *Ibid.*

26 Also excluded from the fast-track ethics review are CTIMPs funded by the US Department of Health and Human Services, and any other type of clinical trial or research study.

be described below, the appeal mechanism for the GTAC's opinions is also relatively exceptionalistic compared with "conventional" REC opinions.

In the US, genetic research is reviewed by IRBs. Although typically limited to blood drawing and the collection of family history information, genetic studies cannot automatically be classified as "minimal risk" studies, qualifying for expedited review. The rationale for this is that genetic studies *exceptionally* generate these non-physical, psychosocial risks: anxiety and uncertainty (e.g., due to the reporting of predictive information about one's health risks); disruption to familial relationships; personal and communal stigmatisation, discrimination, or labeling; and compromising subjects' insurability and future employment opportunities.[27]

As for gene therapy clinical trials in humans, these merely require the approval of an IRB, rather than that of a designated genetics expert committee (as is the case in Israel and the UK). However, an extra regulatory hurdle is set by the requirement for an investigational new drug application (IND) submission to the Food and Drug Administration (FDA), *prior to initiating such clinical studies.*[28] Also, where applicable (i.e., where NIH funding is provided), institutions and researchers must comply with NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules ("NIH Guidelines"),[29] requiring additional approval by an Institutional Biosafety Committee (IBC). The IBC has distinctively separate oversight responsibilities, albeit complimentary to those of the IRB. IBCs are tasked with mitigating risks posed by gene transfer research to laboratory and clinical staff, to public health, and the environment in general, whereas IRBs are tasked with protecting the rights and welfare of participants in clinical trials.

For the EU, although not attached to a specific regulatory pathway, the EU General Data Protection Regulation (GDPR)[30] notably considers genetic information as a special category of personal data [Art. 9(1)], the processing of which is prohibited, unless specific derogations [Art. 9(2)] apply, such as the data subject's explicit consent, or where physically or legally incapable of giving consent – processing is necessary to protect her vital interests. Member States may introduce further conditions, or limitations, with regard to the processing of genetic data, as indeed some have.[31]

Albeit being revisited[32] and increasingly harder to justify, such manifestations of genetic exceptionalism could be attributed to the yet (considerably) higher risk conferred by - and the epistemic gaps inherent to - gene therapy trials, and some (stigmatisation-prone) genetic research.

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27 Protecting Human Research Subjects Guide - Institutional Review Board Guidebook, Genome.gov (1993), https://www.genome.gov/protecting-human-research-subjects-guide (last visited May 1, 2022).

28 FDA, *What is Gene Therapy?* Fda.gov (July 25, 2018), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy.

29 NIH, *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (Apr. 2019)84) FR 17858); NIH, *Investigator Responsibilities under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*, Osp.od.nih.gov (Oct. 2021); https://osp.od.nih.gov/biotechnology/nih-guidelines/; chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fosp.od.nih.gov%2Fwp-content%2Fuploads%2FInvestigator_Brochure_Recombinant_DNA_2021.pdf&clen=818393&chunk=true.

30 Regulation (EU) 2016/679 (General Data Protection Regulation); OJ L 119, 04.05.2016.

31 European Commission, Assessment of the EU Member States' rules on health data in the light of GDPR (2021), EB-01-21-045-EN-N; doi:10.2818/546193 EB-01-21-045-EN-N, at 58, chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fec.europa.eu%2Fhealth%2Fsystem%2Ffiles%2F2021-02%2Fms_rules_health-data_en_0.pdf&clen=2849940&chunk=true

32 *See, e.g.*, Murray's critique and level-headed account of genetic exceptionalism, and his support for the alternative suggested approach of *Genomic Contextualism*: Thomas H. Murray, *Is Genetic Exceptionalism Past Its Sell-By Date? On Genomic Diaries, Context, and Content*, 19 Ajob 13 (2019); doi: 10.1080/15265161.2018.1552038.

c. Appeal mechanisms

IRBs are autonomous entities, and their decisions – binding and typically final.[33] Researchers may seek to appeal an IRB decision, or certain elements therein. Having the recourse of appeal reinforces the legitimacy of the ethical review of clinical trials and enhances justice and fairness of the review process.

To date, no appeal mechanism against an unfavourable opinion, or specific conditions for approval required by an ethics committee, is available to researchers and sponsors under the Israeli Clinical Trials Regulations.

In the UK, the UK Clinical Trials Regulations establish an appeal mechanism for contesting an unfavourable REC opinion. In such cases, the chief investigator may give a notice to the United Kingdom Ethics Committees Authority (UKECA) within a set timeframe (90 days), stating her wish to appeal against the opinion, and setting out her representations with respect to that opinion. However, where the opinion was given by GTAC, within 14 days of being notified of that opinion, the chief investigator has two alternative routes: requesting that GTAC reviews its opinion, or appealing against the opinion to the UKECA, setting out her representations.[34]

In the US, although previously considered within the proposed revisions to the 2018 Common Rule,[35] there is no established appeal process in place for IRB decisions. However, some institutions *voluntarily* implement appeal mechanisms, for example, by reconsidering a decision regarding a research protocol, following a written request submitted by the principal investigators; or by allowing the researcher to present the project to a different IRB, or having it reviewed by a designated "appeal" IRB (composed of members of the institution's other IRBs).[36]

2. Secondary use of health data in research

Gradually departing from traditional biomedical research designs, built on the active participation of human subjects[37] in interventional studies, the largely exploratory big health data research model is taking an increasingly bigger chunk of health and medical research.

Using data originally collected for primary (healthcare) use, stored within primary use repositories, such as Electronic Health Records (EHR) systems and disease registries, is considered *secondary* use ruuj of personal health data.

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33 Changing the Common Rule to Facilitate Multisite Research, *supra* note 15.

34 Cressida Auckland, Blackstone's Statutes on Medical Law (11th ed., 2021), at 277; https://books.google.co.il/books?id=SJg5EAAAQBAJ&pg=PA277&lpg=PA277&dq=%22give+a+notice+to+the+United+Kingdom+Ethics+Committees+-Authority%22&source=bl&ots=rNexUpNOFV&sig=ACfU3U2fPuOBd3jp6mGjvgVyBPY4l7YkjQ&hl=en&sa=X&ved=2a-hUKEwiDkPqNo9T2AhURDewKHbuhDSsQ6AF6BAgCEAM#v=onepage&q=%22give%20a%20notice%20to%20the%20United%20Kingdom%20Ethics%20Committees%20Authority%22&f=false; The Medicines for Human Use (Clinical Trials) Regulations 2004, *supra* note 10, § 16, https://www.legislation.gov.uk/uksi/2004/1031/regulation/16/made?view=plain.

