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Bioethical challenges of gene therapy and regenerative medicine

PhD thesis

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CONTENTS

ACRONYMS

CARTHAGO: Cartilaginous tissue regeneration by gene therapy; taking the hurdles towards efficient delivery (project funded by the European Commission Horizon 2020; Marie Skłodowska-Curie Innovative Training Network, grant number 955335)

ESRs: Early Stage Researchers

FG: Focus Group

GT&RM: Gene Therapy and Regenerative Medicine

IVDD: Intervertebral Disc Degeneration

OA: Osteoarthritis

LIST OF PUBLICATIONS CONSTITUTING THE DOCTORAL THESIS

[1] **Buedo P**, Bianchini A, Klas K, Waligora M.
Bioethics of somatic gene therapy: what do we know so far?
Current Medical Research and Opinion
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The published version of this article is available in Supplementary Material (S1 Appendix).

[2] **Buedo P**, Prieto E, Perek-Białas J, Odziemczyk-Stawarz I, Waligora M.
More ethics in the laboratory, please! Scientists' perspectives on ethics in the preclinical phase.
Accountability in Research
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[3] **Buedo P**, Odziemczyk I, Perek-Białas J, Waligora M.
How to embed ethics into laboratory research.
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THE PHD CANDIDATE CONTRIBUTIONS TO PUBLICATIONS CONSTITUTING THE DOCTORAL THESIS

[1] As the first author of the publication "**Bioethics of somatic gene therapy: what do we know so far?**" (doi: 10.1080/03007995.2023.2257600) I declare that my input in the research included:

a) Conceptualization

b) Data curation

c) Formal analysis

d) Investigation

e) Methodology

f) Visualization

g) Writing: original draft preparation

h) Writing: review and editing

[2] As the first author of the publication "**More ethics in the laboratory, please! Scientists' perspectives on ethics in the preclinical phase**" (doi: 10.1080/08989621.2023.2294996) I declare that my input in the research included:

a) Conceptualization

b) Data curation

c) Formal analysis

d) Investigation

e) Methodology

f) Visualization

g) Writing: original draft preparation

h) Writing: review and editing

[3] As the first author of the publication "**How to embed ethics into laboratory research**" (doi: 10.1080/08989621.2023.2165916) I declare that my input in the research included:

a) Conceptualization

b) Data curation

c) Formal analysis

d) Investigation

e) Methodology

f) Visualization

g) Writing: original draft preparation

h) Writing: review and editing

ENGLISH SUMMARY

Background

Gene therapy and regenerative medicine are biomedical technologies with promising therapeutic value. This is why significant research efforts are being made to advance the field of gene therapy, with a focus on developing regenerative medicine technologies (Hosseinkhani et al., 2023). One of this research effort was funded by European Commission in 2020, a project called "Cartilaginous tissue regeneration by gene therapy; taking the hurdles towards efficient delivery" (acronym: CARTHAGO). The project was carried out by an international, multicenter and multidisciplinary European research consortium funded by Marie Skłodowska-Curie Actions (Grant Agreement No. 955335). The aim of CARTHAGO is to investigate the applicability of somatic gene therapy in osteoarthritis and disc degeneration. CARTHAGO plans to develop preclinical laboratory techniques to provide a solid foundation for this potential treatment. The applicability of these potential therapies requires anticipating possible bioethical issues. The complexity of the technology itself and the way it could change our perception of health and disease make this anticipation more challenging. The challenging aspects requires going beyond traditional approaches to bioethics, such as assessment before or after a research process, or exclusively by a bioethics committee. Especially, there have been calls in recent years to improve ethics in preclinical research. It is suggested that the perspectives of scientists should be taken into account to better promote ethics in preclinical research. The hypothesis is that identification of these bioethical challenges in the preclinical laboratory phase of research will allow for more efficient risk-benefit management in further steps of development of potential treatment. Early identification of ethical issues will lead to the integration of the perspectives of bioethicists, laboratory researchers and industry stakeholders.

The aim of the thesis is: i) to evaluate the bioethical challenges of somatic gene therapy and regenerative strategies for disc and joint pathology in the preclinical, laboratory phase; and ii) to promote and evaluate the integration of bioethics into preclinical research in CARTHAGO.

Methods

The methods used in this thesis was meta-research and empirical qualitative research. Three studies were carried out to achieve the aims of the thesis. Meta-research approach was adapted in the *first study*. We conducted a systematic review of reasons. The aim was to provide a systematic overview of the bioethical debate on somatic gene therapy as documented in the scientific literature. Qualitative empirical research was adapted in the *second* and *third studies*. A *second study* was undertaken to identify ethical issues surrounding gene therapy and regenerative strategies for disc and joint pathology from the perspective of laboratory and industry researchers. I used two different techniques: focus groups and interviews. The two different qualitative techniques were chosen to better adapt to the profiles of the research participants, and in both we shared the same goal and aimed to cover the same

topics/areas of research interest. I performed interviews with experienced researchers and focus groups with early-stage researchers (ESRs). For the *third study*, I developed a series of focus group meetings for ESRs. The *third study* was conducted to embed bioethics and elements of research integrity in the consortium activities.

Results and Discussion

For systematic review of reasons (*first study*), we identified 217 eligible publications retrieved from PubMed, Lilacs, PhilPapers and Google Scholar. We extracted 189 arguments that were grouped into 23 categories. Twelve categories were classified as research-related, including risk-benefit ratio, priorities and limitations, informed consent, review and monitoring. Eleven were classified as societal. Some of these included population impact, human identity, public perception, and human health. The *first study* contributed to the debate on the ethical and social dimensions of somatic gene therapy by providing a database of existing challenges and arguments, which can serve as a basis for normative analysis. Having analyzed the arguments, we recognize that somatic gene therapy could have serious implications and we have no clear answers on how to address them.

Among the ethical challenges identified by researchers in *second study*, they highlighted the importance of the social context of research and its social impact. They agreed that it is important to be socially responsible - to be aware of and sensitive to the needs and views of society. A recurring theme among the ESRs was the impact of health-related pre-clinical research on climate change. They highlighted the importance of strengthening ethical relationships within the scientific community. Experienced researchers focused on the technicalities of the methods used in preclinical research. They stressed the need for more safeguards to protect the sensitive personal data they work with. The *second study* helps to identify key ethical challenges and, when combined with more data, may ultimately lead to informed and evidence-based improvements to existing regulations. One of the main findings is that most researchers participating in the study recognize gaps in their knowledge about ethics and research integrity.

As a result of the focus group series described in *third study*, all researchers changed their perspectives on ethical issues in relation to their planned research, developed the ability to reflect and discuss research ethics, and had an increased awareness of ethical issues in their own research activities. Half of them made changes to their research. The focus group series was evaluated through questionnaires completed by the researchers before and after the sessions, and through analysis of the content of the focus groups. The *third study* provides a concrete strategy for embedding ethics and strengthening accountability in laboratory research. It is a strategy that allows ethical reflection "on the ground" and in "real time" and complements the classical strategy of ethical assessment of the research protocol before the research process starts.

Conclusion

This thesis provides an assessment of the bioethical challenges associated with gene therapy and regenerative medicine for disc and joint pathology, and a proposal on how to integrate bioethics in preclinical biotechnology research in an international, multicenter and multidisciplinary consortium.

POLISH SUMMARY

Wstęp

Terapia genowa i medycyna regeneracyjna to technologie biomedyczne o obiecującej wartości terapeutycznej. Podejmowane są znaczące wysiłki badawcze w celu rozwoju terapii genowej, z naciskiem na rozwój technologii medycyny regeneracyjnej (Hosseinkhani i in., 2023). Jednym z nich jest projekt pt.: *"Cartilaginous tissue regeneration by gene therapy; taking the hurdles towards efficient delivery"* (akronim: CARTHAGO), który został sfinansowany przez Komisję Europejską w 2020 roku. Projekt jest realizowany przez międzynarodowe, wieloośrodkowe i interdyscyplinarne konsorcjum badawcze w ramach programu *Marie Skłodowska-Curie Actions* (Grant Agreement No. 955335). Celem CARTHAGO jest zbadanie możliwości zastosowania somatycznej terapii genowej w chorobie zwyrodnieniowej stawów i zwyrodnieniu dysku (krążka międzykręgowego). CARTHAGO planuje opracować przedkliniczne techniki laboratoryjne, aby zapewnić podstawy dla rozwoju tego potencjalnego leczenia. Możliwość zastosowania tej potencjalnej terapii wymaga przewidywania towarzyszących kwestii bioetycznych. Złożoność samej technologii i sposób, w jaki może ona zmienić nasze postrzeganie zdrowia i choroby, sprawiają, że przewidywanie to staje się wyzwaniem. Trudne aspekty wymagają wyjścia poza tradycyjne podejście do bioetyki, którego przykładem są ocena procesu badawczego wyłącznie przed rozpoczęciem lub po jego zakończeniu lub wyłącznie w oparciu o opinię komisji bioetycznej. W ostatnich latach pojawiły się liczne apele o zwiększenie roli etyki w badaniach przedklinicznych. Sugeruje się, że identyfikacja wyzwań bioetycznych na etapie przedklinicznych badań laboratoryjnych pozwoli na bardziej efektywne zarządzanie ryzykiem i korzyściami na dalszych etapach rozwoju potencjalnego leczenia. Wczesna identyfikacja kwestii etycznych pozwoli na integrację wyzwań dostrzeganych przez specjalistów z zakresu bioetyki, badań laboratoryjnych czy wdrożeń przemysłowych.

Celem pracy jest: i) ocena bioetycznych wyzwań związanych z rozwojem somatycznej terapii genowej i strategii regeneracyjnych w patologii dysków i stawów w przedklinicznej fazie laboratoryjnej; oraz ii) promowanie i ocena integracji bioetyki w obszarze badań przedklinicznych w CARTHAGO.

Metody

Metodami zastosowanymi w niniejszej rozprawie były meta-badania i empiryczne badania jakościowe. Aby osiągnąć cele pracy, przeprowadzono trzy badania. W pierwszym badaniu zastosowano podejście meta-badawcze. Przeprowadzono systematyczny przegląd literatury. Celem było przedstawienie debaty bioetycznej na temat somatycznej terapii genowej na podstawie opublikowanej literatury naukowej. Drugie i trzecie badanie to jakościowe badania empiryczne. Drugie badanie wykonano w celu zidentyfikowania kwestii etycznych związanych z terapią genową i strategiami regeneracyjnymi w patologii dysków i stawów z perspektywy badaczy laboratoryjnych i pracowników przemysłu. Wykorzystano dwie różne techniki: grupy fokusowe z początkującymi badaczami (ang. e*arly-stage*

researchers, ESR) i wywiady z doświadczonymi badaczami. Wybrano dwie różne techniki jakościowe, aby lepiej dostosować się do profili uczestników badań. Na potrzeby trzeciego badania opracowano serię spotkań grup fokusowych dla ESR. Trzecie badanie przeprowadzono w celu oceny włączenia bioetyki i elementów rzetelności badawczej do działań konsorcjum.

Wyniki i dyskusja

Po przeszukaniu baz PubMed, Lilacs, PhilPapers i Google Scholar do przeglądu systematycznego (pierwsze badanie) włączyliśmy 217 publikacji naukowych spełniających kryteria selekcji. Na podstawie dostępnych danych w naszej dyskusji wyzwań bioetycznych na temat somatycznej terapii genowej wyodrębniliśmy 189 argumentów, które zostały pogrupowane w 23 kategorie. Spośród wyodrębnionych kategorii, 12 zostało sklasyfikowanych jako związane z badaniami, w tym stosunek ryzyka do korzyści, priorytety i ograniczenia, świadoma zgoda, przegląd i monitorowanie. Jedenaście zostało sklasyfikowanych jako wyzwania społeczne. Niektóre z nich obejmowały wpływ na populację, tożsamość ludzką, postrzeganie społeczne i zdrowie. Pierwsze badanie przyczyniło się do debaty na temat etycznego i społecznego wymiaru somatycznej terapii genowej, zapewniając bazę danych istniejących wyzwań i argumentów, które mogą służyć jako podstawa do analizy normatywnej. Wykazaliśmy, że somatyczna terapia genowa może mieć poważne konsekwencje i nie mamy jasnych odpowiedzi, jak sobie z nimi poradzić.

Naukowcy biorący udział w drugim badaniu, wskazali znaczenie społeczne badań i ich wpływ społeczny jako jedne z kluczowych wyzwań etycznych. Zgodzili się, że ważne jest, aby być społecznie odpowiedzialnym - być świadomym i wrażliwym na potrzeby i poglądy społeczeństwa. Powtarzającym się tematem wśród ESR był wpływ badań przedklinicznych związanych ze zdrowiem na zmiany klimatu. Podkreślali oni znaczenie wzmocnienia relacji etycznych w społeczności naukowej. Doświadczeni badacze skupili się na technicznych aspektach metod stosowanych w badaniach przedklinicznych. Podkreślili potrzebę wprowadzenia większej liczby zabezpieczeń w celu ochrony wrażliwych danych osobowych, z którymi pracują. Drugie badanie pomaga zidentyfikować kluczowe wyzwania etyczne, a w połączeniu z większą ilością danych może ostatecznie doprowadzić do świadomych i opartych na dowodach ulepszeń istniejących przepisów. Jednym z głównych wniosków jest fakt, że większość naukowców uczestniczących w badaniu dostrzega luki w swojej wiedzy na temat etyki i rzetelności badań.

W wyniku serii grup fokusowych opisanych w trzecim badaniu wszyscy badacze zmienili swoje spojrzenie na kwestie etyczne w odniesieniu do planowanych badań, rozwinęli umiejętność refleksji i dyskusji na temat etyki badań oraz zwiększyli świadomość kwestii etycznych we własnych działaniach badawczych. Połowa z nich wprowadziła zmiany w swoich badaniach. Seria grup fokusowych została oceniona za pomocą kwestionariuszy wypełnionych przez badaczy przed i po sesjach oraz poprzez

analizę treści grup fokusowych. Trzecie badanie zapewnia konkretną strategię wdrażania etyki na etapie rozwoju prac badawczych i wzmacniania odpowiedzialności w badaniach laboratoryjnych. Jest to strategia, która umożliwia refleksję etyczną "na miejscu" i w "czasie rzeczywistym" oraz uzupełnia klasyczną strategię oceny etycznej protokołu badawczego przed rozpoczęciem procesu badawczego.

Wnioski

Niniejsza rozprawa zawiera ocenę wyzwań bioetycznych związanych z terapią genową i medycyną regeneracyjną w patologii dysków i stawów oraz propozycję, w jaki sposób zintegrować bioetykę z przedklinicznymi badaniami biotechnologicznymi w międzynarodowym, wieloośrodkowym i interdyscyplinarnym konsorcjum badawczym.

INTRODUCTION

Gene therapy and regenerative medicine are biomedical technologies with promising therapeutic value. Gene therapy is a technique in which an individual's genes are altered for therapeutic purposes (National Human Genome Research Institute, 2024). This thesis focuses on gene therapy that targets somatic cells and uses non-editing techniques. Somatic gene therapy means that when a person receives a therapy, it is not inherited by their offspring, as is the case with germline therapy (Alhakamy, Curiel & Berkland; 2021). Non-editing technologies refer to the replacement, silencing, or insertion of a gene without the use of molecular tools such as CRISPR-CAS9, a genome editing technology (Landhuis, 2021).

Somatic gene therapy is a promising approach that could provide treatment options for many diseases that currently have no or insufficient therapeutic options (High & Roncarolo; 2019). Many preclinical and clinical studies are evaluating the therapeutic potential of somatic gene therapy (Riva & Petrini, 2019). For example, in relation to cardiovascular diseases (such as coronary artery disease or ischemia), genetic disorders (such as thalassemia or severe combined immunodeficiency), various types of cancer (meningioma and spinal cord, gastrointestinal, breast, etc.), infectious diseases (such as HIV or hepatitis), among others (Alhakamy, Curiel & Berkland; 2021). In addition, there are already somatic gene therapies that have received regulatory approval, such as therapies for spinal muscular atrophy, retinal dysmorphy, hemophilia B, multiple myeloma, and others (FDA, 2024; Shchaslyvyi et al., 2023).

Somatic gene therapy is being evaluated for use in regenerative medicine (Hosseinkhani et al., 2023). Regenerative medicine is an interdisciplinary field combining engineering and life sciences to develop techniques for restoring, maintaining, or enhancing living tissue and organs (Hosseinkhani et al., 2023). Gene therapy could be a powerful tool for sustained tissue repair in affected body parts through stimulating local synthesis (Balmayor, 2023). However, several technical issues remain to be addressed despite significant progress in this area (Hosseinkhani et al., 2023).

One of the research efforts at the intersection of somatic gene therapy and regenerative medicine is being applied to find a treatment modality for osteoarthritis (OA) and intervertebral disc degeneration (IVDD) (Im, 2021). There are many similarities between OA and IVDD in the molecular processes involved as well as in the onset and progression of these pathologies (Fine et al., 2023). They also share a lack of effective and long-lasting treatment (Rustenburg et al., 2018), which is highly problematic for individual and public health due to their high prevalence and the chronic pain they cause, which is reported to be disabling and costly (Nicolson et al., 2017). A research initiative that aims to investigate the applicability of somatic gene therapy for cartilage regeneration in OA and IVDD through preclinical research, is CARTHAGO, an international, multicenter and multidisciplinary European research

consortium funded by Marie Skłodowska-Curie Actions (Grant Agreement No. 955335). CARTHAGO is an acronym for *Cartilaginous tissue regeneration by gene therapy: taking the hurdles towards efficient delivery*. At the intersection of somatic gene therapy and regenerative medicine, CARTHAGO aims to establish a solid foundation for the potential treatment of AO and IVD by conducting research in the preclinical phase.

The applicability of these potential therapies requires anticipating possible bioethical issues. However, the novel and disruptive properties of this biotechnology make this anticipation challenging for a number of reasons (Sugarman & Bredenoord, 2020; Stilgoe, Owen & Macnaghten, 2013). First, because of its cross-cutting complexity, requiring interdisciplinary and multi-method research (Torres-Padilla et al., 2020). Second, while translation from the laboratory to clinical trials is difficult, the translation to the health system and society is even harder (Jongsma & Bredenoord, 2020). In addition, health-related innovations may affect social realities at multiple levels and raise new ethical concerns. These include so-called "soft" impacts related to human values, experiences, identity, relationships and perceptions, as well as "hard" impacts such as distributive justice, health care and market impacts, biosecurity, longevity and enhancement, among others (de Kanter et al., 2023; van Delden, & Bredenoord, 2015). As a soft impact, these biotechnologies could change how society perceives and understands health and disease. For example, in the case of deaf people, many do not see themselves as having a disease, but rather see deafness as a personal characteristic that is part of their healthy status (Scully, 2019). If this potential therapy could play a role in "treating" these different functions through genes, then different functions could be seen as a genetic problem. This could also affect the identity and health perceptions of those who do not see themselves as having a disease that needs to be treated. Another example of a soft impact relates to human identity, as it could increase the perception that the body is malleable in all cases and, for example, change the social acceptance of organ donation or foster unhealthy lifestyles (de Kanter et al., 2023). As a hard impact at the population level, health-related innovations in biotechnology risk increasing social inequalities (Jongsma & Bredenoord, 2020). For example, gene therapy and regenerative medicine could help to extend the average human lifespan or even minimize the effects of aging, raising the question of whether longevity is socially desirable or whether aging should be viewed as a disease or something to be avoided (de Kanter et al., 2023). This could have an impact on pension systems and reduce solidarity with older generations.