35 *See, e.g.*, Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, FEDERALREGISTER.GOV (2011); https://www.federalregister.gov/documents/2011/07/26/2011-18792/human-subjects-research-protections-enhancing-protections-for-research-subjects-and-reducing-burden (last visited July 21, 2022).

36 *Ibid*.; Institutional Review Board policies and procedures, Minnesota Department of Health (January 2019); chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fwww.health.state.mn.us%2Fdata%-2Firb%2Fdocs%2Firbpoliciesprocedures.pdf&clen=323601&chunk=tru

37 Agata Ferretti et al., *Big Data, Biomedical Research, and Ethics Review: New Challenges for IRBs*, 42 E&HR 17 (2020), at 18; doi:10.1002/eahr.500065.

It is widely recognised that big data research can open new prospects to accelerate health-related research, with promising potentialities of advancing medical science and benefitting patients.

The onset of big data trends has led many countries to acknowledge such a paradigm shift in research, as well as recognise that big data research models do not quite "fit within the traditional national review policies for the protection of human subjects."[38] This, with further encouragement from the 2016 WMA Declaration of Taipei[39] and the 2017 OECD Recommendation on Health Data Governance,[40] have prompted adaptations to their respective regulatory frameworks.

Such modifications typically include the addition of a specific class of secondary use of health data for research purposes; the creation of interdependencies between the (non-) identifiability status of private information and informed consent waivers, broad consent, or designated opt-out consent mechanisms. Given the challenges presented by data research to IRBs/RECs' traditional review frameworks, some regulatory changes also address the professional expertise required for reviewing such research applications.

IRB members typically review research applications from the bioethics-laden framework of protecting human subjects. They lack the relevant expertise required to assess public, wide-ranging benefits and impersonal group-risks that are characteristic of health data research.[41] Nor are they proficient in data protection methods, or familiar with anonymisation tools, crucial to reviewing health data research. Such expertise gaps in IRB/REC need to be filled out, to better assess research protocols. To this end, some argue for a need for building capacity of IRB members through additional training in data science and data ethics, and expanding and diversifying relevant competencies, to include data scientists, data ethicists, and data and privacy protection experts. Doing so would enhance researchers' trust in the workings of IRBs, by improving the latter's credibility and ensuring a fairer, expertise-based, ethics review.[42]

In Israel, under the current MoH Guidelines for Clinical Trials in Human Subjects,[43] using existing health data for research purposes requires a somewhat expedited route for review and approval by a narrower IRB **sub**-committee, as this is deemed to be minimal risk, non-interventional, research.

In the UK, secondary use of patients' *identifiable* data for research, without consent, requires *dual* review by REC and the Confidentiality Advisory Group (CAG).[44] The CAG's approval is uniquely required [NHS Act 2006, § 251], in order to set aside the Common Law Duty of Confidentiality owed by care professionals to their patients, requiring explicit or implied consent (or a mandatory legal

38 *Ibid*.

39 WMA Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks (adopted in October 2002; revised in October 2016); https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/

40 Recommendation of the Council on Health Data Governance, OECD, OECD/LEGAL/0433 (Jan 17, 2017); https://legalinstruments.oecd.org/en/instruments/OECD-LEGAL-0433.

41 Ferretti et al., supra note 37, at 25.

42 *Ibid*., at 22.

43 Guidelines for Clinical Trials in Human Subjects, *supra* note 22, definitions, s. 60 [in Hebrew].

44 The CAG is primarily responsible for issues of data security and confidentiality, by reviewing "the legal aspects of a cessing, using, storing and retaining patient identifiable information without consent," and examining compliance with the Data Protection Act 2018, the Human Rights Act 1998 and the Common Law Duty of Confidentiality; *see* Standard Operating Procedures for Research Ethics Committees, Version 7.5.1 (2021), § 14.66 – § 14.82, chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/RES_Standard_Operating_Procedures_Version_7.5.1_August_2021_Final_Accessible_07lVkXt.pdf.

requirement, a court order, or an overriding public interest) for the use of *identifiable* data.[45] The CAG, an independent body, provides researchers with expert advice on the risk of potential identifiability of data subjects and de-identification methods.

HRA approval is *not* required for the establishment of research databases; and ethical review for the collection, storage, use, and distribution of data, and for the release of *non-identifiable* data for analysis by external researchers – is *voluntary*.

In the US, under the Common Rule policy, research involving human subjects is not limited to research conducted on a living individual to obtain information or biospecimens through intervention or interaction, but also applies to the obtention, use and analysis of *identifiable private information* (data, documents, health records) and *identifiable biospecimens* (tissues, pathological or diagnostic).[46] This includes coded biospecimens or information, unless certain conditions for ensuring individuals' anonymity apply.[47]

Unidentifiable biospecimens, or information – stripped of all identifiers to prevent reidentification of sample/data sources – are therefore not considered human subject research, and do *not* require IRB review.[48] Similarly, secondary analysis of *coded* private information, where the investigator(s) cannot readily ascertain the identity of the sample/data sources, is not considered research involving human subjects and is exempt from IRB review.[49] Consequently, big health data research that involves the processing of deidentified data, might not reside under the Common Rule.[50] For the storage, maintenance, and secondary research-use of *identifiable* private information or identifiable biospecimens, *broad* consent may be used, in lieu of informed consent [§ 46.116(d)].[51]

Also, for government-related research using *identifiable* private information (or biospecimens) and involving public benefit and service programs – informed consent can be entirely waived or have its elements altered [§ 46.116(f)(3)], subject to an IRB determination that the research involves no more than minimal risk to subjects, and that other conditions are met [§ 46.116(f)(3)].

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45 *Ibid*., § 11.

46 National Research Council, Proposed Revisions to the Common Rule for the Protection of Human Subjects in the Behavioral and Social Sciences (2014).

47 Ensuring individuals' anonymity entails that biospecimens/information cannot be linked to their living source (individuals), for instance, by destroying the key to decipher the code before the research begins; or through written policies approved by the IRB, preventing the release of the key to investigators under any circumstances. *See* in flowchart for *Research Involving Private Information or Biospecimens*, at: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fgrants.nih.gov%2Fgrants%2Fpolicy%2Fhs%2Fprivate-information-biospecimens-flowchart.pdf&clen=163677&chunk=true; NIH, Human Subjects Research Overview, https://www.nidcr.nih.gov/research/human-subjects-research#:~:text=Research%20involving%20existing%20data%2C%20documents,%E2%80%9Cresearch%20involving%20human%20subjects.%E2%80%9D.

48 *Ibid.*

49 *See* CFR 45 § 46.104(d)(4)(ii), https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/revised-common-rule-regulatory-text/index.html#46.104.

50 Ferretti et al., *supra* note 37, at 18.

51 The option for broad consent was introduced under the 2018 revision to the Common Rule (discussed below), with limited applicability to secondary research use of identifiable private information, or identifiable biospecimens. The other two consent routes (relics of the prior regulations) are study-specific informed consent, or a waiver of such consent (sought by researchers) from the IRB. *See* John W. Maloy and Pat F. Bass, *Understanding Broad Consent,* 20 Ochsner J. 81 (2020); doi:10.31486/toj.19.0088.

Seemingly, unlike the (unfolding) expert-based approach in Israel, and that already established in the UK, no specific capacities or data-protection/analysis proficiencies seem to be required in the US for IRB review of research using (identifiable) private information.

The EU GDPR creates the health data governance, and more specifically – the legal framework (lawful bases) for processing health data for research (among other secondary) purposes [Art. 6(1)]. As earlier mentioned, the GDPR generally prohibits the processing of special categories of data such as health and genetic data [Art. 9(1)]. However, the data subject's explicit consent to the processing of her personal data, as well as the other contextual derogations to the rule [Art. 9(2)], may be applicable for secondary processing of health data for research. These include, e.g., processing necessary for the purposes of preventive medicine, medical diagnosis, or the provision of health care or treatment [Art. 9(2)(h)]; for the performance of a task carried out in the public interest (in the area of public health); or for scientific research purposes [Art. 9(2)(j)].[52]

Member States may each adopt legislation regulating the secondary use of data for research. Disconcertingly, a 2021 *Assessment of the EU Member States' rules on health data in the light of GDPR* indicates that "states have not implemented such legislation in a homogenous way, resulting in a complex and fragmented landscape for researchers to navigate."[53]

For reason of space limitation we shall not further elaborate on the comparative regulation and practicalities of secondary use of health data for research.[54]

To conclude the last sections, there is a point to be made that inter-jurisdiction variations in biomedical research regulation, are not mere technicalities. They echo tensions between interests of various stakeholders: sponsors (pharmaceutical companies); researchers; health maintenance organisations (HMOs), as data controllers; patient groups; and society at large. Consequently, the biomedical research policy in place reflects compromises between commercial and organisational interests on the one hand, and competing public/private interests, on the other.

3. Over-regulation *vs.* under-regulation of biomedical research

This is a policy deliberation, attempting to determine how much regulation (including ethical oversight) is "sufficient" for allowing public interests in safety, autonomy, and transparency to coexist with societal interests in promoting health/medical science and innovation. Ideally, regulation of biomedical research – clinical trials in particular – provides clarity, consistency, and research ethics guidance, for researchers, sponsors and IRB/REC members.

52 European Commission, DG Health and Food Safety, *Assessment of the EU Member States' rules on health data in the light of GDPR* (2021), at 58; doi:10.2818/546193 EB-01-21-045-EN-N,https://op.europa.eu/en/publication-detail/-/publication/8337c9ed-7009-11eb-9ac9-01aa75ed71a1

53 *Ibid*.

54 For a broader analysis of health data research-related ethical issues, *see* Sivan Tamir, *The Precision Medicine Data Environment in Israel*, The Van Leer Jerusalem Institute (2020), https://www.vanleer.org.il/publications/%d7%91%d7%99%d7%92-%d7%93%d7%90%d7%98%d7%94-%d7%95%d7%a8%d7%a4%d7%95%d7%90%d7%94-%d7%9e%d7%95%d7%aa%d7%90%d7%9e%d7%aa-%d7%90%d7%99%d7%a9%d7%99%d7%aa-%d7%91%d7%99%d7%a9%d7%a8%d7%90%d7%9c-2/.

The fundamental regulatory force of biomedical research, initially emerging in the 1960s and perceived as "the model mechanism for ethical peer review," is that of IRBs/RECs'. With a constantly increasing volume of research; the advent of genomics and big health data research, and multinational clinical trials; and newfound privacy concerns[55] – IRBs/RECs' responsibilities have considerably evolved over time. (The practice of ethical committees has in fact become so intricate, to justify the issuance of specifically designed manuals.[56]) Ethical demands from researchers and sponsors have equally grown.

Over-regulation may emerge as an attempt to compensate for past oversight and historical failures in protecting the rights and well-being of human research subjects. But excessive, complex, cumbersome regulation, occasionally dubbed as "hyper-regulation of research,"[57] may turn out to be a disservice to society. Submitting clinical trial applications has increasingly become overly complex and kt byuh time-consuming, discouraging researchers and sponsors alike from pursuing investigative pathways, thereby compromising clinical care (which is research-dependent), and hindering scientific progress. Over-regulation also renders clinical trials prohibitively expensive, driving out independent academic researchers without industry sponsorship. This, in turn, may create professional disparities and lead to the exclusion of such researchers. Consequently, some perceive over-regulation as an actual threat to clinical research – "obstructing high quality science."[58] More ardent critics argue that over-regulation of clinical research amounts to nothing short of a threat to public health.[59]

Notably, one of the most undesirable consequences of over-regulation suggested by Merz is the potential moral "shake off" by investigators, regarding their responsibility for their own ethical conduct. Namely, if research is approved by an IRB/REC – the investigators are off the moral hook, unaccountable for the ethicality of the research as it unfolds ahead.[60]

The regulatory burden of research-related legal and ethical frameworks and the ever-increasing bureaucracy have a "chilling effect" on scientific progress, and are factored into the attractiveness of a country's "research climate". This carries academic, economic, and health implications (e.g., the non-inclusion of its population groups in potentially benefitting research).

Furthermore, some, skeptically question the efficacy of the IRB/REC mechanisms, suggesting that "[w]hether research ethics committees actually improve the ethical quality of research remains largely unknown."[61] This epistemic gap can be attributed to poor transparency standards and significant variability (i.e., intra and inter-committee inconsistencies in opinions), rendering analyses of IRBs'/RECs' (highly subjective) performance and value difficult and challenging to measure.

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55 Jon F. Merz, *The hyper-regulation of research* 363 Lancet 89 (2004); doi: https://doi.org/10.1016/S0140-6736(03)15221-X.

56 *See, e.g.,* Manual for Research Ethics Committees (Sue Eckstein, ed., 2003).

57 Merz, *supra* note 55.

58 Paul M. Stewart et al., *Regulation—the real threat to clinical research*, 337 Bmj (2008); doi: https://doi.org/10.1136/bmj.a1732.