Discussions and training on research ethics are not frequent in the preclinical research environment (Hildt et al., 2022; Laas et al., 2022). This can lead to the overlooking of ethical challenges in preclinical research, as well as the under-identification of other challenges that are subtle or unexpected (Jongsma & Bredenoord, 2020). Calls for improved ethics in preclinical research have increased in recent years (Yarborough et al., 2018). Notable concerns motivating these calls include the reproducibility crisis and poor translation to the clinical research phase (Haslberger et al., 2023; Karp & Reavey, 2019;

Yarborough et al., 2018; Kimmelman & Henderson, 2016). The use of same-sex animals samples for certain types of research has been shown to be problematic for translating research to diverse populations (Karp & Reavey, 2019; Shah, McCormack & Bradbury, 2014). Other practices that contribute to poor translation and the reproducibility crisis include lack of blinding of treatment assignment to animals, exclusion of animals due to unexpected results, and improper characterization of a drug's utility (e.g., testing a drug for a chronic disease in an animal with an acute disease) (Wang et al., 2022; Kimmelman & Henderson, 2016; Macleod et al., 2015).

To promote ethics in the preclinical phase of research and to identify challenging aspects of biotechnology, in this case around gene therapy and regenerative medicine, it is necessary to go beyond traditional approaches to bioethics, such as evaluation before or after a research process, or to provide scientists with guidelines about research integrity and bioethics. While several guidelines on research integrity and bioethics are available, a gap remains in providing a practical approach to integrate ethics in biotechnology research (Bærøe et al., 2022; Roje et al., 2021; McLennan et al., 2020; Pansera et al., 2020; Zwart & Ter Meulen, 2019). Strategies to integrate ethics in the laboratory phase need to be developed, applied, and evidenced in the biotechnology development process (Bærøe et al., 2022; Sugarman & Bredenoord, 2020; Zwart & Ter Meulen, 2019). Furthermore, it has been suggested that scientists' perspectives should be taken into account to better integrate ethics in preclinical research, as scientists have to deal with these issues on a daily basis (Yarborough et al., 2018). Understanding how scientists view the relevance of ethics to their work and their responsibilities as members of society is critical to developing strategies to promote ethical conduct in preclinical research and to foster discussion at this stage of research (Linville et al., 2023; Wäscher, Biller-Andorno & Deplazes-Zemp, 2020).

This thesis has been prepared within the CARTHAGO project, with the aim of:

i) explore the bioethical aspects of somatic gene therapy and regenerative strategies for disc and joint pathology in the preclinical laboratory phase, and

ii) to implement and assess the integration of bioethics into preclinical research at CARTHAGO.

METHODS

Three studies were carried out to achieve the aims of this thesis. The methods used in this thesis were meta-research methods (the *first study*) and empirical qualitative research (the *second* and the *third study*).

First study

The *first study* has the objective to provide a systematic overview of the bioethical debate on somatic gene therapy as documented in the scientific literature. I conducted a systematic review of reasons, that allow us to systematically identify and classify arguments (reasons) found in the scientific literature (Strech & Sofaer, 2012). I reported the data according to the PRISMA Ethics Reporting Guideline for Systematic Reviews on Ethics Literature: development, explanations and examples (Kahrass et al., 2021). The PRISMA Ethics Reporting Guideline for this review can be found in the Supplementary Material (S4 Appendix).

- Eligibility criteria

The publications were selected if they were focused on somatic gene therapy with clear therapeutic goals and if they discussed reasons for the acceptability, importance, value, morality, ethics, or bioethics. The articles were included in either English or Spanish.

- Search strategy

Search strategy was designed for PubMed, Lilacs, PhilPapers, and Google Scholar. I performed the search on 26 July 2021. The four databases were chosen because they cover a wide range of biomedical and philosophical publications from around the world. The search strategy for each database is presented in the Supplementary Material section (S5 Appendix).

- Data extraction

We analyzed selected articles using three data extraction documents that I prospectively designed (S6 Appendix). Two data extraction documents attempted to collect contextual data from the articles, and the third attempts to extract arguments. I extracted arguments from 100% of the articles, and independently, two other researchers extracted arguments from the same 100%, but they distributed half and half of the articles. We used the Constant Comparative Method (CCM) (Gibbs, 2008) to extract and categorize the arguments. CCM is an iterative method for collecting and analyzing the data, and using the findings for further data collection.

- Identification of codes and themes

All extracted arguments were grouped into categories related to a particular topic. I was in charge of developing the categories, which was an iterative process and I did under the consultation of other researchers. After I finished defining the categories, I grouped them into two broad themes.

Second study

The *second study* was undertaken to identify ethical issues surrounding gene therapy and regenerative medicine (GT&RM) for disc and joint pathology from the perspective of laboratory and industry researchers. For this study, I used qualitative empirical methods: focus groups (FG) and interviews. I conducted interviews for experienced researchers and focus groups for ESRs with the same purpose and to cover the same research topics (Figure 1).

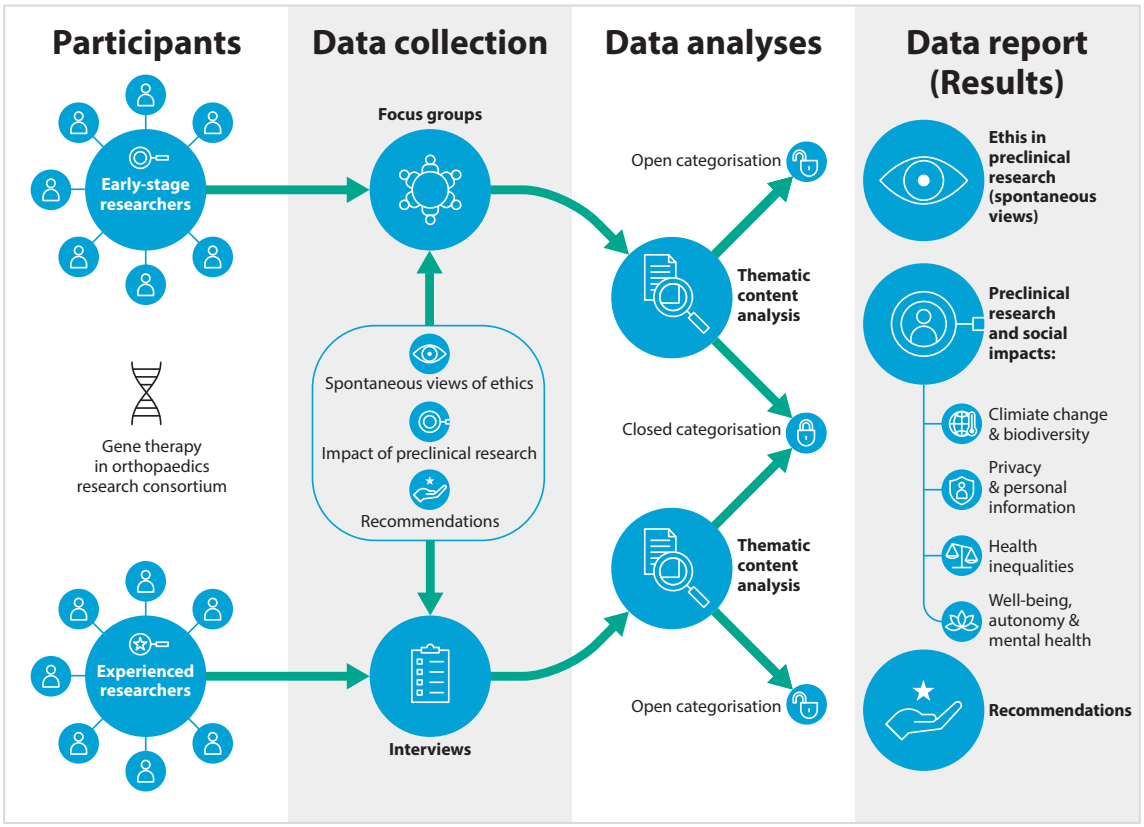

Figure 1: A graphic synthesis of the methods used in this study.

I use the comprehensive consolidated criteria for reporting qualitative research (COREQ) to report this research (Tong, Sainsbury & Craig, 2007), and the checklist is available in the Supplementary Material (S7 Appendix).

- Participants

The participants (n = 25) were all the researchers from CARTHAGO. Participants were divided in two groups according to their career situation. The first group were ESRs (n=14) who had just started their

academic career and the second group were experienced researchers (n=11) who are experts in the gene therapy and regenerative medicine field. The ESRs come from Brazil (2), India (2), Iran (2), Italy, Spain, Taiwan, Germany, China, the Netherlands, Chile, and Egypt. Ten were women and four were men. They are currently working in the Netherlands (4), Switzerland (2), Sweden (2), Denmark (2), Finland, Romania, Germany and Portugal, in universities (10) and companies (4). Experienced researchers work as Principal Investigators in the Netherlands (3), Switzerland (2), Sweden, Denmark, Finland, Romania, Germany and Portugal, in universities (7) and private companies (3). There were seven men and four women.

- Data collection

Focus groups

I conducted five consecutive FG sessions with ESRs between October 2021 and May 2022. Each meeting lasted a maximum of 90 minutes and was conducted in English. Because the ESRs were located in different countries, the FGs were conducted online. The choice of the focus group as a research method for the ESRs stems from the aim to investigate how a broad concept such as ethics evolves in discussions between people whose attitudes have not yet been strongly shaped by the research environment. The complementary aim of the focus group meetings with ESRs was to collaborate on a recommendation for embedding ethics in laboratory research, which is the *third study* in this thesis.

I designed a guide for each FG (S8 Appendix) with the goal of discussing research ethics and integrity in the preclinical research that ESRs were conducting, the impact of the research, and their recommendations for improving ethics and integrity at this stage. The guides were discussed among the research team conducting this study. We organized a pilot FG with ten ESRs working in the study area but not part of the consortium to test the guidelines. I conducted the pilot FG and it was also useful to improve my skills in this activity.

Interviews

I performed semi-structured interviews with the experienced researchers of CARTHAGO between July and September 2022 and lasted between 45 and 70 minutes. They were conducted in English and took place either at a location chosen by the participant (3) or online via a video call platform (8). The choice of interviews as the research method for the experienced researchers arises from the aim to have an in-depth conversation about the interviewee's knowledge and opinion about the state of ethics and integrity in the preclinical phase.

I designed the interview guide (S9 Appendix), which consists of open-ended questions related to research ethics, integrity, and bioethical challenges in the preclinical phase, as well as the impact of the research and its recommendations for improving ethics and integrity in this phase. The guides were discussed among the research team conducting this study. A semi-structured design ensured that topics

discussed by all participants were consistent, but allowed participants to raise or highlight issues different from that proposed. Individual meetings with experienced researchers allowed them to share their experiences and express their views more freely without being confronted with the positions of other members of the academic community.

The interview was piloted with two researchers working in the study area but outside the consortium. I conducted the pilot interview and it was also useful to improve my skills in this activity.

- Data analyses

The focus groups and interviews were recorded, transcribed verbatim, and pseudonymized. The transcriptions were entered into MAXQDA software and analyzed using thematic content analysis (Bergin, 2018; Green & Thorogood, 2018). I developed a coded categorization according to the research objectives of the study and in consultation with the other researcher who analyzed the data. I combined a closed and an open categorization (Taylor, Bogdan & DeVault, 2015). The closed categorization, which I defined prior to analysis, related to research impacts on autonomy, privacy and personal information, climate change, health disparities, social well-being, and mental health. The open codes were derived from transcriptions on spontaneous views and recommendations on ethics in preclinical research. Interview and focus group data were analyzed separately. Once the coding was completed, I established a relationship between the categories in order to further present and discuss the findings of our research.

- Ethical considerations

This study was reviewed and approved by the Bioethics Committee of the Jagiellonian University, Krakow, Poland (No. 1072.6120.209.2021–29/09/2021) (S10 Appendix).

Third study

The *third study* was conducted to implement and evaluate a strategy for integrate ethics and research integrity in CARTHAGO. This strategy, also named as “ethics embedding” strategy was implemented through a series of focus group meetings for ESRs. For the evaluation, we combined two techniques: analysis of changes in the way ESRs discussed ethics through the FG meetings and semi-structured questionnaires answered by ESRs before and after the series of meetings (Figure 2).

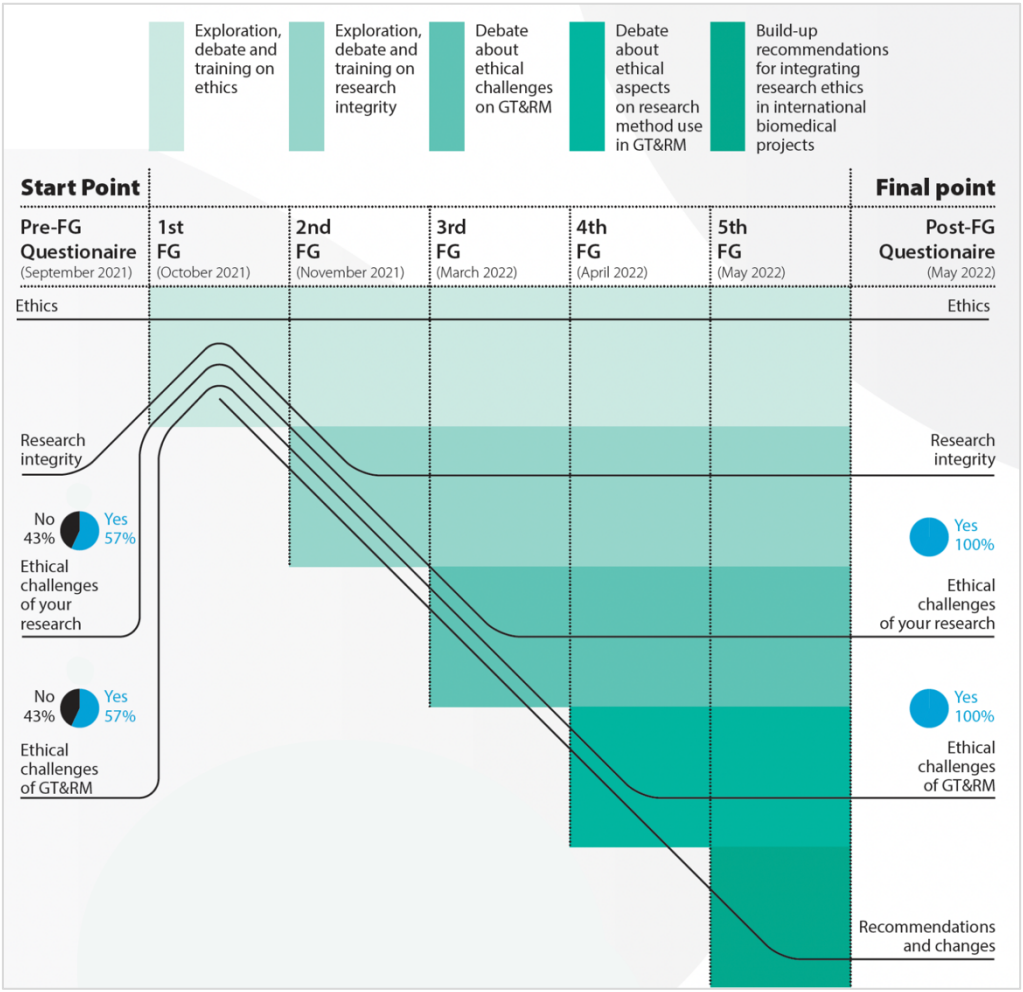

Figure 2: A graphic synthesis of the methods used in this study.

I use the comprehensive consolidated criteria for reporting qualitative research (COREQ) to report this research (Tong, Sainsbury & Craig, 2007), and the checklist is available in the Supplementary Material (S11 Appendix).

- Participants

The participants (n=14) were ESRs from CARTHAGO. Characteristics of this group are mentioned in the Participants section of the *second study* of this thesis.

- Data collection

Semi-structured questionnaires

I designed two questionnaires to evaluate the FG intervention (Creswell, 2009). The two questionnaires were self-administered and provided to the participants via an online forms platform (Microsoft Forms). I sent the first questionnaire to the participants before the start of the FG meetings, with the aim of getting a first insight into the ESRs' perspective on ethics in general and ethical challenges in GT&RM,

as well as their experiences with ethics training (S12 Appendix). After the last FG meeting, I sent the second questionnaire to the ESRs, which consisted of two sections: a first section with a similar set of questions to the first questionnaire and a second section for the evaluation of the strategy (S13 Appendix). This technique allowed us to capture changes and assess the impact of the FG sessions. Both questionnaires were piloted with a group of ESRs outside the project (n=10) to test and improve the final versions.

Focus groups

FG meetings combined with workshop elements were the main technique we used. This combination is a useful tool to integrate the experiences and perspectives of all participants and to introduce new concepts (Hennink, 2007). Since the aim was to apply an embedding ethics strategy, i.e. to discuss and promote ethics while the researchers were actually working in the laboratory, the FGs were an suitable setting as they facilitate social interaction and a common place to share concrete experiences of work with conceptual issues such as ethics (Timmermans et al., 2020).

I conducted the five FG meetings from October 2021 to May 2022 (Figure 2). Each meeting lasted a maximum of 90 minutes. Due to the participation of ESRs from different countries, the FGs were conducted online using the MsTeams platform and in English. I used MIRO boards and Google Jamboards as platforms to work creatively on specific topics. The board content was saved and used for thematic content analysis.

Each FG has a specific aim, and has a separately guide that I designed, and that was discuss with the research team of this study (S8 Appendix). The first meeting was designed to explore participants' previous experiences, expectations, and perspectives on ethical issues in general and for their research projects. In the second session, I introduced the concepts of ethics and integrity in research and we discussed them in the context of laboratory work. In the third session, we analyze the biomedical techniques used by ESRs and the ethical considerations that may arise. In the fourth session, we reflect on how to address these ethical issues. In the final session, we brainstorm ideas to improve research ethics in each ESR's environment.

The FGs were attended exclusively by ESRs; there were no senior researchers or supervisors to influence the opinions of the participants. The atmosphere of the sessions was relaxed and we always ensured that the FGs were a safe place for the expression of any thoughts, ideas or opinions (Sim & Waterfield, 2019). One non-participating ESR from outside CARTHAGO attended every FG and provided technical support.

After each FG, we had a briefing with the research team of this study, where we conducted an evaluation of the session and used this information to plan the next FG. Thus, there was an element of longitudinal qualitative research (Koro-Ljungberg & Bussing, 2013).

- Data analysis

FG discussions were transcribed verbatim and pseudonymized. I analyzed the data using thematic content analysis (Bergin, 2018; Green & Thorogood, 2018) and MAXQDA software. Codes and themes were derived from the data, with the aim of capturing differences in the level of familiarity with the topic since the first meeting and the development of knowledge and analytical skills during subsequent meetings.

Qualitative sections of the questionnaire were analyzed using the same methods I used to analyze the FG transcriptions. The quantitative parts of the questionnaire were analyzed with statistical tools in Excel, using descriptive statistics to summarize the responses.

- Ethical considerations

This study was reviewed and approved by the Bioethics Committee of the Jagiellonian University, Krakow, Poland (No. 1072.6120.209.2021–29/09/2021) (S10 Appendix).

RESULTS

Since the three studies produced different types of results, I will report them separately.

First study

The systematic search retrieved 1701 results. A total of 1621 references remained after duplicate removal. There were 404 potentially eligible documents after title/abstract screening. After full-text screening, 217 articles that met the eligibility criteria were included in the study (Figure 3). The cohort of included articles is detailed in the Supplementary Material section (S14 Appendix).