59 Charles Warlow, *Over-regulation of clinical research: A threat to public health,* 5 Clin. Med. (Lond.) 33 (2005); doi:10.7861/clinmedicine.5-1-33.

60 Merz, *supra* note 55.

61 *Ibid*.

While regulation of biomedical research typically refers to the *ethical* assessment of research applications by IRBs/RECs, it also extends to include a superior layer of legal regulation, such as legal capacity laws (relevant to issues of inclusion, consent and autonomy), privacy and data sharing regulation (relevant, e.g., for multinational trials), etc. This is yet another factor impacting regulatory burden and requiring unwavering compliance, as this body of law relates to core human rights.

But what is the alternative – thinner, or more relaxed regulation? For, surely, *no* regulatory oversight whatsoever – cannot be considered. Under-regulation is less costly for researchers and sponsors, entails lighter scrutiny and speedier timelines for conducting research, but may generate, in turn, poor-quality research, chaos, and uncertainty, leaving research subjects and societal interests insufficiently protected. Moreover, notorious, well-documented experience of past exploitation and harmful research participation have taught us that unethical research – due to lack of ethical guidelines and oversight – also leads to mistrust in medical practitioners and health authorities,[62] among other things.

4. There is more to it than "over/under-regulation"

Upon reflection, however, the grievance of "over-regulation" or concern over "under-regulation" (depending on one's position in the biomedical research play) may be too simplistic a way to look at things. A favourable regulatory climate for biomedical research is measured not only by the weight of the regulation, the regulatory (over)load, or regulatory intelligibility, but also by *a*) its flexibility and adaptability; and *b*) its endorsement of scientific advances.

a. Regulatory flexibility and adaptability

Concerns over the detrimental effects of over-regulation (e.g., the need for more innovation-supportive regulatory pathways), and the recognition that a paradigm shift is needed in the rather uniform regulatory pathway applied to different types of biomedical research, have led to various regulatory revitalisation projects in recent years.

A "one size fits all" regulatory approach, treating research with different interventional depths, patient interactions and foreseen risks, the same – seems to no longer apply under evolved regulatory regimes of biomedical research. Such a differential, proportional approach warrants diverse, flexible regulatory mechanisms. For example, reviewing low-intervention trials (or exempting from such review), in a risk-proportionate manner.[63]

62 Such mistrust permeates generations, fueling future distrust in the medical system, such as that witnessed during the COVID-19 pandemic among the African American community in the US. This has generated skepticism and suspicion with regard to vaccination, causing vaccine hesitancy and declining prioritisation efforts in vaccine rollout. *See, e.g.*, Nicholas St. Fleur, *Health experts want to prioritize people of color for a Covid-19 vaccine. But how should it be done?* Stat (Nov. 9, 2020), https://www.statnews.com/2020/11/09/health-experts-want-to-prioritize-people-of-color-for-covid19-vaccine-but-how-should-it-be-done/; Kiran Stacey, *The fight to overcome vaccine hesitancy among African* Americans, Financial Times (Feb. 24, 2021), https://www.ft.com/content/515d3949-4379-42db-aa69-f11ffa116e39.

63 Proposals for legislative changes for clinical trials, Gov.UK (2022), https://www.gov.uk/government/consultations/consultation-on-proposals-for-legislative-changes-for-clinical-trials/proposals-for-legislative-changes-for-clinical-trials (last visited July 21, 2022).

1. Revitalising regulatory frameworks of clinical trials and health data research

Israel's current IRB sub-committee review for research on existing health data, may be set to change with the enactment of the draft Patient Rights Regulations (Research Use of Health Information), 2019 ("the draft regulations").[64]
The explicit aim of the draft regulations is to improve the quality of medical care and promote medical research, while balancing the desire to encourage and promote sharing of health information for research purposes with the need to protect the privacy of data subjects and the confidentiality of medical information.

The draft regulations establish a designated, expert-based ethics committee mechanism for reviewing health data research applications, both at the organisational and the national levels. The Organisational Review Board is set to include a privacy protection or information security officer, as well as an information analysis expert. The National Review Board will include, inter alia, a data analysis specialist and government and public representatives, experts in the field of privacy protection.

While clinical trials traditionally require informed, opt-in consent, the draft regulations adopt an opt-out approach for secondary research uses of health information, establishing the use of de-identified health information for research purposes as default. Identified, or identifiable health information, will only be used where prior opt-in consent of the data subject is given, or under an existing statutory exemption.[65]

In 2018, after a thoughtful and lengthy update process, the US Common Rule underwent significant revision, seeking to "modernize, simplify, and enhance the current system of oversight."[66] The revised Federal Policy came into effect in January 2019, introducing various changes, affecting researchers and participants alike. Modifications included expanding the categories of research qualifying for IRB exemption (or "limited IRB review") [CFR § 46.104]; setting forth criteria for IRB approval of research [CFR § 46.111]; introducing expedited review procedures for certain kinds of research involving no more than minimal risk [CFR § 46.110]; introducing broad consent for the storage, maintenance, and secondary research use of identifiable private information/biospecimens. The revised Common Rule also introduces general requirements for informed consent [CFR § 46.116], including setting forth basic and additional elements of informed consent.[67]

64 The cautious reader must bear in mind that these regulations are a work in progress, still in draft form and are subject to various revisions; [Draft] Patient Rights Regulations (Research Use of Health Information), 2019, https://www.health.gov.il/Services/Documents/D06102919.pdf [in Hebrew].

65 Limor Shmerling Magazanik, *Evolving National Policies: Using Health Data for Research* (December 2020), chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://techpolicy.org.il/wp-content/uploads/2021/02/Using-Health-Data-for-Research-Evolving-National-Policies-FV-.pdf.

66 Federal Policy for the Protection of Human Subjects, FEDERALREGISTER.GOV (2017), https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects (last visited July 21, 2022).

67 *See* 2018 Requirements (2018 Common Rule), HHS.GOV (2017), https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/revised-common-rule-regulatory-text/index.html#46.117.

In the UK, in January 2022, the MHRA initiated a public consultation, to improve and strengthen UK's clinical trials legislation,[68] seeking proposed changes to "simplify and streamline application processes" and "update requirements" for RECs.[69] Its ultimate goals are reducing burden on those conducting trials and removing legislative blockers to innovation.

More specifically, proposed legislative changes include increasing patient and public involvement and research transparency – e.g., by requiring public inclusion in trial design. Also included is the embedding of risk-proportionality principles, particularly in regulation of lower-risk trials, while ensuring proportionate sanctions and maintaining robust oversight of the safety of trials, where needed.

The proposed changes are expected to facilitate running trials in the UK, build international interoperability, and make its research climate favourable, supportive, and attractive for trial sponsors and researchers.

Revitilisation of clinical trial regulation is also taking place in the EU, although notably, its governance seems to be limited to clinical trials on medicinal products (not governing human research, per se).[70] In January 2022, the EU Clinical Trials Regulation entered into application, repealing the former Clinical Trials Directive (EC) No. 2001/20/EC.[71]

The novel regulation, which does not apply to non-interventional studies,[72] aims facilitating a once non-uniform, hydra-like clinical trial submission process, governed by different domestic rules with unpredictable timelines.[73] This is meant to be achieved through harmonisation and standardisation of the review and supervision processes of clinical trials, throughout the EU.[74]

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68 Consultation on proposals for legislative changes for clinical trials, Medicines and Healthcare Products Regulatory Agency, Gov.UK (Jan. 17, 2022); https://www.gov.uk/government/news/new-proposals-for-the-future-of-uk-clinical-trial-legislation (last visited July 21, 2022).

69 Closed consultation – Annex A – Legal basis and the assessment of the matters set out in section 2 of the Medicines and Medical Devices Act 2021, Gov.UK (Jan. 17, 2022), https://www.gov.uk/government/consultations/consultation-on-proposals-for-legislative-changes-for-clinical-trials/annex-a-legal-basis-and-the-assessment-of-the-matters-set-out-in-section-2-of-the-medicines-and-medical-devices-act-2021 (last visited July 21, 2022).

70 Kärt Pormeister, *Genetic research and applicable law: the intra-EU conflict of laws as a regulatory challenge to cross-border genetic research*, 5 J. Law Biosci. 706–723 (2018); doi:10.1093/jlb/lsy023.

71 Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1–76; https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536.

72 *Ibid*., Art. 1.

73 Vikram Aditya and Aparna Mulupuru, *EU Clinical Trial Regulation – Defining The Change*, Accenture (Sep. 28, 2021), https://www.accenture.com/us-en/blogs/life-sciences/eu-clinical-trial-regulation-defining-the-change.

74 European Medicines Agency, *Clinical Trials Regulation*, Ema.europa.eu, https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation (last visited Aug. 3, 2022). The adaptation to the provisions of the new regulation is already having effect on national clinical trial regulation schemes. For instance, in March 2022, Italy established its "National Ethics Committee for trials conducted by public research organizations and other public organizations of a national nature," replacing the Ethics Committee of the Italian NIH, as part of the reform of its clinical trials regulatory framework. *See* Baker McKenzie, *Italy: The new National Ethics Committee for trials of public research organizations has been established*, Lexology (May 14, 2022), https://www.lexology.com/library/detail.aspx?g=e15f5f6d-15ba-489d-af53-812859a00ee2&utm_source=Lexology+Daily+Newsfeed&utm_medium=HTML+e-mail+-+Body+-+General+section&utm_campaign=Lexology+subscriber+daily+feed&utm_content=Lexology+Daily+Newsfeed+2022-05-17&utm_term.

The research-cooperation between Member States will also be facilitated by the introduction of the Clinical Trials Information System (CTIS) – a centralised portal and electronic database, enabling a single online submission for sponsors (replacing multiple submissions with different dossiers).[75] The CTIS single point of entry for submission, storage and authorisation of clinical trial applications will efficiently generate approval to run multinational clinical trials, streamlining multinational trials in Europe (cutting through segregated, domestic red tape) and contributing to their transparency, as data and documents in the CTIS are publicly available. This, along with a designated website, open both to the general public and to industry professionals, importantly fosters public trust in clinical trials. The system in place will also enhance coordination and information-sharing and improve safety measures for clinical trial participants.[76]

b. Endorsement of scientific advances

A second-order policy question, with relation to the appropriate/desirable regulation of biomedical research, is **whether, or to what extent, the regulation in place is restrictive, or permissive in nature** (i.e., endorsing scientific advances).

When it comes to regulating novel scientific advances, there is typically tension between two regulatory attitudes of policymakers: enthusiasm (i.e., the future-looking endorsement of promising scientific innovation); and skepticism – the product of a precautionary approach – towards insufficiently-understood scientific developments.

The attitude applied in practice will shape biomedical regulation in a way that profoundly impacts a country's research climate. But, while there is considerable variation in regulatory approaches,[77] even more enthusiastic regulatory frameworks will arguably not abandon scientific rigor and robust protection of research participants' rights.

We shall now look into the regulatory approaches towards two, proximate, innovative biomedical technologies: human cloning, and human genome editing, in our jurisdictions of interest. But, in order to grasp the relevant complexities around policymaking and regulation, we shall start by laying out, in brief, the ethical debate around them.

75 Aman Khera and Sarah Bly, *Understanding the new EU Clinical Trial Regulation: seven things sponsors should know*, EPR, HTTPS://WWW.EUROPEANPHARMACEUTICALREVIEW.COM/ART/168043/UNDERSTANDING-THE-NEW-EU-CLINICAL-TRIAL-REGULATION-SEVEN-THINGS-SPONSORS-SHOULD-KNOW/ (Jan. 28, 2022).

76 Aditya and Mulupuru, *supra* note 73.

77 Shaun D. Pattinson and Timothy Caulfield, *Variations and voids: the regulation of human cloning around the world*, 5 BMC MED. ETHICS (2004), https://doi.org/10.1186/1472-6939-5-9.

1. Human cloning: ethical aspects

Human cloning techniques allow us to "produce genetically identical copies of a biological entity."[78] The regulatory attitude towards human cloning is typically diverged into therapeutic/research cloning,[79] and reproductive cloning.[80] The latter, having hereditary effects, is a more deterring application of the technology, having cross- and intra-generational effects, and largely prohibited by national and universal legislation.[81]

Proponents of human cloning argue for autonomy and reproductive freedom (broadly interpreted to include the right to have children with "desirable" genes). Ethical objections to human cloning, emanating from its clash with religious and societal values, typically invoke the following concerns: moral and social objections to genetic intervention in germ cells, e.g., "playing God"-type arguments; a Posthumanism vision; potential effects on human nature; and cross-species' dilemmas. Further cloning-related apprehensions include safety and efficacy concerns; the potential infringement of human dignity; the lack of a distinctive identity, non-uniqueness and individuality of the cloned individual; harms to individual freedom and autonomy; the objectification of children, and a distortion of parent-child relationships.

2. Human genome editing: ethical aspects

In symmetry with the therapeutic/reproductive divergence in regulatory attitudes towards human cloning, ethico-legal approaches to human genome editing are split into the more lenient treatment of somatic cell genome editing, and a skeptical restrictive attitude towards human germline gene editing (HGGE), given its hereditary effects.