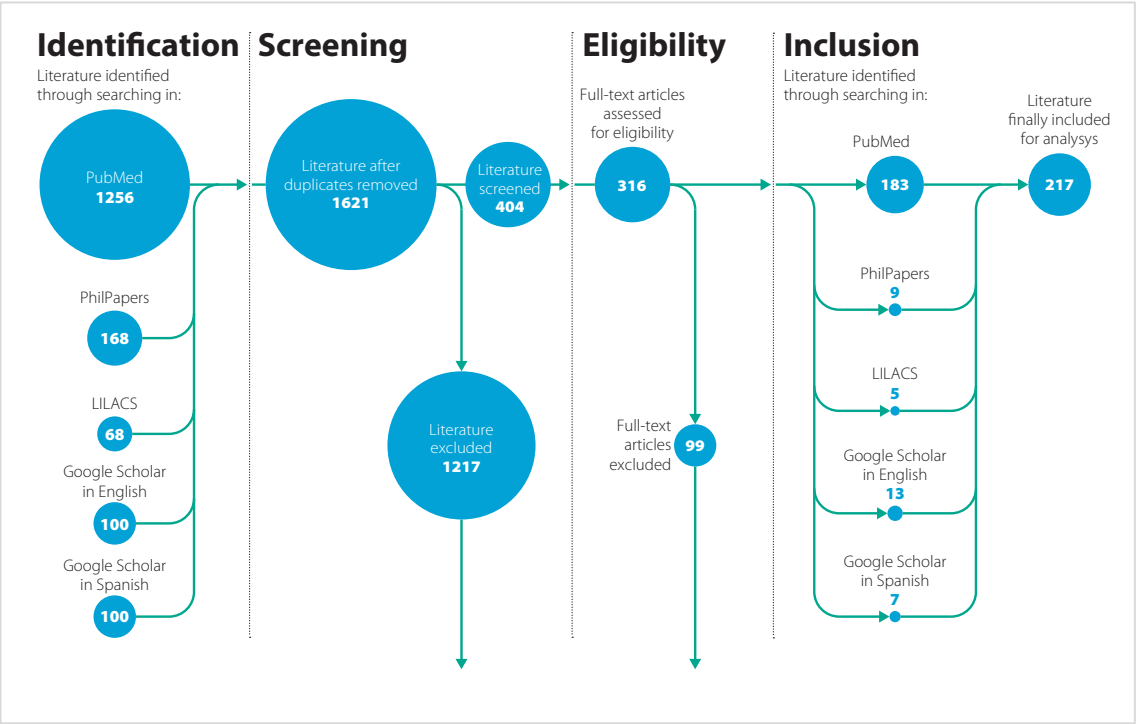

Figure 3. The PRISMA flow diagram of the study selection process.

- Characteristics of publications

Out of 217 articles, 206 (94.9 %) were published in English and 11 (5.1 %) in Spanish. The earliest dates back to 1972, the latest to 2020. Reviews and theoretical/conceptual papers were the most common types of publications. Nearly half of the authors (46.7%) of all selected publications were from the United States. Canada (12.4%) and the United Kingdom (9.8%) followed. Human Gene Therapy (n=36; 16.6%) was the journal that published the largest number of articles included in this study. The majority of articles were in the academic field of bioethics and genetics. Further details of the cohort of articles can be found in the Supplementary Material section (S15 Appendix).

- Results of syntheses

A total of 189 arguments were extracted from the articles that were included. These arguments were grouped into 23 categories. The categories were grouped into two broad themes: research-related and society-related (Figure 4). All research-related and society-related arguments by category and with references are presented in the Supplementary Material section (S16 Appendix). Below I describe some relevant features of the categories.

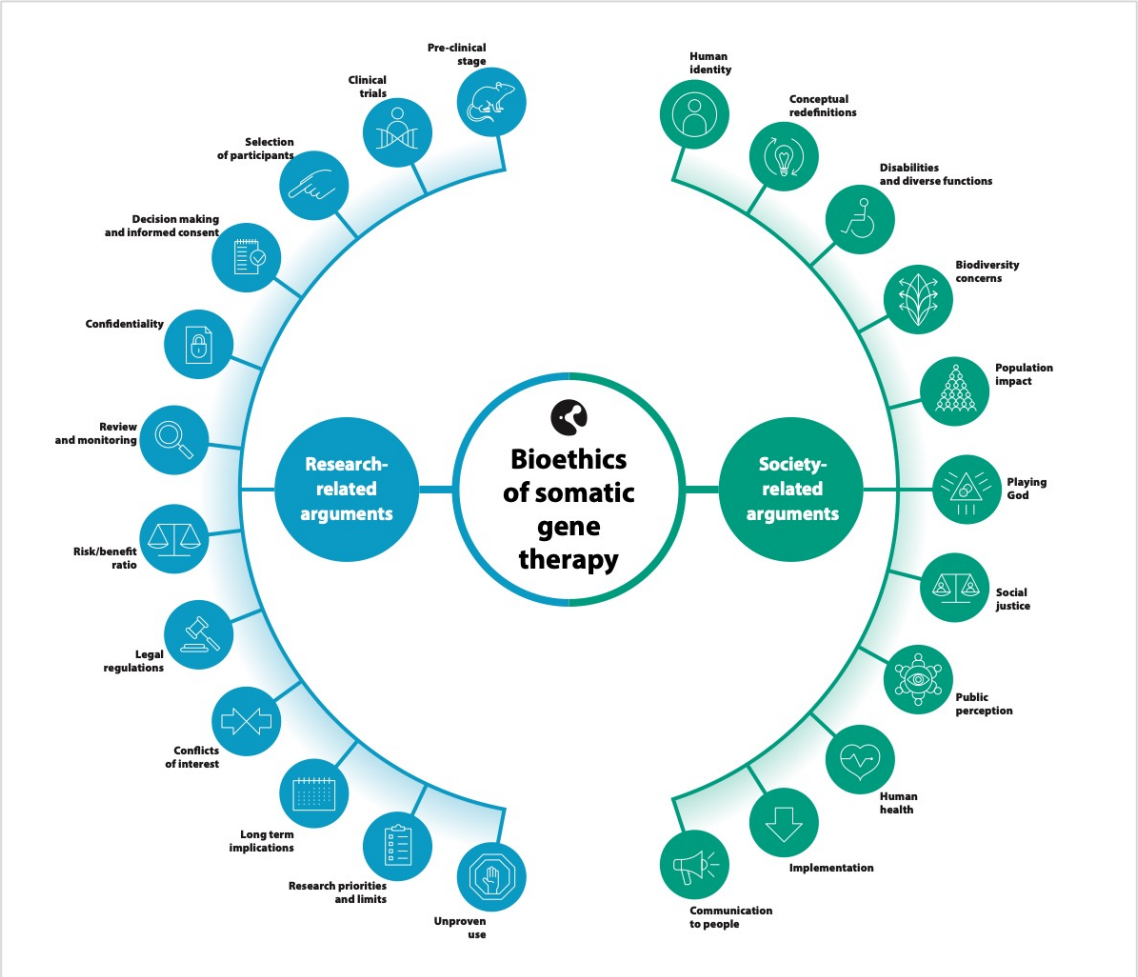

Figure 4. Categories grouped in research-related and society-related.

Research-related categories

• Pre-clinical stage

While most articles agreed that animal studies are necessary to assess safety, efficacy, and long-term effects, it was also noted that extrapolation from animal studies to human studies, while important, is not always possible. In addition to testing the gene therapy technology itself, basic pathophysiological studies are needed because of the difficulty in establishing causality in the development of disease.

• Clinical trials

Some argue that clinical trials of somatic gene therapy are new and may be associated with high/uncertain risks. In the case of adverse events in clinical trials, some have argued that the presence

of such events should not invalidate the therapy because of the experimental nature of the trials and the serious illness of many patients. In light of this, some articles have defended the idea that clinical trials of somatic gene therapy should not be delayed because people suffering from the gene therapy target diseases could benefit from them.

• Selection of participants

The risk of exploitation related to what it is call collateral affective benefits (hope and altruism) for research participants is highlighted in the context of somatic gene therapy clinical trials. Furthermore, there are difficulties in ensuring fairness in the selection of subjects for clinical trials. Some claim that people with life-threatening diseases with no therapeutic alternative can participate. On the contrary, there are those who argue that terminal illness should not be used to justify exposing participants to greater risks.

• Decision making and informed consent

Many arguments focus on the informed consent process itself in terms of the decision-making process of potential trial participants. Several have argued that participants may decide based on the hope that it will benefit them or end their struggle with a life-threatening disease. Potential participants may overestimate the benefits, resulting in invalid informed consent. Inadequate information given to potential participants about the clinical trial intervention is also highlighted as a major concern. Many authors argue that the term "gene therapy" in the context of research creates confusion and exacerbates existing problems of informed consent. It is suggested that informed consent might require a different strategy than usual to ensure genuine choices.

• Confidentiality

A number of articles have highlighted the difficulty of protecting privacy and confidentiality, and the potential harm that information gathered during a trial may have for the patient and the patient's family.

• Review and monitoring

Some articles argue that somatic gene therapy research protocols do not require special evaluation because they raise ethical issues similar to other medical technologies. Others, however, defend the need for special review and auditing of somatic gene therapy protocols because they have very specific and unique ethical complexities compared to other medical procedures. In this regard, it is recommended that the ethical complexity of gene therapy should not be addressed solely by ethics committees, and that the public should be involved in the review and oversight of protocols as appropriate.

• Risk/benefit ratio

There have been claims that gene therapy should be treated in the same way as conventional medical therapy in terms of risk-benefit ratios, because the risks do not appear to be different from those of any standard medical therapy. However, other articles show that gene therapy has novel properties that may affect humans in unpredictable ways. Major risks include technical problems with the quality and stability of transgene expression, immune response to both the vector and the transgene, activation of

an oncogene or inactivation of a tumor suppressor gene by the gene vector, transfer of an unwanted gene, administration of replication-competent viruses or bacterial contamination of the vector preparation, and unintended modification of germ cells. Therefore, gene therapy raises concerns about long-term safety and efficacy, as well as serious and/or irreversible side effects. Beneficence could be based on the potential for net benefit to the population as a whole, with minimal harm to the individual.

• Conflicts of interest

The difficulties of managing conflicts of interest were highlighted in several articles, showing that important stakeholders have a strong interest in gene therapy as a commercial product. It is clear that investigators should not have personal financial relationships with companies that may benefit from the results. It is also mentioned that conflicts of interest are not always financial. For example, the overlapping roles of physician and researcher could lead to potential conflicts in the recruitment of subjects.

• Regulations

Some articles expressed that gene therapy research is the most highly regulated procedure in medicine with overly strict rules, with no scientific or medical foundation. Over-regulation of gene therapy may slow its testing and eventual adoption. One article proposes a global and general regulation, including bioethics, for somatic gene therapy. Others argued that each type of gene therapy should be regulated on its own merits and risk analysis.

• Research priorities and limits

Some have suggested that gene therapy as such is no longer being debated, but rather its application to specific diseases or specific patients. In terms of priorities, there is concern about who should decide what to investigate: companies, scientists, or others? Pharmaceutical companies and other corporate interests often set research priorities that may not be in line with public health needs. There is a need to redefine the rights and responsibilities of all stakeholders. There is also a strong proposition to include public participation in genetic research policy and in the ethical debate on gene therapy, as the human gene pool is considered a collective property.

• Unproven use

Unproven use refers to access to potentially beneficial therapies prior to approval and without a trial. For some rare diseases, experimental approaches to gene therapy may be the only way to provide a potential treatment option. However, a failed gene therapy trial may prevent a patient from trying a similar intervention again. Because some gene therapies are single-dose treatments and rare disease patients are a small customer base, there may be an economic disincentive for unproven use.

• Long term implications

In addition to the need for adequate follow-up and continued care of participants, the need to consider long-term effects has been raised in some articles.

Society-related categories

• Human identity

Many arguments emphasize that somatic gene therapy could change human identity, humanity or personal perception and be a threat to human dignity. For example, there could be a perception that the human body is an enemy or a source of weakness which can be perfected by technology. It should also be noted, however, that human identity is more than just a pool of genes and that it is constantly being redefined, not only by biomedicine, but also by culture.

• Conceptual redefinitions

Some authors warn that gene therapy could create a need to redefine concepts such as disease/illness, prevention, and treatment. In addition, it may be difficult to distinguish between enhancement and treatment in some cases, and enhancement or eugenic therapy could be captured as human gene therapy. In this sense, it is emphasized that experiments in somatic gene therapy must not be tainted by past associations with eugenics.

• Disability and diverse functions

Social attitudes towards disability could be affected by gene therapy. The possibility of treating certain disability-related conditions that gene therapy could bring could lead to more discrimination against people with disabilities. Some do not think of disabilities as such, but as different functions or bodies, and they think that it does not imply anything that should be prevented or treated. In some cases, these different functions or bodies are seen as an integrated aspect of a person's identity. For example, deaf people argue that the only reason that deafness is a disadvantage in society is because of social discrimination. In some of the articles it is mentioned that it is not necessary to overcome every human "limitation" and that instead of working on solutions that are based on social prejudices, we need to think again about our social values.

• Biodiversity concerns

There appears to be little concern about the impact of gene therapy on biodiversity, as there was little mention of it in the literature we reviewed. Few articles suggest that gene therapy could be a substitute for the use of animal tissue culture in current treatments. Others point out that gene therapy commercial production could be environmentally hazardous.

• Population impact

Gene therapy research is an important scientific step for the well-being of the population, as it could provide therapeutic options for diseases for which there are currently no treatments. However, new approaches have novel properties that may have unpredictable effects on populations. For example, the use of gene therapy in one group of people could have adverse effects on others, such as an increase in the incidence of genetic diseases in each generation following somatic gene therapy. In addition, gene therapy could motivate or exacerbate value conflicts and transform social problems into genetic problems. Issues of fairness, justice, or equity in access to therapy could also arise, which are discussed in the next point, but I mention them here because they also have a population impact.

• Social justice

In terms of social justice, gene therapy could be available only in countries or for people with high incomes, because it could be very expensive. Others agree that even if it could be costly at the beginning of implementation, gene therapy could be more cost-effective compared to current therapies, opening the possibility that gene therapy could be available for universal access to health care and thus for low or middle income countries.

• Public perception

Perceptions of gene therapy are not unanimous. Some authors show that people do not know the term "gene therapy". Others report that people know about gene therapy and do not trust it. The most common reasons for not accepting gene therapy are fear of side effects, high costs, and the belief that it goes against nature and is very risky. They also fear that genetic engineering could be misused for commercial purposes and lead to genetic discrimination. The potential consequences of manipulating genes or designing human beings also raise fears.

In contrast, many studies have found high public support for gene therapy for serious diseases, but not for human enhancement. Most people see gene therapy as a worthwhile addition to their health care options.

• Human health

A common argument regarding human health is that gene therapy could prevent and/or treat serious diseases that cause human suffering and improve the quality of life. It may be the only way to treat certain diseases, but it also holds the promise of preventing them, and could help relieve the anxiety or depression associated with the life-threatening nature of the underlying disease.

• Implementation

The implementation of gene therapy in medicine may raise difficulties. There may be a need for specific standard operating procedures and cooperation between health care professionals. In addition, some authors stated that genetic diagnosis is needed prior to therapy. Therefore, it should already be available for the implementation of gene therapy. And if alternative treatments exist, implementing gene therapy will depend on their effectiveness, cost, and inconvenience to patients.

• Communication with society

According to some authors, terminology has been shown to influence perceptions of risk and benefit, as the term "gene therapy" used in research does not accurately reflect whether it is therapy or research. It has been shown that the potential benefits of somatic gene therapy may have been exaggerated and potential risks minimized. In addition, the overselling of gene therapy research could lead to a slowdown in gene therapy if something bad happens. The public should be adequately informed about gene therapy, and scientists must spend sufficient time communicating science to the media to build support for public confidence in gene therapy.

• Playing God

Some articles express the "playing God" argument, referring to actions that should not be done by humans, such as altering human nature such as genes. Some stated that science is a human activity

aimed at improving the quality of human life, and gene therapy is one of the actions that could help achieve this.

Second study

The *second study* was an empirical qualitative study designed to explore researchers' perspectives on ethics in the preclinical phase of GT&RM.

Following the themes and categories I developed during the analysis phase of the research (Table 1), I report the findings in three sections. The first section is a summary of the researchers' spontaneous views on what is ethically important in preclinical GT&RM research. The second section presents researchers' views on the different types of impacts that preclinical research on GT&RM has or could have. Finally, the third section presents the researchers' recommendations for improving ethics in preclinical biotechnology research.

Table 1: Themes and categories developed from focus groups and interviews.

Themes	**Categories in Focus Groups**	**Categories in interviews**
1. Spontaneous views on ethics in preclinical research	*Animal experimentation*	
	The use of human biological material and how it is obtained	
	Integrity	*Institutional procedures*
	Relationships in scientific community	*Standard/no-need ethics*
	Impact in society	*Safety, toxicity and long-term effect*
	Footprint on environment	
2. Preclinical research and social impacts: the case of gene therapy in orthopedics	*Impact on privacy and personal information*	
	Impact on health inequalities	
	Impact on social well-being, autonomy and mental health	
	Impact on climate change and biodiversity	
3. Recommendations or what we can do better in health-related preclinical research	*Research integrity strategies*	
	Ethics training	
	Avoid sex bias	
	Equity	*Science communication*
	Mental health of researchers	*Citizen engagement*
	Environmentally friendly laboratories	

- Spontaneous views on ethics in preclinical research

Animal experimentation and the use of human biological material and how it is obtained were the two issues that both experienced researchers and ESRs spontaneously associated with ethics in preclinical GT&RM research.

Both groups also agreed on the importance of being sensitive to the needs and views of society, notwithstanding the fact that their work takes place in a laboratory environment.

Experienced researchers associate ethics with the procedures and requirements of the institutions in which they conduct research. This group of researchers also associated ethics with guidelines and external approval. A minority mention that ethics is not needed at all at the preclinical stage. Others suggest that there is already over-regulation of ethics in the academic context. Safety, toxicity, adverse events, and long-term effects were also mentioned by most experienced researchers as ethically relevant issues.

ESRs related ethical issues to professional integrity, study reproducibility, and data management. They emphasized the importance of reporting all the details of the experiment in a publication and of the publication of so-called "negative results". Authorship was also mentioned by some of them as an ethically sensitive issue. In addition, the ESRs placed ethics in the context of relationships within the scientific community. They referred to improving mentoring, respecting other researchers, working more collaboratively, and the need for more multidisciplinary and multicultural teams. They expressed that it is important to consider the potential societal impact of research at the preclinical stage, rather than focusing solely on the individual's scientific topic. Finally, the impact of preclinical research on climate change, with in-depth discussions on waste generation, chemical treatment and sustainable research, was a recurring theme among the ESRs.

- Preclinical research and social impacts: the case of gene therapy for cartilage regeneration

Impact on climate change and biodiversity

Scientists from both groups reflected that preclinical research in GT&RM has an environmental footprint. These included the use of plastics in laboratories, the generation of chemical and biological waste, the use of energy to keep some biological samples at a constant temperature, and the use of large amounts of water in testing. The ESRs also mentioned that scaling up a new GT&RM treatment may require more infrastructure, which could have an even greater impact on the environment.

Some experienced researchers expressed that the environmental impact of preclinical research is underestimated and should be taken into account.

Impact on privacy and personal information

A number of experienced researchers pointed out that researchers in pre-clinical research are working with sensitive personal data and that there is a need for more safeguards to protect this type of data. Some of them mentioned that the details of the donors of the human tissues should not be traceable.

Impact on health inequalities

Following a general question on the topic, scientists from both groups focused on the economic dimension of health inequalities. They argued that biotechnological therapies can be expensive and therefore only affordable by wealthy people in developed countries. But they also reflected that if these new therapies are more effective, they may be cheaper in the long run.
They mention that the role of chromosomal sex, ethnic origin, and age of the biological material could affect the efficacy of the therapy in different populations. Therefore, these should be taken into account in advance in preclinical research.
Researchers mention that technical dimensions in the development of potential therapeutics should also be considered in preclinical research related to health disparities. For example, the type of storage that would be required, the technical capacity to deliver the treatment, the technical needs for follow-up, and others. If more complex conditions are required to use or apply a treatment, it may be difficult to make the treatment available in all economic and cultural settings around the world.

Impact on social well-being, autonomy and mental health
All researchers agreed that positive results from their GT&RM research, i.e. effective cartilage regeneration, could reduce pain and increase mobility. These two issues would improve the quality of life, especially in aging societies, and have a positive impact on global health. Increased mobility could improve the overall autonomy of future patients and they would be less dependent. Increased mobility provides the opportunity for sport and exercise, which can have a positive impact on other types of disease and increase overall wellbeing. It could also have a positive impact on social life and mental health by preventing isolation of future patients.
The researchers also mentioned the economic burden of chronic disease. They believed that the potential new therapy could also have a positive impact in this area by helping to reduce orthopedic chronic disease.

- Recommendations for health-related preclinical research
Researchers expressed the need for more research integrity policies, more attention to the mental health of researchers, and mandatory ethics training. ESRs recommended focusing on responsible laboratory waste management and waste reduction strategies. Experienced researchers mentioned that preclinical scientists should be more involved in science communication. Further recommendations are presented in Figure 5.

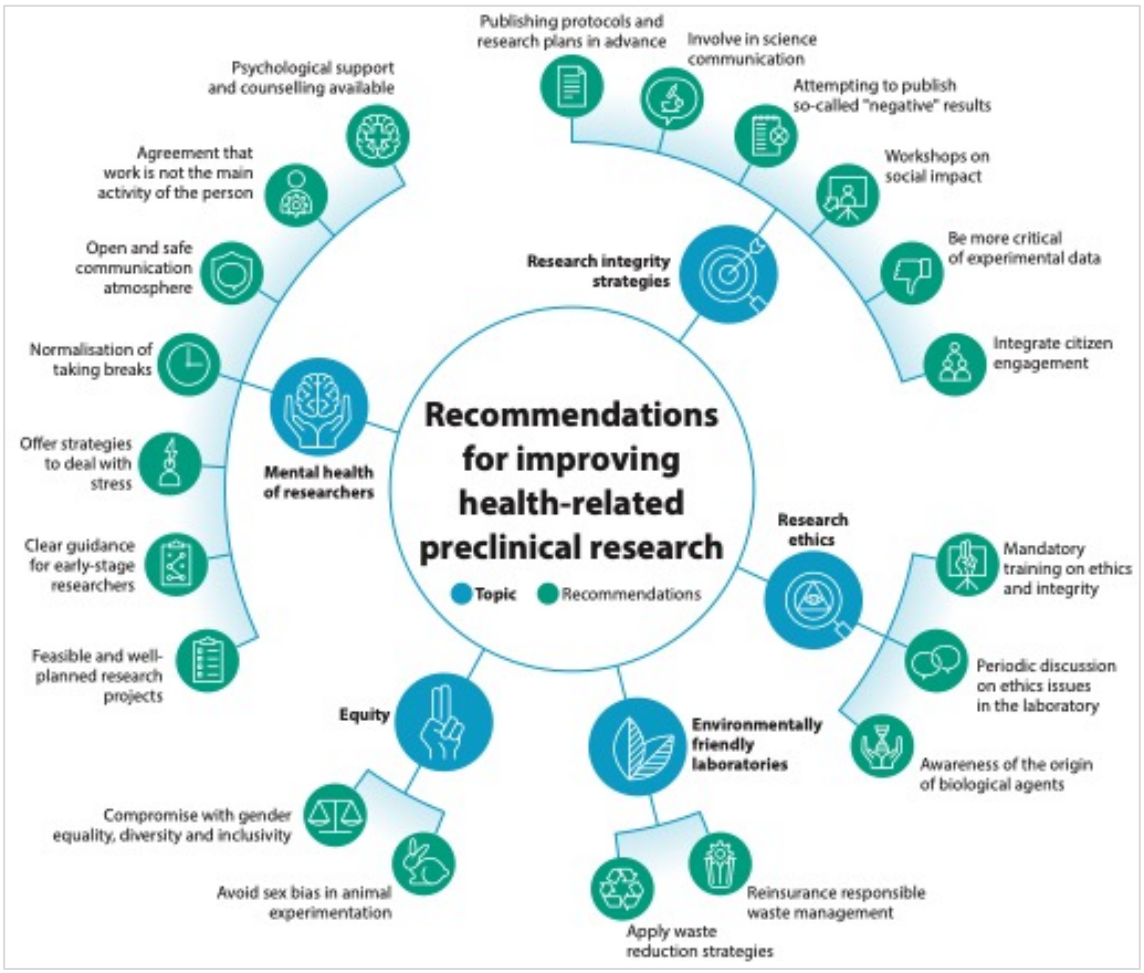

Figure 5. Researchers' recommendations for improving health-related preclinical research.

Third study

The *third study* was a longitudinal empirical qualitative study designed to provide and assess a strategy for integrating research ethics and integrity into the preclinical phase of GT&RM development for ESRs.

- Starting point

Prior to the FG meetings, almost half of the ESRs (42.9%, 6 out of 14) did not think that GT&RM could pose ethical challenges or that their research topics and methods could pose potential ethical challenges. In addition, only 35.7% (5 out of 14) of the ESRs reported having received training or taken courses on ethics, research ethics or research integrity.

- The FG process

In the first meeting, participants had abstract intuitions about what "ethics" is or relates to, which evolved through the FG process into more complex definitions of ethics. In terms of research ethics, the topic we approached in the second meeting, participants focused on the issues of animal use,

manipulation of human embryos, and falsification and fabrication of data. These initial topics became broader and deeper with each meeting. In the third session, we applied what we had learned about ethics and research ethics to GT&RM research. In the fourth and fifth meetings, the ESRs were able to reflect on their own activities in the laboratories and the research methods they use.

- Ending point

Development and strengthening of skills

Most participants agreed that the meetings helped them to learn about research ethics and research integrity concepts, to develop the ability to reflect on and discuss research ethics, and to increase their awareness of ethical issues in their own research activities (Figure 6).

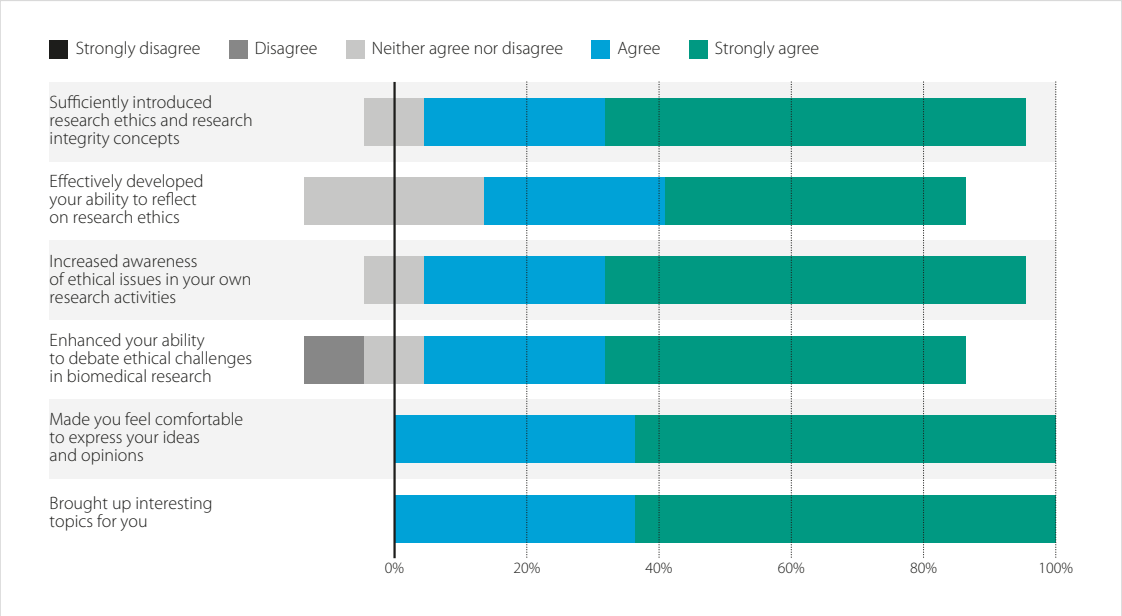

Figure 6. The extent to which ESRs are in agreement or disagreement with the development and strengthening of skills as a result of the FG process.

Implications for GT&RM research

At the end of the strategy, all participants agreed that GT&RM, their research topics and methods may face potential ethical challenges. All participants indicated that they would make changes to improve their research in terms of ethics and integrity. During the period of the FG meetings, half of them had already changed practices or taken additional measures related to research integrity or ethics in their own project.

Participants' receptivity

All participants agreed that they were satisfied with the FGs, that they felt comfortable expressing their ideas, and that the topics were interesting to them (Figure 6). They appreciated that the FGs were designed in such a way that they had the opportunity to reflect together and talk to each other, sharing questions and doubts without feeling judged. They emphasized that traditional training ("sitting and listening," as one participant defined it) would not allow for full engagement with the topic. Mixing the laboratory research activity with the in vivo ethics approach was a combination they appreciated. Finally, the ESRs felt that the meetings were important not only for improving their research process, but also for thinking about ethics in everyday life. In the post-FG questionnaire, one of the participants stated:

> “I just want to point out how useful and insightful these sessions have been. It was very nice to have a safe space where we could discuss everything that concerned us in our journey as PhDs and it provided us a great opportunity to understand how ethics are present in our day-to-day life, not only as scientists but as people :) Thank you!”

DISCUSSION

This thesis examined the bioethical aspects of somatic gene therapy through a systematic review, which was an essential starting point to deepen the views and perspectives of preclinical scientists working in somatic gene therapy and regenerative strategies for disc and joint pathology in the preclinical laboratory phase. All this was a great input to elaborate a strategy for the integration of bioethics in preclinical research.

To my knowledge, the systematic review of the bioethical rationale for somatic gene therapy is the first of its kind. Somatic gene therapy, following conventional techniques, has the potential to be a great step forward for science and human welfare (Riva & Petrini, 2019). At the same time, and after analyzing all the arguments presented in this review, we can agree that this technology could have repercussions if used on a large scale. Procedural, conceptual, and social issues regarding somatic gene therapy need to be addressed, and there is no clear direction on how to do so (Aiyegbusi et al., 2020; Mills & Tropf, 2020). As stated in many of the reviewed articles, society should be involved in the debate to define the priorities and limits of gene therapy research, the ethical acceptability, and the nuances regarding its acceptance by certain communities and for certain uses (Mills & Tropf, 2020). All of this could also have a positive impact on helping somatic gene therapy to develop (Delhove et al., 2020).

Nevertheless, the ethical challenges of GT&RM should also be addressed in the preclinical phase of research and involve scientists working in this phase, as this is their daily work. The real needs and problems that arise in preclinical research may be overlooked if the perspectives of researchers are not understood. In this regard, one of the most important findings is that most researchers in our study can relate to ethics and research integrity in some way, but recognize knowledge gaps, as found elsewhere (Niemansburg et al., 2015; Silva Costa et al., 2011). Scientists are motivated to reflect on ethical issues in their work and to participate in ethical discussions and training when opportunities arise, as reported in other studies (Silva Costa et al., 2011; McCormick et al., 2009). In our study, researchers were also interested when the topic came up, and in most cases they agreed that it was useful for them to reflect on issues they rarely think about.

There is a growing need for better integration of ethics in various fields (McLennan et al., 2022; Diaz-Martinez et al., 2019). The embedding ethics strategy is a step in this direction, but is still developing clear standards of practice (Plemmons et al., 2020). Our study on the integration of the ethics strategy, mostly through FG meetings with ESRs, was an example of the involvement of researchers actually working in the laboratories.
The strategy allowed us to provide contextualized and real-time ethical guidance, to support good scientific practices, and to recognize the social implications of the biotechnologies under development.

What the ESRs most appreciated was the bidirectional relationship between discussions in the FGs and simultaneous real-time empirical laboratory research. They have also been actively involved in the rethinking and discussion of the ethics of their own research process.

The impact of the strategy can be clearly seen in the changes they have already made to their laboratory practices. Some of these changes include, among others, waste disposal, attention to the sex of donor cells or tissues, handling of "negative" results, animal welfare, and increased awareness of the impact of actions.

Limitations

This thesis consists of three studies, each of which has limitations that are described. I also describe a justification, when possible, as well as some mitigation measures that were taken in consideration of them.

In the systematic review (*first study*), some search terms related to ethics and bioethics, such as informed consent or risks/benefits, were not included in the search strategy. This was done deliberately to make the systematic review feasible. Second, another group of researchers might have selected or clustered the included reasons differently. Thirdly, there was no assessment of the scientific validity of the articles in the review.

Different interviewers/facilitators may have focused on different aspects of the participants' interventions and the authors may have analyzed the data differently in the *second* and *third studies*. In addition, FGs depend on the dynamics and personalities involved in the FGs. For example, there may be times when three or four people are in control of the discussion. My attempt to limit this was through the moderation of the sessions. In addition, although from different countries and with different backgrounds, all the participants and the facilitator/interviewer (me) came from the same research consortium. Nevertheless, the sharing of a professional scenario between the facilitator/interviewer and the participants could contribute to a quicker adaptation to the situation of the interview/focus group, without much effort or calculation (Criado, 1998). This is a desirable scenario to engage with the participants to address sensitive issues. It creates a space of trust and allows them to be more open. The fact that the analysis group was pre-established is a limitation of the *third study* in particular, as it could make the intervention more effective. Another particular limitation of the *third study* could be the online setting, which could influence the way participants interact. However, the online setting is not necessarily a drawback, as some studies comparing on-site and online FG settings show that discussions are similar, with sensitive topics discussed more openly in some instances in online settings (Daniels et al., 2019; Woodyatt, Finneran, and Stephenson, 2016).

CONCLUSION

This thesis provides:

i) A systematic re-evaluation of the ethical arguments regarding somatic gene therapy, which could serve as a basis for normative analysis before it becomes a large-scale procedure.

ii) The perspective of scientists working in laboratories on ethics and integrity in preclinical GT&RM research. This is helpful to identify key ethical challenges and, combined with more data, lead to informed and evidence-based improvements to existing regulations.

iii) A concrete approach to integrate ethics in real-time preclinical development and effectively serve as a tool to strengthen responsibility in research. This should stimulate further research to eventually allow building an evidence base of methods and techniques on how to embed ethics in laboratory research.

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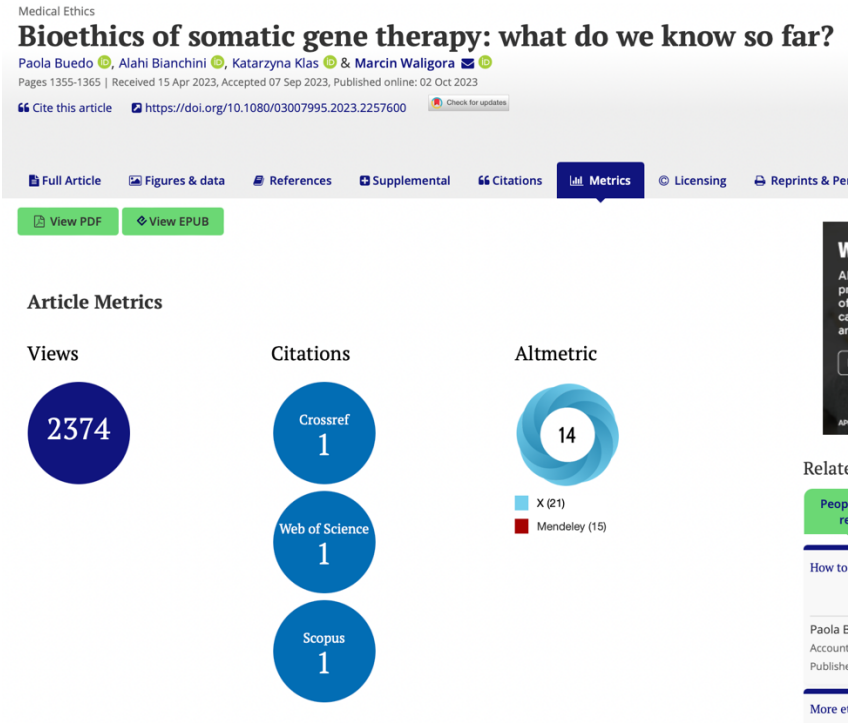
IMPACT OF THE PUBLICATIONS CONSTITUTING THE DOCTORAL THESIS

Below I share the print screen of the metrics directly from the official journal website where each article is published, where there are data about views of the article, citation and altmetrics (print screen made on 17/06/2024).

- How to embed ethics into laboratory research

- Bioethics of somatic gene therapy: what do we know so far?



- More ethics in the laboratory, please! Scientists' perspectives on ethics in the preclinical phase

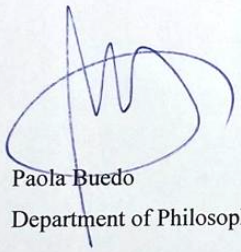
STATEMENTS OF CO-AUTHORS

Krakow, 11 June 2024

Paola Buedo

As the first author of the publication "Bioethics of somatic gene therapy: what do we know so far?" (Current Medical Research and Opinion, doi: 10.1080/03007995.2023.2257600) I declare that my input in the research included:

a) Conceptualization
b) Data curation
c) Formal analysis
d) Investigation
e) Methodology
f) Visualization
g) Writing: original draft preparation
h) Writing: review and editing



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As a co- author of the publication "Bioethics of somatic gene therapy: what do we know so far?" (Current Medical Research and Opinion,doi: 10.1080/03007995.2023.2257600) I declare that my input in the research included:

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As corresponding author of the publication "Bioethics of somatic gene therapy: what do we know so far?" (Current Medical Research and Opinion, doi: 10.1080/03007995.2023.2257600) I declare that my input in the research included:

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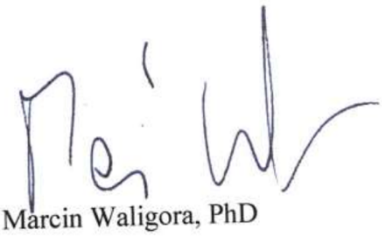
b) Funding acquisition
c) Methodology
d) Project administration
e) Supervision
f) Writing: review and editing



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Paola Buedo

As the first author of the publication "More ethics in the laboratory, please! Scientists' perspectives on ethics in the preclinical phase" (Accountability in Research, doi: 10.1080/08989621.2023.2294996) I declare that my input in the research included:

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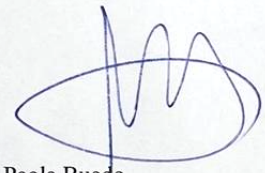
g) Writing: original draft preparation
h) Writing: review and editing



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a) Formal analysis
b) Writing: review and editing

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As a co-author of the publication "More ethics in the laboratory, please! Scientists' perspectives on ethics in the preclinical phase" (Accountability in Research, doi: 10.1080/08989621.2023.2294996) I declare that my input in the research included:

a) Methodology
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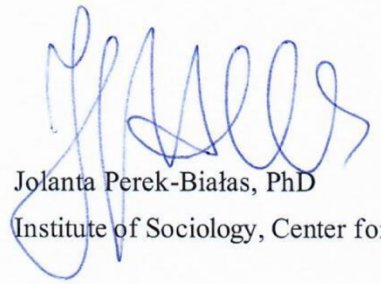
c) Writing: review and editing



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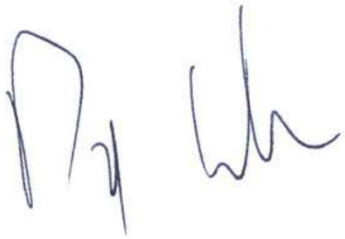

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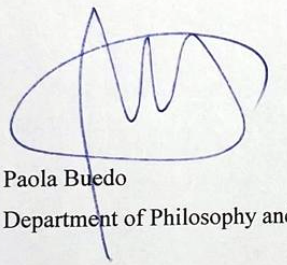

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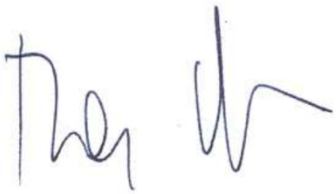

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SUMMARY OF ACTIVITIES DONE BY THE PHD CANDIDATE DURING PHD STUDIES

During my doctoral studies, I presented my work at **international conferences**:

1) Bioethics of somatic gene therapy: What do we know, so far? ESPMH Conference, Riga, Latvia, 2023.
2) How to embed ethics in laboratory research. Oxford Global Health & Bioethics International Conference, Oxford, UK, 2023.
3) Ethics Lab: real-time research ethics in development of biotechnologies. 16th World Congress of Bioethics, Basel, Switzerland, 2022.
4) Bioethics of human gene transfer: what do we know, so far? A systematic review of reasons. 16th World Congress of Bioethics, Basel, Switzerland, 2022.
5) Ethics Lab: real-time ethics in biotechnology research. 7th World Conference on Research Integrity, Cape Town, South Africa, 2022.