A non-exhaustive list of ethical concerns includes efficacy and safety dreads, namely – the fear of unintended edits ("off-target" DNA alterations); adverse effects on future generations (e.g., the introduction of new heritable diseases into the human gene pool); inappropriate (human) meddling with the human genome, and a slippery slope-type argument (drifting from therapeutic goals – to, typically criticised, elective genetic enhancement); adverse societal implications (e.g., devaluing and increasing the stigmatisation of people living with genetic disorders[82]); and a wider threatening impact on wildlife and ecosystems (e.g., biosafety, re-introduction of extinct species).[83]

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78 NIH, National Human Genome Research Institute, *Cloning Fact Sheet*, GENOME.GOV, HTTPS://WWW.GENOME.GOV/BOUT-GENOMICS/FACT-SHEETS/CLONING-FACT-SHEET#:~:TEXT=THE%20TERM%20CLONING%20DESCRIBES%20A,REFERRED%20TO%20AS%20A%20CLONE (last updated Aug. 15, 2020).

79 Therapeutic cloning entails "the creation of a cloned embryo for the sole purpose of producing embryonic stem cells with the same DNA as the donor cell," namely – that are a perfect genetic match for the patient. These stem cells are then used in research to better understand disease and for developing new treatments for diseases; *Ibid.*

80 Reproductive cloning, presently – a highly inefficient technique, has "the potential of creating a human that is genetically identical to another person who has previously existed or who still exists." It is typically carried out via the use of somatic cell nuclear transfer technology (SCNT); *Ibid.*

81 Pattinson and Caulfield, *supra* note 77.

82 UK Parliament, The Parliamentary Office of Science and Technology, *Human Germline Genome Editing*, POSTNOTE No. 611 (Jan. 2020), at 4; chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://researchbriefings.files.parliament.uk/documents/POST-PN-0611/POST-PN-0611.pdf.

83 *See, e.g.*, European Group on Ethics in Science and New Technologies, *Ethics of Genome Editing*, EC.EUROPA.EU, Opinion no. 32 (Mar. 19, 2021), chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://ec.europa.eu/info/sites/default/files/research_and_innovation/ege/ege_ethics_of_genome_editing-opinion_publication.pdf.

Ethical arguments supporting genome editing, include personal and global beneficence – e.g., the potential for having healthy children, as well as a positive impact on wildlife and ecosystems; non-maleficence by proactively preventing harm to future generations (through HGGE); an expression of the New Liberal Eugenics;[84] genome editing as a moral duty of (self-) improvement; and genetic enhancement as a tool for maximising social well-being.

3. Regulatory approaches to human cloning and genome editing in the jurisdictions of interest

Israel

Israel was among the first countries to regulate human cloning through *lex specialis*.[85] The 1999 Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law 5759-1999[86] ("the Cloning Act"), generally prohibits human reproductive cloning and the use of reproductive cells that have undergone a permanent intentional genetic modification (germline gene therapy) in order to cause the creation of a person. The law is silent, however, on therapeutic/research cloning and is interpreted as permissive toward the practice (which, would require review by the Supreme Helsinki Committee).

Furthermore, the Cloning Act (§ 5) articulates a relaxed, yet responsible attitude, by permiting through (as yet unissued) regulations the presently prohibited use of genetically modified germline for reproductive purposes, where this will not harm human dignity.

The Cloning Act uniquely sets a renewable, five-year moratorium to allow revisions to the current (mostly prohibitive) policy. Arguably, this reflects a flexible, cautious yet supportive mechanism, for scientific innovation.

Human genome editing is regulated vicariously through § 3(2) of the Cloning Act, banning HGGE for reproductive purposes. Broadly interpreted, however, this section seems to *allow* therapeutic, somatic gene editing.[87]

According to the Global Gene Editing Regulation Tracker's index,[88] Israel's ratings for therapeutic gene modification (i.e., gene editing of adult human cells, including gene therapy and stem cell therapy that is used to treat and cure disease) is – "lightly regulated," namely, regulated with minimal restrictions and requirements. The regulation of germline gene editing (of the human embryo or germline that results in heritable genetic modifications) is rated as "mostly prohibited."

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84 The New Liberal Eugenics advocates respect for individuals' reproductive freedom, namely personal and parental autonomy in genetically shaping one's children, alongside state neutrality on the matter. *See* Nicholas Agar, *Liberal Eugenics*, 12(2) Public Aff. Q. 137 (1998).

85 Pattinson and Caulfield, *supra* note 77.

86 Prohibition of Genetic Intervention (Human Cloning and Genetic Manipulation of Reproductive Cells) Law, 5759-1999.

87 Somatic cell gene editing is a non-heritable gene therapy, conducted on the body's non-reproductive cells, aimed at "modifying a patient's DNA to treat or cure a disease caused by a genetic mutation." *See also* therein for further information on somatic *vs.* gene editing. Mary Todd Bergman, *Perspectives on gene editing*, Harvard Gazette (Jan. 9, 2019), https://news.harvard.edu/gazette/story/2019/01/perspectives-on-gene-editing/.

88 Genetic Literacy Project, *Israel: Germline/Embryonic*, Global Gene Editing Regulation Tracker, https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/israel-germline-embryonic/#:~:text=1999%3A%20Israeli%20parliament%20passes%20the,Cells)%20banning%20germline%20gene%20editing (last visited Aug. 3, 2022).

UK

Reproductive cloning in the UK, regulated by the Human Fertilisation and Embryology Act (2008),[89] is prohibited by banning the placing in a woman gametes that have been subject to any alterations to their nuclear or mitochondrial DNA,[90] or embryos created by artificial gametes or genetically modified gametes (§ 3ZA).[91] Non-reproductive, therapeutic cloning (including the creation of cloned embryos for stem cell research) is legally permitted, under licence of the Human Fertilisation and Embryology Authority (HFEA).[92]

Gene therapy,[93] being an experimental technique, requires a license from the MHRA, and regulatory oversight from the Human Tissue Authority (HTA) and the HRA, through GTAC. Consequently, the UK's gene editing index rating is "highly regulated," for both therapeutic and germline gene editing.[94]

HGGE is illegal in the UK. The Human Fertilisation and Embryology Act 1990, as amended in 2008, prohibits any embryo that has had its germline DNA altered in any way (e.g., genome editing), from being placed inside a woman. But, for specified purposes, the Act allows the HFEA to grant licences for research involving human embryos – outside the body. Such licence was indeed granted by the latter in 2016, for a project involving genome editing of human embryos.[95] Drawing on the UK's 2015 regulations permitting (under licence) research into mitochondrial donation and its clinical application[96] – thereby, challenging the typically prohibitive global policy around HGGE[97] – some speculate that "germline genome modification may become a licensable treatment in the future."[98] Somatic genome editing (essentially a type of gene therapy) – is permitted in the UK and is being used in clinical trials.[99]

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89 The Human Reproductive Cloning Act 2001, formerly regulating the matter, was repealed in 2009 by the Human Fertilisation and Embryology Act 2008 (c. 22), ss. 3(6), 68(2), Sch. 8 Pt. 1.