At the Oxford Global Health & Bioethics International Conference, 2023, I received the Best Poster Prize for the poster presentation: How to embed ethics in laboratory research.

I did two **internships** during my PhD:

1) the University Medical Center Utrecht, in Utrecht, The Netherlands, from 04/07/2022 to 30/08/2022. I was involved in the laboratory activities of CARTHAGO and to conducted interviews.
2) World Health Organization, the Health Ethics and Governance Unit, Geneva, Switzerland, from 15/10/2023 to 28/10/2023. The aim of the internship was to learn about the implementation of the Human Genome Framework.

I became a Certified Research Integrity and Ethics Trainer by completing the program organized by VIRT2UE + The Embassy of Good Science, two European Union projects, in 2021.

I have been invited as a **speaker and lecturer** at the international workshops and seminars:

1) Inclusive bioethics research methodology video series “Data analysis: critical epidemiology”. Black and Brown in Bioethics, University of Bristol, UK, 2024.
2) Mind, literature and collage. National University of Distance Education, Spain, 2023-2024.
3) Bioethics and mental health: a feminist perspective. Master of Bioethics and Law, University of Barcelona, Spain, 2024.

4) Relational autonomy. National Bioethics Commission, Mexico, 2023. https://www.youtube.com/watch?v=j0Rl3C5m888
5) Bioethics in mental health, autonomy and vulnerability from feminist and community ethics. Doctorate in Law, National University of Rosario, Argentina, 2023.
6) Bioethics and mental health. Association of Bioethics and Law, University of Barcelona, Spain, 2023. https://www.bioeticayderecho.ub.edu/es/sesion-abd-bioetica-y-salud-mental
7) Shared decision-making and relational autonomy. FLACSO-Fogarty Intensive Seminar, Argentina, 2023. https://www.youtube.com/live/SJdHKWB_6iQ?feature=share
8) Bioethics and mental health. Valle University Psychiatric Hospital, Colombia, 2023.
9) Bioethical tools to approach the Stigma-Discrimination Complex (SDC). Seminar Workshop on the SDC and ethical challenges of language used on mental health field: opportunities and challenges, Mexico, 2023. https://lafuente.mx/?p=862
10) Bioethics and mental health. Bioethics University Program, UNAM, Mexico, 2023. https://www.youtube.com/watch?v=JkqXumnvXuk

I have participated in **science communication** activities such as:

1) Writing a blog post with my supervisor published in the BMJ Journal of Medical Ethics Blog: "We need to eliminate ethics-washing" (2022). https://blogs.bmj.com/medical-ethics/2022/06/16/we-need-to-eliminate-ethics-washing/
2) Producing and co-hosting the podcast "Bioethics for drinking" [Bioética para beber], Latin American School of Social Sciences. There are 23 episodes available: 10 from the first season, 10 from the second season and 3 from the current third season.
   In Spotify: https://open.spotify.com/show/13HlwiLzr0ROIx94MReNQi
   In YouTube: https://www.youtube.com/channel/UCKHSzCMfN33jmCYbU_iYJfQ
3) Organizing and editing a video to explain CARTHAGO research to the public: https://itn-carthago.sites.uu.nl/project-updates/

I became a member of Marie Curie Alumni Association.

LIST OF OTHER SCIENTIFIC CONTRIBUTIONS PUBLISHED BY THE PHD CANDIDATE DURING PHD STUDIES

Scientific articles

- Alegre V, Alvarez M, Bianchini A, **Buedo P**, Campi N, Cristina M, Del Huerto Revaz M, Larrán S, Martinez Damonte V, Massaro L, Milano Gil A, Morante M, Moreira G, Moya Díaz G, Sabie M, Sipitria R, Luna F. Salud digital en América Latina: legislación actual y aspectos éticos. Revista Panamericana de Salud Pública. 2024;48:e40. https://doi.org/10.26633/RPSP.2024.40

- Buedo P, Daly T. A contextual understanding of the high prevalence of depression in Latin America. The Lancet Regional Health – Americas. 2024;32:100717. https://doi.org/10.1016/j.lana.2024.100717

- Daly T, **Buedo P**. Applying Ethics to Mental Health and Climate Change. 2024;48:104–105. https://doi.org/10.1007/s40596-023-01913-3

- Buedo P, Daly T. Grounding mental health in bioethics. Nature Mental Health. 2023. https://doi.org/10.1038/s44220-023-00146-5

- García Valiña L, **Buedo P**, Daly T. Socrates in the machine: the "house ethicist" in AI for healthcare. Journal of Radiological Nursing. 2023. https://doi.org/10.1016/j.jradnu.2023.08.001

- Buedo P, Sanchez L, Ojeda M, Della Vedova M, Labra B, Sipitria R, Centineo Aracil L, Cosentino S, Varela I, Yabar Varas C, Apaza G, Krasnow A, Vilchez S, Luna F. Informed consent and living wills: comparative analysis of the legislation in Latin America [Consentimiento informado y directivas anticipadas: análisis comparado de la legislación en América Latina]. Revista De Bioética Y Derecho. 2023;58:25–44. https://doi.org/10.1344/rbd2023.58.41678

- Millaqueo S, Salas M, **Buedo P**. Social conditions of the trans-gender population in Bahía Blanca, Argentina [Condiciones sociales de la población trans en Bahía Blanca, Argentina]. Tramas y Redes. 2022;3:175-195. https://doi.org/10.54871/cl4c308a

- Salas M, **Buedo P**. How do older people perceive mistreatment towards them? [¿Cómo perciben las personas mayores el maltrato hacia ellas?]. Iberoamerican Journal of Bioethics. 2022;19:1-11. https://doi.org/10.14422/rib.i19.y2022.002

- Buedo P, Salas M. Health management in times of pandemic: the experience in a social work for the elderly during the year 2020 [Gestión en salud en tiempos de pandemia: la experiencia en una obra social para personas mayores durante el año 2020]. Health, Education and Society. 2022;1(1):22-35. https://revistaseys.ugr.edu.ar/index.php/inicio/article/view/7

- Buedo P, Luna F. Shared decision-making in mental health: a novel proposal. Revista de Medicina y Ética. 2021;32(4):1087-1110. https://doi.org/10.36105/mye.2021v32n4.05

- Buedo P. Feminist bioethics: a framework to think autonomy in mental health [Bioética feminista: un marco para pensar la autonomía en salud mental]. Rev. Redbioética/UNESCO. 2021;12(23):13-18. https://redbioetica.com.ar/revista-redbioetica-unesco-no-23/

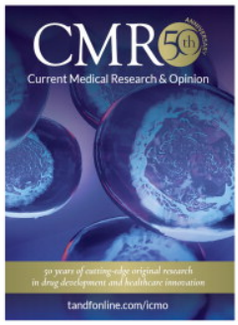
Book chapters

- Buedo P, Luna F. (2023). Bioética feminista para pensar la salud sexual y reproductive. In: Lubertino M (editor). Los derechos sexuales, reproductivos y no reproductivos, incluido el derecho al aborto, como derechos humanos y derechos personalísimos. (p. 99-107) ISBN 978-950-23-3393-9, Editorial EUDEBA.

Book

- Buedo P. Ethos Mental. Bioética para re-pensar la salud mental [Mental Ethos. Bioethics to rethink mental health]. ISBN 978-987-816-432-8, Editorial Prometeo, 2022. 162 pages. https://www.flacso.org.ar/publicaciones/ethos-mental-bioetica-para-repensar-la-salud-mental/

SUPPLEMENTARY MATERIAL



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REVIEW ARTICLE

Bioethics of somatic gene therapy: what do we know so far?

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ABSTRACT

Objective: To provide a systematic overview of bioethical debate on somatic gene therapy as documented in the scientific literature.

Methods: We performed a systematic review of reasons, following Strech and Sofaer approach, which is a method to systematically identify and classify arguments (reasons) used in the scientific literature. We identified 217 eligible publications retrieved from PubMed, Lilacs, PhilPapers, and Google Scholar. A meta-synthesis was performed to analyze the data.

Results: We extracted 189 arguments. Arguments were grouped into 23 categories. Twelve categories were classified as research-related, including the risk/benefit ratio, priorities and limits, informed consent, review, and monitoring. Eleven were classified as society-related, including population impact, human identity, public perception, human health.

Conclusion: Our study provides a database of existing challenges and arguments of somatic gene therapy and may serve as the basis of normative analysis. By presenting collected arguments, we contribute to the discussion about the ethics and social dimensions of somatic gene therapy.

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KEYWORDS
Gene therapy; somatic cells; bioethics; risk assessment; ethics; social impact

Introduction

Gene therapy is defined as a technique that modifies a person's genes for therapeutic purposes[1,2]. Introducing a new copy of an exogenous gene[3], replacing or inactivating a gene[1,2] or editing genes[4] are some techniques used in the gene therapy field. According to the cellular target, gene therapy can also be classified in somatic and germline gene therapy. Somatic gene therapy is oriented to treat only the person receiving the therapy, whereas germline gene therapy treats the person, and the results of this procedure can be inherited by his/her descendants[5,6]. Most current research focuses mainly on somatic gene therapy[7].

Somatic gene therapy is a promising approach that could provide treatment options for many diseases[8]. There are many preclinical and clinical studies that evaluate the therapeutic potential of interventions in human genes[5,7]. For example, in relation to curing various types of cancer (meningiomas and spinal cord, gastrointestinal, breast, etc.), genetic disorders (such as thalassemia or severe combined immunodeficiency), infectious diseases (such as HIV or hepatitis), cardiovascular diseases (such as coronary artery disease or ischemia), among others[7].

The latest and more innovative techniques used for gene therapy are cutting-edge molecular tools that correct errors within genes, like CRISPR-CAS9, which is a simple, precise and rapid genome editing technology. Replacing, silencing or inserting an entire gene is now a kind of conventional somatic gene therapy after the emergence of CRISPR[4].

Conventional somatic gene therapy (i.e. non-editing somatic gene therapy) currently gets less attention in the discussion about ethics implications since the debate of CRISPR technologies[9,10]. However, complex techniques or more invasive ones – such as CRISPR – should not distract us from the important ethical debate and unresolved questions. Somatic gene therapy will soon transform into a massive scale medical procedure: thus the unresolved ethical challenges need to be re-examined[5,6,11–13].

In the following, we identify, categorize and analyze arguments on bioethical challenges of conventional somatic gene therapy. The aim of our study is to provide a systematic overview of the arguments used in the discussion about human gene therapy in somatic cells using conventional techniques that are documented in scientific literature.

Methods

We performed a systematic review of reasons[14], following Strech and Sofaer approach, which is a method to systematically identify and classify arguments (reasons) used in the scientific literature. We described the methods in

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detail below. A meta-synthesis[15,16] was performed to analyze all data. The study protocol was prospectively registered on Open Science Framework (see https://osf.io/fxuwj) (S1 Appendix).

Eligibility criteria

Publications were eligible if they had focused on somatic gene therapy with clear therapeutic goals and discussed reasons or premises about acceptability, importance, value, morality, ethics, or bioethics. We included articles in English or Spanish and the following types: (i) normative articles focusing on somatic gene transfer/therapy and its ethical/bioethical aspects; (ii) articles focusing on public perception or use of somatic gene transfer/therapy; (iii) articles focusing on professionals and researchers about ethical aspects of somatic gene transfer/therapy; (iv) narrative reviews, editorials, commentaries, opinions, letters, guidelines and policy recommendations. To make the search feasible, we excluded articles focused entirely on the ethics/bioethics of germline gene transfer or genome editing because it was out of the scope of our study; articles that focused on intrauterine, fetal, or prenatal gene transfer because we understand that this particular context could raise other ethical issues apart from those of the gene therapy itself; reports of interventional studies of gene transfer/therapy, as our objective is the ethical approach of the technique; articles from press and books, book chapters, comments on books, and congress abstracts/posters.

Search strategy

We performed the search in PubMed, Lilacs, PhilPapers, and Google Scholar on 26 July 2021. We chose these databases because they cover a wide range of biomedical and philosophical publications from all over the world. Choosing Lilacs, which is the most important Latin American database, allowed us to be sensitive to cultural or otherwise region-dependent differences. We performed the search without time restrictions. The only restriction that we used was in Google Scholar database because of the large number of articles that the search retrieved. We decided to use the first 100 hits[17]. The search strategy for each database is presented in the Supplementary Material section (S2 Appendix).

Selection process

Based on the pre-specified eligibility criteria, PB, AB, and KK independently screened the search results in two stages: first, titles and abstracts and second, the full texts. At each stage, we independently double screened all references. In case of any disagreements, a discursive consensus was reached.

Data extraction

The selected articles were analyzed using three prospectively designed data extraction documents (S3 Appendix). Contextual data from the included articles i.e. year, journal and language of publication, article type, field (according to Journal Citation Reports (JCR); if the journal were not indexed, we classified the journal field according to the journal scope based on its website), number, affiliation, and country of authors, were obtained using the first data extraction document. Subsequently, all arguments related to the bioethics of human gene therapy were extracted and organized in another data extraction document, including the argument extracted and the number of references. At this stage, we used the constant comparative method (CCM)[15]. Before starting the extraction, researchers were trained in CCM.

Identification of codes and themes

We grouped the extracted arguments into categories related to a certain topic[18]. The formulation of the categories was an iterative process. Categories are not supposed to be exhaustive or exclusive. There may be some arguments that correspond to two or more categories. However, we decided to include each argument only in one category to make our results more comprehensive. We discussed the categories several times among all researchers to find the best match for each argument. The categories were also grouped into two broad themes.

Quality appraisal

As described in the "Selection process" section, the article screening and extraction process was carried out independently by three researchers, who have different professional backgrounds (pharmacist, medical doctor and philosopher, with post-graduate studies in bioethics). The multidisciplinary approach was important to consider different points of view and ways of thinking. Screening, extraction, and category formulation were supervised by a bioethics expert (MW).

Data reporting

The data report follows the PRISMA Ethics – Reporting guideline for systematic reviews on ethics literature: development, explanations and examples[19]. The PRISMA-Ethics Reporting Guideline of this review can be found in the Supplementary Material section (S4 Appendix).

Results

Publication selection process

The systematic search yielded 1701 results. Removal of duplications left 1621 references. Title/Abstract screening resulted in 404 potentially eligible documents. After full text screening, we included 217 articles that met the eligibility criteria (Figure 1). The cohort of included articles is listed in Table 1, and with full details in the Supplementary Material section (S5 Appendix).

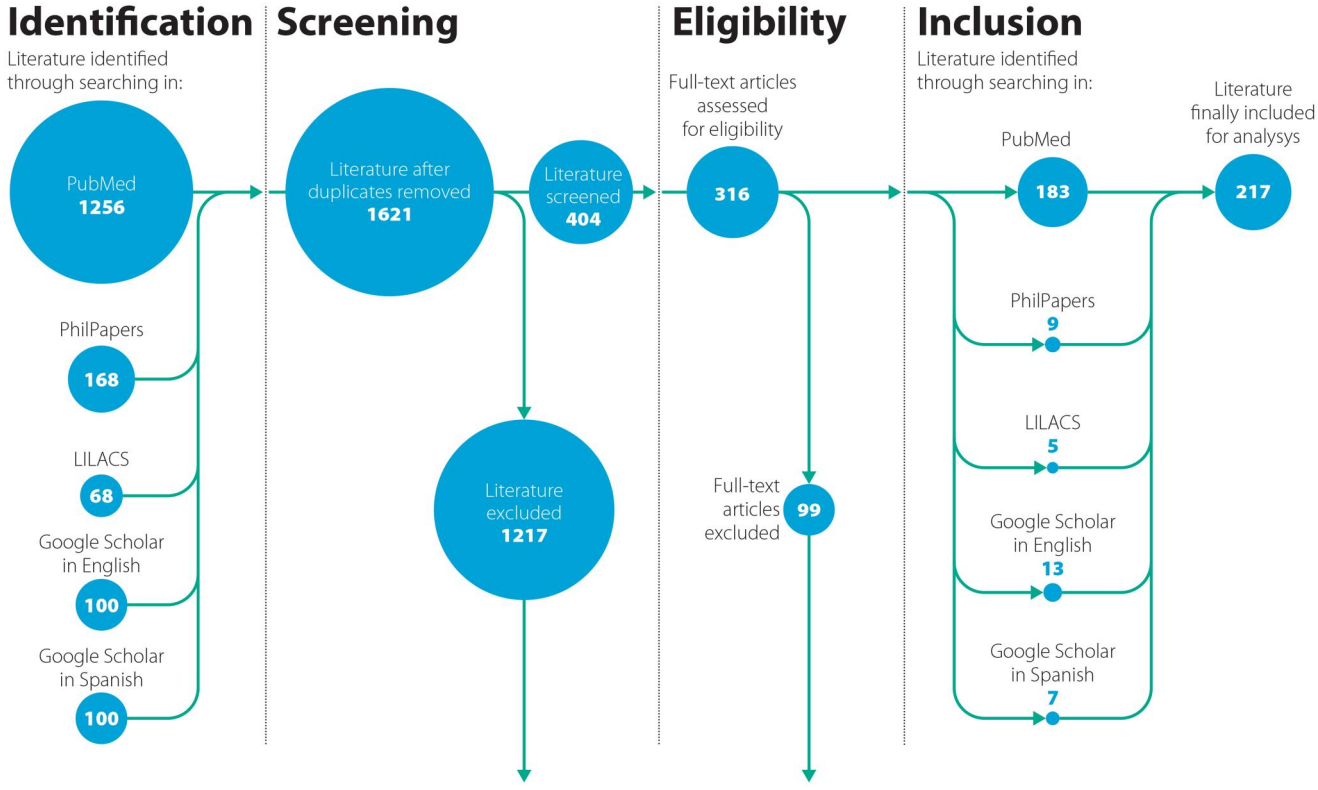

Figure 1. The PRISMA flow diagram of the study selection process.

Characteristics of publications

Of the 217 articles included, 206 (94,9%) were published in English and 11 (5,1%) in Spanish. The earliest came from 1972, the last from 2020. The most prominent types of publications were reviews and theoretical/conceptual papers. Almost half of the authors (46,7%) of all selected publications were from the US, followed by Canada (12,4%) and the UK (9,8%). The journal that published the highest number of articles was Human Gene Therapy ($n = 36$; 16,6%). The largest number of articles were from the academic field of bioethics and genetics. More details can be found in the Supplementary Material section (S6 Appendix).

Results of syntheses

In total, 189 arguments were extracted from the included articles. These arguments were classified into 23 categories. All categories were grouped into two broad themes: research-related and society-related (Figure 2). We present all research-related and society-related arguments by category and with references in the Supplementary Material section (S7 Appendix). Below we describe some relevant features of the categories, with the reference number of the article listed in Table 1 where they are mentioned.

Research-related categories

Pre-clinical stage

As many articles agreed on the need for animal testing to evaluate safety, efficacy, and long-term effects (31, 35, 52, 56, 57, 59, 71, 97, 99, 100, 117, 123, 124, 155, 189, 191, 214), others argued that even when this is important, it is not always possible to extrapolate directly from animal experiments to human studies (7, 10, 17, 18, 22, 64, 88, 154, 161, 189, 209). Not only is it necessary to test the gene therapy technology itself, but also basic pathophysiology studies are required because there is difficulty in establishing causality in the occurrence of the disease (10, 45, 110, 161, 184, 189).

Clinical trials

Although some arguments are around the idea that clinical trials on somatic gene therapy are new and could have high/uncertain risks (10, 18, 22, 28, 32, 40, 41, 68, 90, 102, 104, 114, 117, 174, 175, 121), an article stated that these trials are not fundamentally different from those associated with other experimental therapies (173). Regarding adverse events in trials, some articles argued that even if they are present, they should not invalidate the therapy itself, as it is experimental and many patients are seriously ill (38, 45, 124, 154, 174, 175). This could be related to the idea that there should not be a delay in starting clinical trials, because this could also be a harm to people suffering from diseases that somatic gene therapy could prevent or treat (31, 81, 97, 104, 113, 143, 211). However, one concern was that many clinical trials lack adequate statistical power to draw valid conclusions about possible racial or ethnic differences in response to or toxicities of new treatments (141). The need for public input in the research process is emphasized (5, 10, 16, 53, 62, 66, 81, 141, 148, 149, 150, 151, 152, 184, 210, 213).

Table 1. ID, authors and year of articles included in the cohort.

1= Traulsen et al. 2008
2= Addison et al. 2017
3= Thrasher et al. 2013
4= Barns et al. 2000
5= Carmen 2001
6= Hughes 2019
7= Riva et al. 2019
8= Steele 2000
9= Bonatti et al. 2002
10= Ledley 1995
11= Holtug 1997
12= Baird 1994
13= Kim et al. 2009
14= Podhajcer et al. 1998
15= Sturgis et al. 2005
16= Kimmelman 2012
17= Freire et al. 2014
18= Swazo 2006
19= Walter 2003
20= Fischer 2000
21= Pepper et al. 2018
22= Ledley 1991
23= Friedmann 2004
24= Lowenstein 2008
25= Moseley 1991
26= King et al. 2005
27= Campbell et al. 1998
28= Tauer 1990
29= Scully 2001
30= Kimmelman et al. 2005
31= King et al. 2008
32= Nicholson et al. 1995
33= Levin 2016
34= Flotte 2015
35= Fletcher 1985
36= Penticuff 1994
37= Shannon 1999
38= Fost 1992
39= Bernstein et al. 2004
40= Zhang 2008
41= Haan 1990
42= Kimmelman 2012
43= Valenzuela 2003
44= Fletcher 1990
45= Nevin 1998
46= Kaji et al. 2001
47= Goering 2000
48= Drugan et al. 1987
49= Bertolaso et al. 2010
50= Royal Commission on New Reproductive Technologies 1994
51= Kaspar et al. 2009
52= Danks 1993
53= Dimichele et al. 2003
54= Giangrande 2004
55= Dimichele 2005
56= Friedmann et al. 1972
57= Anderson et al. 1980
58= Hoshino 1995
59= Weatherall 1991
60= Ashcroft 2004
61= Robinson et al. 1996
62= Wolf et al. 2009
63= Spink et al. 2004
64= Roth et al. 2002
65= Mavilio 2010
66= Rabino 2003
67= Jin et al. 2008
68= Cohen-Haguenauer 1997
69= Hillman et al. 1996
70= Smith 2003
71= Hoose 1990
72= Fuchs 2006
73= Amor 2001
74= McKenny et al. 1999
75= Farrelly 2004
76= Cole-Turner 1997
77= Fost 1993
78= Churchill et al. 1998
79= Chadwick et al. 1998
80= Friedmann 2019
81= Gustafson 1992
82= Lacadena 2005
83= Williams 2002
84= Kaplan et al. 2000
85= Gage 1987
86= Costea et al. 2009
87= Savulescu 2001
88= Editorial 1993
89= Health Department of the United Kingdom Gene Therapy Advisory Committee 2001
90= Wirth et al. 2013
91= Messer 1999
92= McGleenan 1995
93= Larson 1990
94= Launis 2002
95= Carmen 1993
96= Holtug 1993
97= Walters 1991
98= Krimsky 1990
99= Anderson 1985
100= Leiden 2000
101= Anderson 1989
102= Patel 1993
103= Ellliot 1993
104= Kahn 2008
105= Zänker et al. 1997
106= Macer et al. 1995
107= Richter et al. 1998
108= Editorial 1996
109= Fitzgerald 2002
110= Ruiz-Perez 1993
111= Casanova Perdomo 2011
112= Green 2005
113= Dickens 1996
114= Areen 1990
115= Wilson 2009
116= Robin et al. 1987
117= Palmer 1991
118= Nunes et al. 1996
119= Neel 1997
120= Barreiro 1999
121= Baramt 2001
122= Crisp 1995
123= Gafo 2000
124= Friedmann 2000
125= Swiss Academy of Medical Sciences 1999
126= Winter et al. 1995
127= Bruce 2006
128= Stahl 2015
129= Fletcher 1983
130= Turriff et al. 2019
131= Lenk et al. 2007
132= Ebbesen et al. 2006
133= Scully et al. 2004
134= Benjaminy et al. 2014
135= Miller 1995
136= Cohen-Haguenauer 1995
137= Steele 2000
138= Brooks et al. 2019
139= Aiyegbusi et al. 2020
140= Konduros 2019
141= King et al. 2010
142= Dettweiler et al. 2001
143= Gansbacher 2002
144= Robillard et al. 2014
145= Górecki 2001
146= Shalala 2000
147= Kimmelman 2003
148= Pattee 2008
149= Delhove et al. 2020
150= Horst 2007
151= Zallen 1996
152= Sato et al. 2006
153= Kimmelman 2008
154= Kimmelman 2005
155= Anderson 1991
156= Areen 1985
157= Leavitt 2001
158= Black 1998
159= Cornetta et al. 2002
160= Cornetta 2003
161= Orkin et al. 1995
162= Committee 1992
163= Priest 2009
164= Ragni 2002
165= Temin 1990
166= Lagay 1999
167= Lebo et al. 1991
168= Weatherall 1995
169= Anderson 1990
170= Nelles et al. 2015
171= Motulsky 1989
172= Ledley 1987
173= Ledley 1992
174= Kimmelman 2007
175= Lyngstadaas 2002
176= Kimmelman 2008
177= Glass et al. 1999
178= Norfolk et al. 1990
179= Bayertz et al. 1994
180= Xiang et al. 2015
181= Risco 2006
182= Espin-Villacres et al. 2001
183= Rodriguez Yunta 2003
184= Agudelo Vélez et al. 2013
185= Smith et al. 2010
186= Pace 2004
187= Ledley et al. 1992
188= Wilson 2010
189= Walters 1986
190= Kimmelman 2008
191= Dyer 1997
192= McDonough 1997
193= Bunch et al. 2000
194= Friedmann 1990
195= Farrelly 2004
196= Nycum et al. 2007
197= Fletcher 1998
198= Kraj 2002
199= Sadler et al. 2004
200= Juengst 1990
201= Kong 2004
202= Karpati et al. 1997
203= Walter 1999
204= Henderson et al. 2006
205= Kimmelman et al. 2005
206= Kimmelman 2009
207= Gilbert 2008
208= Kass 2000
209= Henderson et al. 2004
210= Teichler Zallen 2000
211= Anderson 1992
212= Robillard et al. 2013
213= Stockdale 1999
214= Ponder et al. 2008
215= Chapman et al. 2019
216= Porter 1990
217= Keenan 1990

Note: For full cohort details, see S5 Appendix.

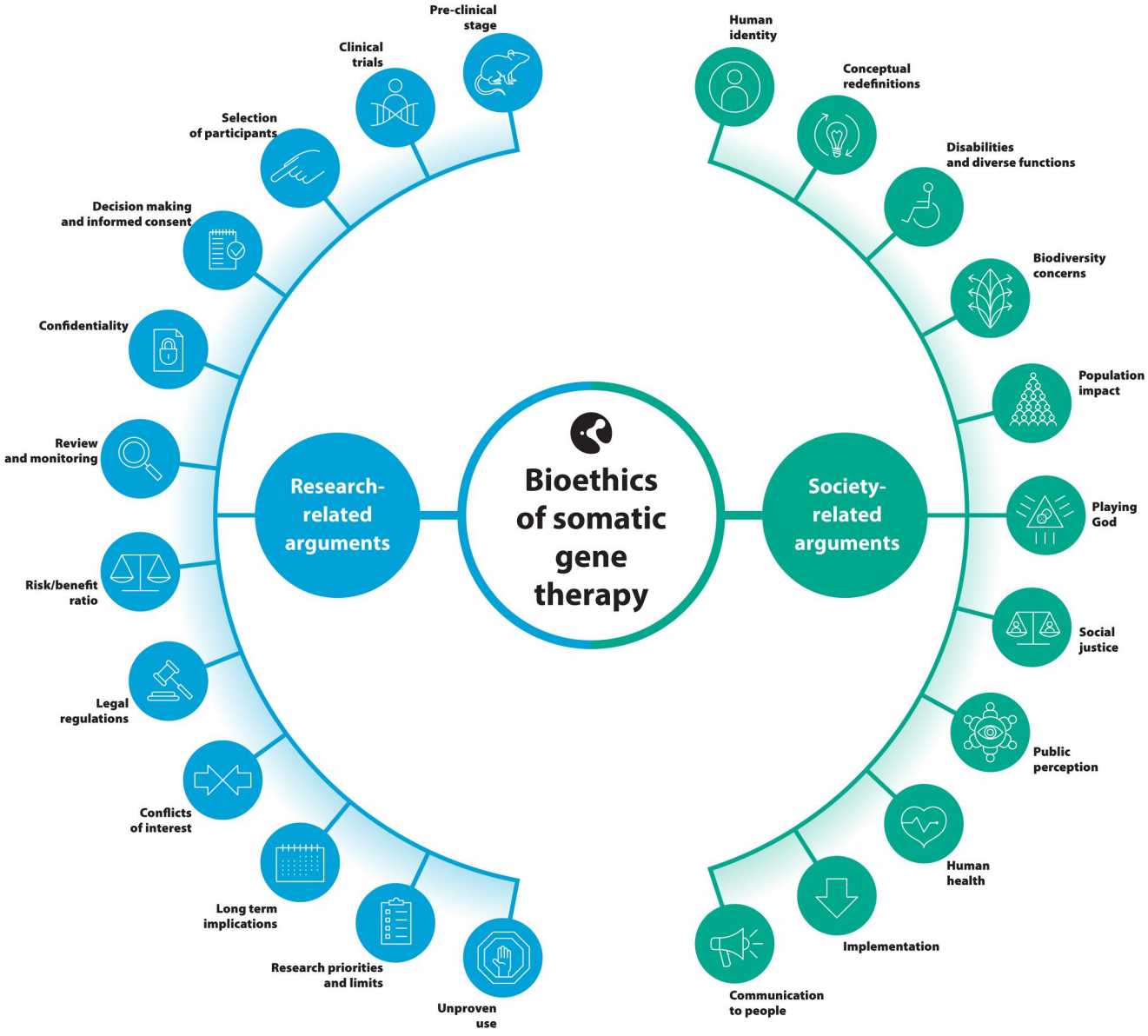

Figure 2. Categories grouped in research-related and society-related.

Selection of participants

It is reported that there is a pressure to enroll record numbers of human subjects in record numbers of trials (207), but it is difficult to ensure fairness in the selection of subjects (7, 22, 31, 33, 40, 55, 64, 83, 97, 117, 129, 153, 176, 192, 200). Some argue that it could be justified in life-threatening diseases without any therapeutic alternative (55, 56, 57, 72, 74, 89, 100, 101, 110, 123, 158, 162, 183). On the contrary, end-stage disease should not be used to justify exposing participants to greater risks (196). But there is also a risk of exploitation related to what we call collateral affective benefits (hope and altruism) for research participants (196). It is reminded that the good of society should not come at the expense of individual persons (193, 200), and that society's ethical commitments to people living today should be prioritized over those who may benefit in the future from gene therapy (176). It is claimed that it is unethical to recruit subjects from economically disadvantaged countries because they may not have access to gene therapy in the future, but, on the other hand, people from both developing and developed countries have something to gain by participating in gene therapy trials (214).

Decision making and informed consent

Regarding the decision-making process of potential participants in the trials, many arguments focus on informed consent itself. One of them highlights that consent form is an influential component of the consent process (209), another that informed consent seems to protect institutions and not participants (151) and some that there could be problems with understanding the nature of the intervention and risks for participants (1, 14, 42, 51, 104, 114, 149, 152, 165, 184, 201, 213). Several argued that participants may decide based on the hope that they will benefit themselves (28, 31, 32, 35, 104, 117, 130, 213) or that they will stop struggling with life-threatening diseases (51, 60, 66, 69). In summary, there are concerns based on evidence that the research subjects could

overestimate the benefits and provide invalid informed consent (174, 176, 200, 204, 205, 209). It is important to provide very detailed information to patients participating in gene therapy trials to prevent unrealistic hopes (170, 196). The risks should be communicated even if they are unlikely to happen (8, 12, 18, 46, 50, 51, 159, 160, 214). It is also emphasized that receiving insufficient information about treatment is a main concern (144). On the other hand, some people prefer to wait for strong evidence before considering enrolling in a clinical trial (8, 73, 86). So far, we have mentioned empirical problems. In relation to conceptual problems that affect practice, many authors argue that the term gene therapy referring to research brings confusion and intensifies existing problems of informed consent (26, 31, 36, 40, 78, 174, 196, 201, 204, 205, 209). It should be clear that personal benefit does not overlap with the scientific purpose of the study (9, 13, 89, 95, 117, 122, 209) and that the benefits for the participants are not the same as the benefits for society (19, 174).

It is said that we should not only rely on the consent process to determine an acceptable level of harm, burden, or risk of harm (196) but also that informed consent could require a different strategy than usual to guarantee genuine decisions (51, 70, 81, 125, 138, 142, 148, 149, 189). Another thing to consider is that gene therapy could be irreversible, so the right to revoke one's consent is not applicable here compared to continuing medical treatment and should be carefully explained (50).

Confidentiality

Many articles point out the difficulties in protecting privacy and confidentiality (4, 12, 36, 47, 64, 97, 162, 171, 187, 197, 198, 217), and that the information obtained during trials could be prejudicial to the individuals treated or to their families (50, 171, 187, 197, 198, 217).

Review and monitoring

As some articles discuss, there is no need for a special evaluation of the somatic gene therapy protocol (100, 107, 216) because somatic gene therapy arises ethical issues similar to other medical technologies/treatments (4, 6, 12, 18, 19, 22, 28, 32, 37, 38, 41, 44, 50, 63, 65, 66, 69, 70, 71, 72, 73, 76, 77, 78, 85, 93, 94, 96, 100, 102, 105, 111, 114, 122, 124, 126, 128, 143, 158, 162, 168, 171, 175, 178, 179, 181, 185, 191, 216). Others focus on the idea that there is a need for special evaluation and audit of somatic gene therapy protocols (11, 35, 40, 45, 57, 62, 81, 100, 113, 118, 121, 124, 131, 150, 154, 159, 160, 188, 190, 192, 200, 202, 210, 213), because gene therapy has very specific and unique ethical complexities compared to other medical practices (2, 39, 46, 71, 90, 119, 190, 208). Therefore, the bioethical implications of these experiments must be carefully considered (5, 16, 20) and security issues should not be confused with ethical issues (32). The protocol should be strictly followed, and any changes to the protocol must be documented (110, 115, 62, 89, 115, 137, 145, 187, 188) and should be an effective means of control and discipline after the protocol is approved (162). There is an obligation to avoid harm (19, 40, 87) and any adverse event must be reported (46, 62, 89, 115, 145).

The ethical complexity of gene therapy should not be approached only with an ethics committee (2, 147, 151, 154, 158, 159, 160, 162) and the public should be involved in the review and monitoring protocols as necessary (127).

Risk/benefit ratio

There is a claim that gene therapy should be treated as a conventional medical therapy when determining risk/benefit ratios (192) because the risks do not appear to be different from those encountered by any standard medical therapy (85). But other articles reveal that gene therapy has novel properties that can affect humans in unpredictable ways (7, 16, 61, 63, 64, 70, 90). Probabilities and outcomes for adverse events related to gene transfer are difficult to define (7, 10, 18, 22, 40, 42, 51, 63, 67, 104, 114, 117, 165, 184, 190). Gene therapy raises concerns about long-term safety and efficacy (12, 16, 17, 31, 40, 41, 45, 59, 60, 61, 63, 64, 67, 69, 76, 77, 89, 90, 105, 123, 166, 175, 182) and about serious and/or irreversible side effects (10, 17, 18, 23, 43, 50, 54, 60, 64, 69, 71, 85, 86, 88, 90, 100, 101, 114, 126, 167, 176, 183, 192).

Principal risks include technical issues in terms of the quality and stability of transgene expression (17, 31, 41, 59, 70, 85, 90, 110, 161, 168, 183, 184, 192, 196, 200, 202, 213), transfer of an unwanted gene, administration of replication-competent virus or bacterial contamination of vector preparation (177, 196, 202), immune response against both the vector and the transgene (54, 62, 118, 161, 164, 165, 168, 169, 175, 176, 177, 194, 196, 202, 213), activation of oncogene or inactivate a tumor suppressor gene caused by gene vector (164) and unintentional modification of germinal cells (31, 54, 64, 67, 85, 88, 107, 114, 117, 125, 126, 164, 175, 177, 180, 202).

On the other hand, viral vectors seem effective but are still not quite safe (17, 39, 61, 62, 64, 70, 71, 73, 90, 99, 100, 110, 118, 131, 142, 161, 165, 167, 183, 187, 196, 202, 213), non-viral vectors could be safer but still not efficient (17, 39, 62, 67, 70, 73, 131) and transgene expression worked but in long term is limited (142).

There are difficulties in balancing benefits and risks in relation to the burden and prognosis of the disease (18, 34, 40, 41, 48, 63, 95, 100, 104, 114, 121, 125, 190), but also because the risks are uncertain and cannot be reduced to a single utility (176, 193).

Furthermore, difficulties in the balance of risk/benefit relate to how potential social benefits should be balanced against individual risks (196, 201). There could be subtle social benefits of gene therapy (88, 100, 125). The problem with social benefit is that it can be as broad or narrow as one chooses (201). Beneficence is based on the potential for net benefit in the entire population while doing minimal harm to the individual (32, 81), and the distinction between medical benefits and collateral benefits is highlighted (196).

Conflicts of interest

The difficulties in managing conflicts of interest were highlighted in several articles (33, 39, 40, 53, 77, 85, 93, 100, 102, 121, 124, 115, 145, 146, 188, 207, 213), showing that important stakeholders have deep interests in gene therapy as a product (127, 155). Therefore, due to the great investments, scientists face a high pressure for success to develop gene therapy (4, 53, 117, 121). It is clear that clinical investigators should not have a personal financial relationship with companies that may benefit from the results (46). It is also shared that conflicts of interest do not need to be financial. They can be personal. For example, most Institutional Review Boards members in medical schools are employees of those institutions and have personal relationships with researchers (207). The overlapping roles could lead to potential conflicts in subject recruitment (104).

Regulations

Some articles expressed that the regulatory system is likely to be challenged by gene therapy (6, 21, 22, 31, 45, 67, 66, 68, 69, 121, 159, 160, 190). Regulations cannot be a general "blanket," but each type of gene therapy must be evaluated on its own merits and risk analysis (149). However, others showed that gene therapy research is, without any scientific or medical basis, the most highly regulated procedure in medicine (135). Gene therapy is subject to too strict rules and is affected by overregulation (65, 68). No other form of therapy has ever been subjected to such strict control in its development and clinical trials as somatic gene therapy (179). Therefore, overregulation of gene therapy can lead to increased bureaucracy (207) and can profoundly slow its testing and ultimate adoption (135). An article suggests a worldwide accepted and controlled bioethics convention for somatic gene therapy (126).

Research priorities and limits

Some articles proposed that gene therapy per se is no longer being debated, but its application to particular diseases or particular patients is (179, 193, 216). In this sense, some authors mention that gene therapy used in diseases should be evaluated in advance (71, 85, 101, 125) or that the goal of the therapy has yet to be determined (175). There is also a back and forth about when to apply gene therapy. One position is that there should be more efforts to prevent rather than treat (4). The other is that gene therapy should not be a "first line" of defense therapy as long as an alternative is available (18). About priorities, there is a concern about who should decide what to investigate: companies, scientists or other? Pharmaceutical companies and other corporate interests often determine research priorities, which may not be aligned with public health needs (4, 191). Furthermore, scientists should decide about gene therapy research priorities on the basis of enlightened and broad-based public opinion (156).