90 An exception to the rule: The Human Fertilisation and Embriology (Mitochondrial Donation) Regulations 2015, later amended the Human Fertilisation and Embryology Act 2008 to allow for cases involving mitochondrial (donation) replacement techniques and granted HFEA licence, as part of in vitro fertilisation (IVF) treatments. *See* The Human Fertilisation and Embriology (Mitochondrial Donation) Regulations 2015, N. 572 (2015), http://www.legislation.gov.uk/ukdsi/2015/9780111125816/contents; UK Parliament Postnote No. 611, *supra* note 82.

91 Human Fertilisation and Embryology Act, UK Public General Acts c. 22 (2008), https://www.legislation.gov.uk/ukpga/2008/22/section/3.

92 Shaun D. Pattinson and Vanessa Kind, *Using a moot to develop students' understanding of human cloning and statutory interpretation*, 17(3) Med. Law Int. 111 (2017); doi: 10.1177/0968533217726350.

93 Gene therapy – the genetic modification of a person's genes to treat or cure disease. The technique includes *replacing* a disease-causing gene with a healthy copy of the gene; *inactivating* ("knocking out") a mutated gene that is functioning improperly; and *introducing* a new gene into the body to help fight a disease; FDA, *What is Gene Therapy? supra* note 28.

94 Genetic Literacy Project, *United Kingdom: Therapeutic/Stem cell*, Global Gene Editing Regulation Tracker, https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/united-kingdom-therapeutic-stem-cell/.

95 UK Parliament Postnote No. 611, *supra* note 82.

96 The Human Fertilisation and Embriology (Mitochondrial Donation) Regulations, *supra* note 90.

97 Britta C. van Beers, *Rewriting the human genome, rewriting human rights law? Human rights, human dignity, and human germline modification in the CRISPR era*, 7(1) J. Law Biosci. 1 (2020), at 9, https://doi.org/10.1093/jlb/lsaa006.

98 James Lawford Davies, *The Regulation of Human Germline Genome Modification in the United Kingdom*, *in* Human Germline Genome Modification and the Right to Science – A Comparative Study of National Laws and Policies (Andrea Boggio, Cesare P. R. Romano and Jessica Almqvist, eds., 2020); https://www.cambridge.org/core/books/abs/human-germline-genome-modification-and-the-right-to-science/regulation-of-human-germline-genome-modification-in-the-united-kingdom/61BC2D408DA62431D47A7C4785C6CC95.

99 Hayley Clissold, *Human genome editing – the issues explored,* Sangerinstitute.blog (Dec. 20, 2018), https://sangerinstitute.blog/2018/12/20/human-genome-editing-the-issues-explored/; UK Parliament Postnote No. 611, *supra* note 82, at 2.

US

In the US, there is no federal legislation prohibiting cloning per se,[100] however, such legislation partially exists at the state level, with significant variation in governance approaches between cloning laws. Some states[101] clearly prohibit both reproductive and therapeutic/research cloning; some[102] have limited their bans to reproductive cloning, while permitting therapeutic/research cloning; and in other states,[103] the law is either silent on the matter, or there are laws in place that indirectly address human cloning, in terms of (providing or withholding) government funding for cloning research, or by protecting physicians' conscientious objection to (partake in) human cloning.[104]

Human gene editing is considered by the FDA – regulating cellular and gene therapies[105]– to be a form of gene therapy and is addressed in US regulation within the framework for gene-transfer research and, where approved – for gene therapy. Gene therapy is permitted (upon FDA approval). HGGE in the US is not outrightly banned. While federal funding for such trials is prohibited by federal law (the Consolidated Appropriations Act of 2022 [CAA]),[106] there are no laws or regulations in place banning HGGE conducted through *private* funding.[107] (The question is, whether withholding governmental funding serves as an effective deterrent against conducting such research.)

Notwithstanding the absence of a federal ban, as research involving human embryos (e.g., producing human embryonic stem cells, or genetically editing/cloning them) is a highly charged issue in the US, correlated with debates over the moral status of embryos, several US states have enacted laws governing or banning research using human embryos.[108]

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100 Save for laws and policies restricting federal funding for human cloning research. *See* The Witherspoon Council, *The Threat of Human Cloning*, *Appendix: State Laws on Human Cloning*, The New Atlantis (Summer 2015), https://www.thenewatlantis.com/publications/appendix-state-laws-on-human-cloning.

101 E.g., Arizona, Arkansas, Michigan, and Virginia.

102 E.g., California, Connecticut, Maryland, and New Jersey.

103 E.g., Colorado, Georgia, and Florida.

104 The Witherspoon Council, *supra* note 100.

105 In its regulation of cellular and gene therapies, the FDA issues timely guidances for both researchers and the industry, to promote flexibility and efficiency in product development, and speed clinical trials, among other things. For instance, in March 2022, it issued a draft guidance document for "*Human Gene Therapy Products Incorporating Human Genome Editing*." *See, e.g.,* FDA, Center for Biologics Evaluation and Research, *Human Gene Therapy Products Incorporating Human Genome Editing,* Fda.gov (Mar. 21, 2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-products-incorporating-human-genome-editing.

106 The CAA bans funding of human embryo research (entailing either the *creation* of human embryos for research purposes, their *destruction*, or knowingly subjecting them to *risk of injury or death*) (s. 508; commonly known as the Dickey–Wicker Amendment). It also prohibits the FDA from considering applications for clinical trials involving the intentional creation or modification of a human embryo, to include a heritable genetic modification (s. 737); *see* H.R.2471 - Consolidated Appropriations Act 2022, Public Law No: 117-103, § 508 & § 737; https://www.congress.gov/bill/117th-congress/house-bill/2471/text.