The need to redefine the rights and responsibilities of all involved actors is noted (14, 17, 109, 117, 150, 152, 155, 184, 210, 213), as well as the need for public participation in genetic research policy (200). Lay people and stakeholders should be involved in the ethics discussion about gene therapy (4, 53, 58) as human gene pools are viewed as collective property. Public debate is necessary (50). But, with so many stakeholders, it could be difficult to design a regulation considering both political and cultural differences (17, 62, 60, 63, 64, 68, 76, 83, 85, 120, 127, 152, 201).

Unproven use

Unproven use refers to pre-approval, non-trial access to potentially beneficial therapies (3). For some rare diseases, experimental therapies such as gene therapy may be the only way to provide a treatment option (3). Patients who have exhausted other therapeutic options may not meet the restrictive criteria for inclusion in the trial (3). However, a failed use attempt with gene therapy may make a patient unable to try similar intervention again (215). In this sense, companies that might produce gene therapies want to "preserve the pool of future customers" and the reputation image, so they restrict unproven use (215). Moreover, since some gene therapies are one-dose treatments and the rare diseases patients are a small number of customers, there could be a commercial disincentive for unproven use (215).

Long term implications

The need to consider long-term implications was raised in some articles (4, 154, 162, 164) along with the need for adequate follow-up and ongoing care for the participants (10, 22, 54). However, this is not easy, as several factors seem to complicate the achievement of follow-up of patients participating in gene therapy trials (187).

Society-related categories

Human identity

Those who do not believe that somatic gene therapy could change human identity state that the essence of the human person is not something that we can change at will, regardless of our technological capabilities (216). Human identity is more than a pool of genes (127) and is constantly redefined in biomedicine (76, 91, 105). Furthermore, an article states that gene therapy objectifies the disease in the person rather than the person (217).

However, others declare that somatic gene therapy could modify human identity, humanness or personal perception (11, 19, 27, 47, 69, 79, 101, 103, 109, 123, 131, 133, 191, 199, 212, 216) and could threaten human dignity (208). The body could be perceived as an enemy or as a source of weakness that is perfectible by technology (133), and eventually, the use of gene therapy could make certain human individuals cease to exist (4, 103). Gene therapy could reshape the ideas on how to live better (2), that effort is part of what makes us appreciate our life, so we do not have to eliminate all the pain or suffering (47). If we do so, we could lose our caring characteristics (47). Finally, gene therapy is said to not be used to change human traits (162).

Conceptual redefinitions

Gene therapy could open up some conceptual redefinitions. Some authors announce that could create a need for new disease/illness prevention and treatment concepts (11, 14, 49, 81, 110, 113, 122, 126, 133, 208). Additionally, it could be difficult to distinguish enhancement from treatment (11, 14, 29, 44, 47, 64, 66, 72, 74, 80, 81, 85, 94, 96, 97, 101, 102, 109, 110, 113, 114, 120, 122, 126, 132, 179, 185), and enhancement or eugenic therapy could be captured as human genetic therapy (167). In this sense, experiments in somatic gene therapy cannot be tainted by past associations with eugenics (172). Biotechnology is said to highlight moral problems, but not create them (44). Another conceptual issue that appears in some articles is that there are no ethical differences between germline and somatic gene therapy (25, 29) and that we are not conceptually forced to allow all types of gene therapy once we allow one (96).

Disability and diverse functions

Gene therapy could have an impact on social attitudes toward disability (133). On the one hand, gene therapy could not increase discrimination, but could make us aware of it (6, 81). On the other hand, the possibility of treatments could lead to more discrimination for disabled people (47). This is because diverse functions or bodies do not imply disabilities to prevent or treat, for example, deafness, but that community may argue that the only reason that deafness confers any disadvantages in society is because of societal discrimination (47). Also, in some cases, disability could be an integrated aspect of a person's identity (133). Some articles mention that it is not necessary to overcome every human "limitation" (4, 47, 79, 81, 83, 91, 103, 105), and instead of working on solutions based on social bias, we need to think again about our social values (47).

Biodiversity concerns

There seems to be little concern about the impact of gene therapy on biodiversity (4). Gene therapy could replace the use of animal tissue culture used in current treatments (164), but the manufacture of gene therapy could be hazardous to the environment (1). In another sense, this field seems to avoid the issue that we are part of the environment because we put an anthropocentric distance ourselves from nature as if it were something different from human beings (4), and so gene therapy needs to consider the environmental effects on genes (4, 47, 49, 50).

Population impact

Gene therapy could have an impact on the population in different ways. To start, gene therapy research is a significant step in science evolution and therefore for well-being of humanity (40, 65, 67, 69, 70, 72, 74, 76, 78, 83, 105, 106, 107, 118, 124, 126). However new approaches have novel properties that may affect humans in unpredictable ways (142). There is a need to consider broad and long-range research consequences: public health, environmental and evolutionary concerns (200, 201).

Gene therapy for one person could have adverse repercussions on others (16, 27, 37, 44, 70, 77, 82, 85, 90, 93, 97, 114, 121, 126, 157, 200), for example, by making genetic diseases more prevalent in each generation after somatic gene therapy (37, 43, 202). In this sense, it is said that it could modify human evolution (37, 43, 76, 77, 81, 82, 91, 93, 94, 96, 101, 109, 122, 123, 126, 157, 167, 183, 184, 212, 217) because "bad" genes are needed from the viewpoint of the species (106). In opposition, other article advised that gene therapy will not affect human evolution (165).

Gene therapy could increase the possibility of the development of other new genetic technologies that have undesirable consequences (4, 35, 71, 72, 80, 93, 94, 96, 97, 101, 106, 122, 123, 128, 165, 183, 191, 199). For example, this could lead us to accept eugenic medical goals (4, 49, 52, 74, 81, 85, 94, 96, 157, 172, 208, 217), to a willingness to modify the color of the skin or change personality (167, 171) or that we are logically committed to accepting germline therapy (44, 72, 122, 208).

Despite the fact that gene therapy is offered with a focus on individual patient choice (70, 72, 79), it could motivate/-deepen conflicts between values (17, 35, 101, 107, 121, 152, 163) and turn social problems into genetic problems (4, 29, 85, 93). In addition, gene therapy could raise issues of fairness, justice, or equity in access to therapy (69, 67, 75, 81). Gene therapy could cause population aging (180) and longevity could cause loneliness and overpopulation, despite improving quality of life (1).

Social justice

Across social justice and similarly to what happened to other biomedical innovations, gene therapy could only be available in countries or for people with high income (1, 14, 17, 21, 33, 34, 36, 76, 77, 79, 90, 96, 101, 102, 183, 189, 197). It could be discriminatory to people who do not have access to gene therapy (11, 28, 36, 63, 81, 84, 101, 123, 185, 198, 212). An article argued that these economic inequities could affect human biology (112). Some propose that justice debates should take seriously the fact of scarcity in the field of gene therapy (195, 197), because it may also relegate funding from other areas of healthcare (4, 21, 32, 34, 36, 38, 61, 64, 69, 83, 75, 77, 79, 85, 112, 119, 125, 197, 202). The fact that gene therapy could be cost-effective compared to current therapies (50, 53, 55, 69, 143, 162, 164, 189, 202, 215) opens the possibility that gene therapy can be available for universal access to health care (86, 197).

Public perception

There is an ambivalence about the perception of gene therapy (208). Some authors show that people are unaware of the term "gene therapy" and its availability (69, 86, 97, 126). Others reported that there is no public trust in gene therapy (4, 8, 127) and that gene therapy has a long way to go before gaining widespread acceptance (180). The frequent reasons for not accepting gene therapy are fears of adverse

effects, high cost, and a belief that it went against nature (180, 216). There are concerns about the political uses of gene technology, genetic discrimination, and misuse of power (180, 208). The possible consequences of manipulating genes or designing humans arise fear (9, 15, 60, 86, 93, 97, 98, 101, 105, 106, 126, 212). People think it is a risky procedure (127). It still provokes negative emotional reactions due to the stories of deaths (23, 62, 121, 131, 150, 163, 165, 210). On the other hand, many articles describe that there is high public support for the use of gene therapy to cure serious diseases but not for human enhancement (9, 19, 45, 50, 61, 63, 66, 67, 73, 74, 81, 85, 90, 97, 101, 106, 107, 113, 144, 167, 180, 212). Gene therapy is seen by most as a desirable extension to the range of available medical options (179) and people are interested in learning about gene therapy (212). The guarantee of sound research in general and the safety of patients is crucial for public support and recruitment (146).

With regard to religions, if it is for therapeutic purposes, gene therapy is accepted and encouraged, as long as proper precautions are taken (186, 198) considering that genetic manipulation leads to a delicate issue about soul alteration (186).

Human health

A common argument with respect to human health is that gene therapy could prevent and/or treat serious diseases that cause humanity to suffer and improve quality of life (60, 64, 68, 69, 73, 74, 80, 83, 84, 133, 140, 143, 169, 182, 185, 192, 199, 211). Furthermore, it could be the only possibility of treatment in particular diseases (11, 23, 31, 43, 50, 60, 62, 68, 70, 110, 111, 123, 128, 175, 179, 181, 182, 183, 185, 192). Therefore, there is a moral obligation to develop gene therapy if we consider it to be the only treatment for particular diseases (12, 19, 33, 36, 76, 125, 129, 194). It is also underlined that gene therapy has many potential applications, in addition to its application in monogenetic diseases (59, 62, 64, 69, 70, 73, 145, 161, 175, 181). Not only what gene therapy could do, but how: gene therapy may provide a curative rather than a symptomatic approach to diseases (143), holds the promise of preventing diseases (155) and restoring functions (175). An article presents that the progress in gene therapy is clearly relevant to women's health for understanding and treating common diseases (197). Two important points were that gene therapy could avoid anxiety associated with the life-threatening nature of the underlying disease (53) and that therapeutic abortion could be rare if genetic diseases could be treated (53, 129).

Implementation

Gene therapy could create problems in its implementation in medicine (38, 59, 66, 67, 68, 131, 159, 165, 193, 194, 213). Specific standard operational procedures and cooperation between healthcare workers may be needed (64). Furthermore, some authors said that a genetic diagnosis is needed prior to therapy, so it should already be available (56, 81, 84, 123, 189). Therefore, if alternative treatment exists, the use of gene therapy will depend on its efficiency, costs, and level of discomfort for patients (59).

Communication with society

Many articles support the need for public trust on the basis of proper knowledge and transparency in the research process (14, 15, 17, 62, 68, 66, 81, 84, 90, 100, 108, 150, 152, 161, 163, 165, 184, 213). Hence, public opinion should be adequately informed about gene therapy (81), and scientists must spend adequate time communicating science to the media (8, 137, 149, 212).

According to some authors, terminology has been shown to influence risk and benefit perception (205, 209), and here the term "gene therapy" used in research does not reflect whether it is a therapy or research (50, 53, 54, 89, 93, 95, 104, 107, 113, 117, 124, 150, 161, 201, 204, 213). It has been shown that the potential of somatic cell gene therapy may have been exaggerated, especially in relation to the timeline of its successful implementation (202, 216) with a tendency to amplify potential benefits and minimize potential risks (68, 66, 78, 124, 134, 190). Reinforcing this, the oversell of gene therapy research could cause a slowdown in gene therapy if something bad happens (155). As an emotionally volatile topic, if no patient is helped, the negative reaction can halt the entire field of gene therapy (169). However, advances have been made during the last few years, and there are reasons to hope clinically important results will be presented (175).

Playing God

Some articles came with the topic of "playing God," referring to actions that could be done without any limit and have serious effects on people's lives, as someone could have unlimited power. Some stated that humankind should not play God (76, 81, 91, 106, 122, 157, 167, 208), others that we are not playing God with gene therapy, as science is a human activity (127), and that there may be both proper and improper ways of "playing God" (203).

Discussion

To our knowledge, this article constitutes the first systematic review of reasons in bioethics for somatic gene therapy. Systematic reviews of reasons are relatively new in descriptive ethics. Recent articles that have applied this method include bioethical debates about organoids models[20], permissibility in research with great apes[21], germline modifications[22], genome editing in non-human animals[23], among others. Systematic reviews of reasons provide broader perspective of the chosen topic.

Somatic gene therapy following conventional techniques has the potential to be a major step in science and humanity's well-being[5]. After analyzing all the arguments provided in this review, we can agree that at the same time, this technology could have repercussions on a massive scale and we do not have clear answers how to deal with these challenges[6,11,24].

The impact that gene therapy could have -or already has had- on society is different from any other social impact of a non-genetic health-related biotechnology[13,24,25]. The role that we give to genes impacts in how we understand our health and the functionality of our body[26]. We are targeting genes as mediators of human illness, which play a role in some kinds of disease; but they are not always the whole explanation and the social considerations surrounding them should be seriously considered[13,27]. Somatic gene therapy on a massive scale could have repercussions on human identity[24]. For example, many deaf people do not consider themselves as a person with disability, but rather identify deafness as personal feature that is part of their identity[25]. If somatic gene therapy could play a role in "treating" this diverse function through genes, then diverse functions could be seen just as a genetics problem. In this context, people with deafness might be seen as people with a genetic abnormality that may have impact on the identity of those who do not consider themselves with an abnormality. And in this context, deciding not to "treat the abnormality" will be out of a personal decision, but on the social framework of an abnormal who actually needs to correct the abnormality. The deaf situation is one example of how somatic gene therapy is very close to the genetic determination idea, and this is one of the reasons it is not similar to other non-genetics biotechnologies. Another specific issue is that we cannot guarantee that all people could eventually access this kind of therapy. This should be considered in advance, because there is a great risk of transforming genetics modifications into a social disadvantage based on the economic situation of a person[25].

Although new techniques in the genetic field, like CRISPR, raise ethical challenges and attention, we want to highlight the problems of conventional somatic gene therapy that already exist[26]. Debates on certain topics should not be marginalized because other challenges appear, but rather that there is a minimum consensus on the discussion[24,28], which has not yet been consolidated in the case of conventional somatic gene therapy. As we demonstrate in this review of arguments, procedural, conceptual, and social issues about somatic gene therapy remain issues that need to be addressed.

Moreover, society should be part of the debate, defining priorities and limits in gene therapy research, ethical permissibility and nuances regarding its acceptance by certain communities and for certain uses[9,24]. All of this could also have positive influences on the development of the somatic gene therapy field[9].

Our analysis should be interpreted in light of the following limitations. First, there were some terms that were not included in the search strategy that may be associated with ethics and bioethics, for example informed consent or risks/benefits. This was intentional to make the systematic review feasible. Second, we are aware that a different group of researchers could have selected or grouped the included reasons in a different way. Third, we did not assess the scientific validity of the articles included.

Conclusion

This article is a starting point in a systematic re-evaluation of the ethical arguments before somatic gene therapy will transform into a massive-scale procedure. Our study provides a database of existing challenges and arguments of somatic gene therapy and may serve as the basis of normative analysis.

Transparency

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More ethics in the laboratory, please! Scientists' perspectives on ethics in the preclinical phase

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ABSTRACT

In recent years there have been calls to improve ethics in preclinical research. Promoting ethics in preclinical research should consider the perspectives of scientists. Our study aims to explore researchers' perspectives on ethics in the preclinical phase. Using interviews and focus groups, we collected views on ethical issues in preclinical research from experienced ($n = 11$) and early-stage researchers (ESRs) ($n = 14$) working in a gene therapy and regenerative medicine consortium. A recurring theme among ESRs was the impact of health-related preclinical research on climate change. They highlighted the importance of strengthening ethics in relations within the scientific community. Experienced researchers were focused on technicalities of methods used in preclinical research. They stressed the need for more safeguards to protect the sensitive personal data they work with. Both groups drew attention to the importance of the social context of research and its social impact. They agreed that it is important to be socially responsible – to be aware of and be sensitive to the needs and views of society. This study helps to identify key ethical challenges and, when combined with more data, can ultimately lead to informed and evidence-based improvements to existing regulations.

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Preclinical research; bioethics; integrity; biotechnology; biomedical research

Introduction

In recent years, there have been calls to improve ethics in preclinical research (Dodson and Pawlik 2014; Landis et al. 2012; Yarborough et al. 2018). Poor translation to the clinical research phase and the replicability crisis are some of the notorious issues motivating these calls (Haslberger et al. 2023; Karp

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and Reavey 2019; Kimmelman and Henderson 2016; Yarborough et al. 2018). The use of same-sex animals for certain types of research has been shown to be problematic for translating research to diverse populations (Karp and Reavey 2019; Shah, McCormack, and Bradbury 2014). Other examples include lack of blinding of treatment allocation to animals, exclusion of animals because of unexpected results, and mischaracterization of the utility of a drug (i.e., a drug for a chronic human disease is tested on animals during an acute illness) (Kimmelman and Henderson 2016; Macleod et al. 2015; Wang et al. 2022). However, discussions and training on research ethics are not frequent in the preclinical research environment (Hildt et al. 2022; Laas et al. 2022). This could lead to ethical challenges in preclinical research being overlooked, but also to a lack of awareness to identify other challenges that may be subtle and difficult to recognize (Dranseika, Piasecki, and Waligora 2016; Jongsma and Bredenoord 2020).

In addition, some preclinical developments in health-related biotechnology could have an impact on society and raise new ethical concerns. They could change the way society perceives and understands health and disease, increase discrimination or redefine human identity (Buedo et al. 2023a; Jongsma and Bredenoord 2020; Torres-Padilla et al. 2020; van Delden and Bredenoord 2015). For instance gene therapy could have an impact on the identity of certain groups, such as deaf people, many of whom do not see themselves as having a disability, but rather see deafness as a personal characteristic that is part of their identity. If somatic gene therapy could play a role in "treating" these diverse functions through genes, then diverse functions could be seen simply as a genetic problem and could impact on the identity of those who do not see themselves as having an abnormality (Buedo et al. 2023a).

Promoting ethics in preclinical research should take into account the perspectives of scientists since scientists have to deal with these issues on a daily basis (Yarborough et al. 2018). Exploring how scientists perceive the relevance of ethics to their work and their responsibilities as members of society is crucial for efforts to promote ethical behavior in preclinical research, and moreover, to foster discussion in this research phase (Linville et al. 2023; Wäscher, Biller-Andorno, and Deplazes-Zemp 2020).

Using qualitative methods, we collected views on ethical issues in preclinical, laboratory research from experienced and early-stage researchers in a consortium working on developing gene therapy. We focused on this group of researchers because they work in the preclinical phase of research, and also because they are involved in genetic research, which adds a layer of complexity to the observation and analysis of ethical challenges in this phase of research.

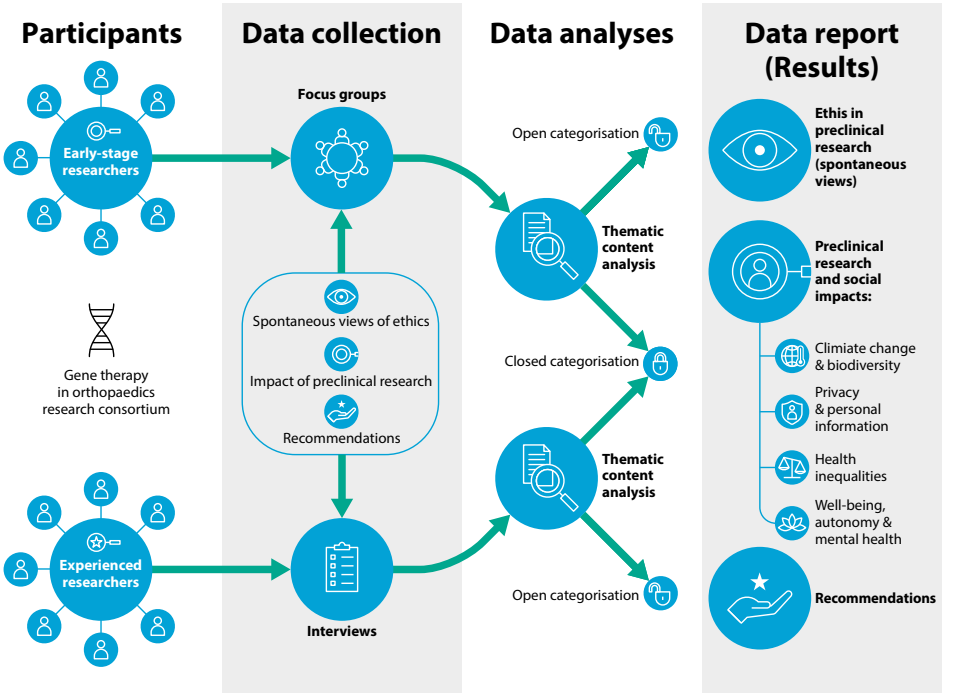

Figure 1. An illustrative synthesis of the methods used in this study.