107 Françoise Baylis et al., *Human Germline and Heritable Genome Editing:The Global Policy Landscape*, 3(5) Crispr J. (2020); doi: 10.1089/crispr.2020.0082; Genetic Literacy Project, *United States: Germline/embryonic*, Global Gene Editing Regulation Tracker,https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/united-states-embryonic-germline-gene-editing/#:~:text=Federal%20law%20prohibits%20the%20use,restrictions%20regarding%20human%20genetic%20engineering. al., *id.*

108 Committee on Human Gene Editing, *Human Genome Editing: Science, Ethics, and Governance*, National Academies of Sciences, Engineering, and Medicine (2017), https://www.ncbi.nlm.nih.gov/books/NBK447266/; Baylis et al, *id.*

As a result of said governance, therapeutic gene modification in the US has been rated as "highly regulated," whereas germline gene modification is remarkably rated as outright prohibited,[109] a rating somewhat inconsistent with other analyses of the relevant US regulation.[110]

EU

The EU's rather restrictive policy on research or clinical implementation of human genetic modification technologies is set through two legal instruments:[111]

a) Art. 13 of the Council of Europe's 1997 *Convention on Human Rights and Biomedicine*,[112] which clearly prohibits HGGE;[113] and

b) Art. 90 of the 2022 EU Clinical Trials Regulation, stipulating that "[n]o gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity."[114]

As a supranational entity, the aforesaid EU policies apply in accordance with individual Member States' national policies on health issues.[115] Therefore, the effect of said EU policies would seemingly be most tangible, in terms of research funding. For instance, while the EU supports funding of embryonic stem cell research,[116] its Horizon Europe Framework Programme explicitly *excludes* from Union funding research activities aiming at reproductive human cloning; research intended to make heritable genetic modifications in humans (i.e., HGGE); and the creation of human embryos solely for the purpose of research, or stem cell procurement, including by means of somatic cell nuclear transfer (SCNT).[117] Consequently, therapeutic cloning is not legally banned but is effectively restricted, in the EU.[118]

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109 Genetic Literacy Project, *United States: Therapeutic/Stem cell*, Global Gene Editing Regulation Tracker, https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/united-states-gene-therapy-stem-cells/.

110 *See, e.g.*, Liu's representation of human genome editing in the USA, as a practice that "is not banned, but a moratorium is imposed under vigilance of the […] FDA." Shuang Liu, *Legal reflections on the case of genome edited babies*, 5 Glob. Health Res. Policy (2020), at 2, https://doi.org/10.1186/s41256-020-00153-4. *See* also Baylis et al., claiming that the literature often provides inaccurate accounts of policy landscapes concerning HGGE – classifying the US policy on HGGE (not used for reproduction) as permitted (with private funding). Baylis et al., *supra* note 107; and Genetic Literacy Project, *United States, supra* note 107.

111 Santa Slokenberga, *What Would It Take to Enable Germline Editing in Europe for Medical Purposes?* Eur. J. Health Law, 1-22 (2022), https://brill.com/view/journals/ejhl/aop/Art-10.1163-15718093-bja10074/Art-10.1163-15718093-bja10074.xml.

112 The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No 164) (1997); https://www.coe.int/en/web/bioethics/oviedo-convention; Art. 13: "[a]n intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is *not to introduce any modification in the genome of any descendants*" [my emphasis – S.T.].

113 Notably, the Oviedo Convention is legally binding (*mutatis mutandis*) in the 29 countries that have ratified it. Baylis et al., *supra* note 107.

114 Regulation (EU) No. 536/2014, *supra* note 71, Art. 90, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex-%3A32014R0536#d1e3290-1-1.

115 European Parliament, *Fact Sheets on the European Union*, Europarl.europa.eu (Aug. 2, 2022), https://www.europarl.europa.eu/factsheets/en/indexsearch?query=health.

116 Kirstin Matthews, *Stem Cell Research: A Science and Policy Overview*, Cnx.org, https://cnx.org/contents/MrC2GmrU@1.1:4O_mfmxO@1/Overview-of-World-Human-Cloning-Policies.

117 Establishing Horizon Europe — laying down its rules for participation and dissemination 2021 O.J. (C 506/25) (EU), chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52021AP0124.

118 Kirstin Matthews, *Overview of World Human Cloning Policies*, Cnx.org, https://cnx.org/contents/MrC2GmrU@1.1:4O_mfmxO@1/Overview-of-World-Human-Cloning-Policies.

An initial indication of a paradigm shift from this restrictive-precautionary approach towards a more pragmatic innovation-promoting approach, may, however, be found in the European Group on Ethics in Science and New Technologies (EGE), 2021 opinion on *Ethics of Genome Editing*,[119] recommending, e.g., the establishment of a European and/or global registry for HGGE research.[120]

119 European Group on Ethics in Science and New Technologies, *Ethics of Genome Editing*, Opinion no. 32, Directorate-General for Research and Innovation (Ec) (Mar. 19, 2021), chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://ec.europa.eu/info/sites/default/files/research_and_innovation/ege/ege_ethics_of_genome_editing-opinion_publication.pdf.

120 The EGE's opinion also recommends that for somatic genome editing, "access to clinical studies and, once approved, to clinical application in healthcare is granted according to the principle of social justice and without discrimination." It further suggests that "guidelines for safety assessments and risk/benefit determinations of clinical trials involving genome editing and research involving human embryos (where permitted), are developed […] to ensure high-standing and consistent application of ethical standards." *Ibid.*, pp. 87-88.

CONCLUSION

This was a non-exhaustive comparative account of several regulatory frameworks for biomedical research. One could think of many other valuable points of comparison between regulations. For instance, regulatory frameworks' commitment to social justice, namely, to ensuring equity and diversity by inclusion of underrepresented, marginalised populations (e.g., ethnic and racial minorities, women, etc.), in clinical trials and medical research databases, while protecting vulnerable populations (by exclusion) from potentially harmful participation.[121] IRBs/RECs play a key role in this, with the support of laws, guidance, and best practices, by evaluating the inclusion/exclusion criteria in a given research, with such a wider social commitment in mind.

After comparatively considering the biomedical research regulatory frameworks of Israel, the UK, US and the EU, through several prisms, and scrutinising the grievance of over/under-regulation, the following points can be concluded:

First, the over/under-regulation critique is naturally highly subjective, as excessive/lacking regulation is in the eye of the beholder. Researchers and sponsors typically complain of over-regulation, whereas ethicists and ethics-aware patient groups argue the area is under-regulated, suffering from regulatory gaps.

Second, all regulatory efforts aim to strike a balance between the ethical imperative of maintaining scientific rigor and robustness of experimental design, particularly to protect the rights and welfare of human research subjects and data subjects, and having in place such regulation that will not effectively discourage beneficial research, to the detriment of society. This is a delicate task, the results of which probably leave both sides – dissatisfied to some degree.

121 https://mrctcenter.org/diversity-in-clinical-research/tools/irb-and-hrpp-toolkit/ (last visited Aug. 4, 2022).