Our aim is to explore the perspective of researchers at different stages of academic careers and gain insight into their approach to ethics in biotechnologies in the early stage of development.

Methods

To fulfil the aims of the study we applied a qualitative research strategy (Figure 1). We chose two different qualitative techniques, focus groups and individual interviews, to better adjust to the research participants' profiles. Considering their characteristics, career situations and ways of acquiring and transmitting knowledge and information, we divided participants into two research groups. The first research group were early-stage researchers (ESRs) who had just started their career and the second research group were much more experienced experts in the field. However, in both, we share the same goal and aim to cover the same topics/areas of research interest.

We use the comprehensive consolidated criteria for reporting qualitative research (COREQ) to report our research (Tong, Sainsbury, and Craig 2007) (checklist available in Supplementary Material S1).

Participants

All participants ($n = 25$) were recruited from a consortium created with a Horizon 2020 Marie Skłodowska-Curie grant (agreement No. 955335). The consortium focused on the preclinical development of gene therapy in orthopedic regenerative medicine. Project's research topics include cell delivery and gene modulation efficiency, tissue/organ delivery tools, repair in tissue and organ culture, and in vivo imaging of regeneration and gene therapy efficacy.

The first group participated in focus group meetings and consisted of fourteen ESRs from Brazil (2), India (2), Iran (2), Italy, Spain, Taiwan, Germany, China, the Netherlands, Chile and Egypt. Ten were women and four were men. They currently work in the Netherlands (4), Switzerland (2), Sweden (2), Denmark (2), Finland, Romania, Germany and Portugal, in universities (10) and companies (4).

The second group participated in individual interviews and were eleven experienced researchers working as Principal Investigators in the Netherlands (3), Switzerland (2), Sweden, Denmark, Finland, Romania, Germany and Portugal, in universities (7) and private companies (3). There were seven men and four women.

Data collection

We collected data using two different techniques: focus group discussions and semi-structured individual interviews between October 2021 and September 2022.

Focus groups

The focus groups consisted of five consecutive meetings between October 2021 and May 2022. The topics discussed were research ethics and integrity in the preclinical research that they were conducting, the impact of the research and their recommendations for improving ethics and integrity at this phase. The choice of focus group as a research method for ESRs group results from the desire to examine how a comprehensive concept such as ethics develops in discussions between people whose attitudes have not yet been strongly established by the influence of the research environment. We also wanted to capture the initial differences in the level of familiarization with this topic and develop the knowledge about it during subsequent meetings. The complementary aim of focus group meetings held with ESRs was to work together on recommendation how to embed ethics into laboratory research (Buedo et al. 2023b). ESRs share other educational activities as a group, thus such workshops were matched with their curriculum.

Focus group discussions were conducted by PB (one ESR from the consortium, female, MD, MA). Each meeting lasted a maximum of 90 minutes. As the ESRs were located in different countries, the FGs were conducted online. A guide for each FG was designed (Supplementary Material S2) and discussed among the research team conducting this study. One focus group was piloted with ten ESRs working in the study area but not being the part of the consortium. Technical support was provided by an ESR from outside the consortium (IOS), who was present at each FG.

Interviews

Semi-structured interviews performed with experienced researchers who work in different institutional contexts were treated as expert interviews. The aim was to have an in-depth conversation regarding the interviewee's knowledge and opinion of the state of ethics and integrity in the preclinical phase. The guide consists of open-ended questions related to research ethics, integrity and bioethical challenges in the preclinical phase, as well as the impact of the research and its recommendations for improving ethics and integrity in this phase. The semi-structured design ensured consistency in the topics discussed by all participants, but also allowed participants to raise or emphasize issues different from those suggested. Separate meetings with experienced researchers allowed them to share their experience and express their views more freely, without having to confront them with the positions of other members of the academic community. The individual interviews did not include an educational supplement.

Interviews were conducted between July and September 2022 and lasted between 45 and 70 minutes. They were conducted in English and took place either at a location chosen by the participant (3) or online via a video call platform (8). The interviewer (PB) and the participants had brief prior contact at two consortium meetings. The interview guide (Supplementary material S3) was developed and discussed among the research team conducting this study. The interview was piloted with two researchers working in the study area but outside the consortium.

Data analyses

Interviews and focus groups were recorded, transcribed verbatim and pseudonymised.

Transcriptions were read several times to familiarize ourselves with the data. Transcriptions were entered into MAXQDA software for analysis. We analyzed all data using thematic content analysis (Bergin 2018; Green and Thorogood 2018). The coded categorization (PB, EP) was developed according to the research objectives of the study. In doing so, we combined a closed

and open approach to codes, meaning that we defined only some of the codes prior to analysis (Taylor, Bogdan, and DeVault 2015). The closed categorization related to research impact on autonomy, privacy and personal information, climate change, health inequalities, social well-being and mental health. Open codes were based on the data from the transcriptions of spontaneous views on ethics in preclinical research and recommendations. As the interview and focus group data were analyzed separately, once the coding was complete, we established a relationship between the categories in order to further present and discuss our findings.

Ethical considerations

The protocol, informed consent form, the General Data Protection Regulation (GDPR) form and participant information page were approved by the Bioethics Committee of the Jagiellonian University, Krakow, Poland (No. 1072.6120.209.2021–29/09/2021). Participants were informed individually by e-mail about the aims of the study, what their participation would involve, why they were invited, the risks and benefits of their participation, and that the sessions would be recorded. We also emailed them the GDPR form and the informed consent form. We explained that the information obtained from the interviews and focus groups would only be used for research purposes and, if published, all data would be anonymized (Daniels

Table 1. Themes and categories developed from focus groups and interviews.

Themes	Categories in Focus Groups	Categories in interviews
1. Spontaneous views on ethics in preclinical research	*Animal experimentation*	
	The use of human biological material and how it is obtained	
	Integrity	*Institutional procedures*
	Relationships in scientific community	*Standard/no-need ethics*
	Impact in society	*Safety, toxicity and long-term effect*
	Footprint on environment	
2. Preclinical research and social impacts: the case of gene therapy in orthopaedics	*Impact on privacy and personal information*	
	Impact on health inequalities	
	Impact on social well-being, autonomy and mental health	
	Impact on climate change and biodiversity	
3. Recommendations or what we can do better in health-related preclinical research	*Research integrity strategies*	
	Ethics training	
	Avoid sex bias	
	Equity	*Science communication*
	Mental health of researchers	*Citizen engagement*
	Environmentally friendly laboratories	

et al. 2019; Sim and Waterfield 2019), so there would be no way to link opinions to a specific person.

Results

We report the findings in three sections according to themes and categories that we developed during the analysis phase of the research (Table 1). Section one summarizes participants' spontaneous views on what is ethically important in preclinical research. Section two presents researchers' views on the different types of impacts that preclinical research has or could have. Finally, section three provides recommendations from both groups of researchers on how to improve ethics in preclinical biotechnology research.

Spontaneous views on ethics in preclinical research

There were two themes that both experienced and early-stage researchers spontaneously associated with ethics in preclinical research: animal experimentation and the use of human biological material and how it is obtained. Both groups also agreed that even though their work is based in a laboratory setting, it is important to be sensitive to the needs and views of society, to be socially responsible in three senses: to let people know what they are doing, to be mindful of the research funding source and to be aware that what they do has consequences, and therefore to consider the social impact of research.

Experienced researchers associated ethics with procedures and requirements of the institutions where they conduct research, with guidelines and with external approval. Some of them expressed that preclinical research needs "standard ethics," but if the research project is granted by a highly recognized institution, few expressed that there is no need to consider additional ethical issues as they relied on the institution to ask them to address particular ethical challenges if they considered it necessary. A minority mention that ethics is not needed at preclinical stage at all. Others suggest that there is already overregulation in terms of ethics in the academic context. Safety, toxicity, adverse events and long-term effects were also presented by most experienced researchers as ethically relevant topics.

Early-stage researchers related ethical issues to data production and management, such as integrity, reproducibility and security. They stressed the importance of reporting all experimental details in a publication and of publishing so-called "negative results." Some of them mentioned authorship as an ethically sensitive topic. Furthermore, ESRs placed ethics in the context of the relationships within the scientific community, referring to improving mentoring, respecting other researchers, being able to work more collaboratively and the need for more multidisciplinary and multicultural teams. They expressed that, at the preclinical phase, it is important to take into account

the potential impact of the research on people and society, rather than just focusing solely on the individual's scientific topic. Finally, a recurring theme among ESRs was the impact of preclinical research on climate change, with in-depth discussions on waste generation, chemical treatment and sustainable research.

Preclinical research and social impacts: the case of gene therapy in orthopaedics

The overall aim of the research consortium where participants of this study are working is to investigate the applicability of non-viral gene therapy in osteoarthritis and disc degeneration through cartilage regeneration. The societal implications of this preclinical research may be partly topic-specific. However, we have included them because some perspectives and views are general enough to be applicable to other areas of research. They may also be useful in a wider debate about ethics and integrity in preclinical research.

Impact on climate change and biodiversity

Scientists from both groups reflected that preclinical research produces an environmental footprint. All ESRs emphasized the footprint consequences of their research activities, with the issue being raised repeatedly. On the other hand, five experienced researchers were not convinced that preclinical research has an impact on climate change, or that there are other major players responsible for the "real" environmental impact, such as big pharmaceutical companies. ESRs and experience researchers who thought there was an impact cited the use of plastics in preclinical research, the production of chemical and biological waste, the energy used to keep the temperature of some biological samples constant, and the large amount of water used in experiments. ESRs also mentioned that scaling up a new treatment may require more infrastructure, which could generate even more footprint.

Some experienced researchers suggest that the environmental impact of preclinical research is underestimated and should be addressed, and that regulation could help make the process more sustainable. One experienced researcher mentioned the "green lab" strategy as a possible way to address this issue. In addition, some researchers in both groups felt that air travel by researchers should be reduced.

Impact on privacy and personal information

Some experienced researchers emphasized that personalized medicine techniques may pose some risks of donor identification. They also suggested that researchers in preclinical research work with sensitive personal data and that more safeguards are needed to protect this type of data. Some of them

mentioned that details of human tissue donors should not be tracked. Conversely, seven experienced researchers were convinced that preclinical research could have no impact on or influence on privacy. ESRs did not elaborate much on this issue.

Impact on health inequalities

After a general question on the topic, scientists from both groups came up with the economic dimension of health inequalities. They agreed that innovative therapies can be expensive and therefore only affordable by wealthy people in developed countries. They also suggested that these types of treatment may be more efficient and therefore cheaper in the long term. Researchers suggested that these innovations should be accessible and eventually included in insurance or public health plans. Both groups agreed that it is important to discuss the use of public funding for health-related research, as people are researching treatments for rare diseases when many people are dying from prevalent diseases, such as malaria.

They mention the role that the "sex of cells" (verbatim from participants, "sex of cell lines" was what they referred to (Shah, McCormack, and Bradbury 2014)) as well as the ethnic origin and age of the biological material could affect the efficacy of the therapy in diverse populations, so these should be taken into account in advance in preclinical research.

Technical dimensions during the development of the potential therapeutics (i.e., the type of storage that would be required, the technical capacity to deliver the treatment, the technical needs for follow-up) should also be considered at the preclinical stage of research in relation to health inequalities. If more complex conditions are required to use or apply a treatment, it may be difficult to make the treatment available in all economic and cultural settings around the world.

Impact on social well-being, autonomy and mental health

When asked about the potential impact of their research on societal well-being, all participants agreed that positive results from their gene therapy research could improve the quality of life, especially in aging societies, so that the results could have an overall positive impact on global health. Both groups stated that this could also increase the overall autonomy of future patients. Patients could be more autonomous because their mobility could increase and they would be less dependent. Experienced researchers stated that increased mobility provides the opportunity for sport and exercise, which can have a positive impact on other types of illness and increase overall wellbeing. Increased mobility and the possibility of pain relief could have a positive impact on social life and mental health by preventing isolation of future patients.

Both groups also mentioned the economic burden caused by chronic diseases and believed that the potential new therapy could also have a positive impact in this area, as it could help to reduce orthopedic chronic diseases.

Regarding the negative impact that preclinical research may have in the well-being dimension, the ESRs mentioned that taking tissue from dead donors may negatively affect the emotions of the donor's family, as some people have strong feelings against compromising the wholeness of the body. Some of the experienced researchers mentioned that new treatments involving genes may create new frictions in society. If the new treatment has adverse effects, citizens may lose confidence in other similar treatments in the future.

Recommendations or what we can do better in health-related preclinical research

The majority of both groups agreed that more research integrity policies are needed, that more attention should be paid to the mental health of researchers, and that ethics training should be mandatory. ESRs were very concerned about climate change, so their recommendations were to focus on responsible laboratory waste management and waste reduction strategies. They emphasized the need to work on gender equality, diversity and inclusivity in the research process and research ecosystem. Experienced researchers mentioned that scientists working in the pre-clinical phase need to be more involved in science communication. More detailed recommendations are presented in Figure 2.

Discussion

This article provides an overview of the perspectives and views of scientists at different stages of their careers on ethics and integrity in preclinical research.

One of the most important findings is that although most researchers participating in our study can relate to ethics and research integrity in some way, they also recognize gaps in their knowledge. Recent findings indicate a significant discrepancy between what was expected regarding ethics and what was presented in the research proposal of Horizon 2020 (Buljan, Pina, and Marušić 2021; De Waele et al. 2021; Tabarés et al. 2022). A case study conducted with scientists in the field of nanomedicine (Silva Costa et al. 2011) and an in-depth interview study with scientists in regenerative medicine research (Niemansburg et al. 2015) showed similar results. Most scientists in our study linked ethics to guidelines and legal frameworks, and they also reiterated that if an ethical issue is related to their own research, it is similar to others that already exist and have been addressed. This approach

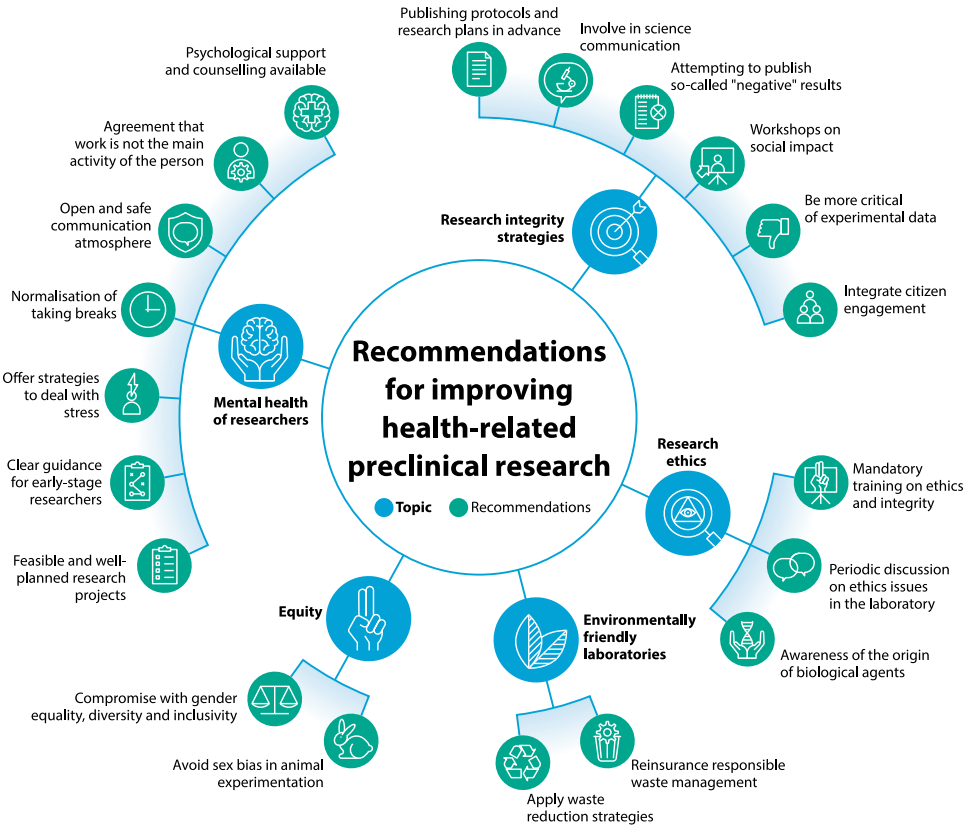

Figure 2. Recommendations for improving health-related preclinical research.

was described by Wolpe (2006), who concludes that scientists avoid thinking about ethics because they consider that their work has little to do with ethics and also that "others will make the ethical decisions" (Wolpe 2006). Jensen et al. (2011) reported data along these lines, showing that scientists perceive ethical and social issues as an external agenda that is somehow imposed on them (Jensen et al. 2011). Similarly, Wäscher, Biller-Andorno, and Deplazes-Zemp (2020) showed in an interview study that scientists emphasized that ethical issues go beyond the expertise of their professional role. They also analyzed that some interviewees expressed the idea that knowledge is morally indifferent, which was also the feeling of our respondents (Wäscher, Biller-Andorno, and Deplazes-Zemp 2020). This could be one reason why scientists in our study did not extensively address unconscious bias as has been found in another studies (Cairns et al. 2021; Davies 2019). Unconscious bias has been associated with unethical behavior, for example, research hypotheses could be framed by incorporating socio-cultural prejudices in designing experiments (Cairns et al. 2021; Davies 2019).

In contrast, Ladd et al. (2009) found that some researchers are aware that scientific processes do not take place in a vacuum and that laboratories exist

in social contexts (Ladd et al. 2009). The ESRs in our study had a similar view of science and were keen to point out that although their research could be very specific and technical, they should keep in mind what they called "the bigger picture," meaning that what they are doing has a social purpose. Moreover, ESRs were also concerned about the research impact on ecology. We found that these concerns relate to the fact that they have a clear idea that research is connected to the social and environmental contexts. This is quite different from what is usually seen in research ethics in biotechnology, and we were surprised when this topic came up. ESRs were not just concerned about these impacts, but they were informed on different strategies that could deal with this situation.

Systemic or institutional issues are mentioned by scientists as an important factor for conducting ethical research, but also for creating a friendlier working environment. Scientists participating in our study are aware that the workplace is an important factor for exercising integrity and ethics in research. Similar results were presented elsewhere (Cairns et al. 2021; Davies 2019; Solomon et al. 2022). On the other hand, ESRs in our study associate ethics and integrity with wellbeing and working in a healthy environment. During the focus groups, they often paused to analyze how their mental health affects the way they work, and how this might somehow make them less sensitive to ethical issues.

As reported in other studies, scientists are motivated to reflect on ethical issues in their work and to participate in ethical discussions and training when opportunities arise (McCormick et al. 2009; Silva Costa et al. 2011). In our study, ESRs showed interest and engagement with the ethical issues, deep reflection on integrity and their own daily experiences as scientists, and a desire to make things better. Experienced researchers were also interested and, in most cases, were available for more than an hour-long interview, stating that the questions were useful for them to reflect on issues they rarely think about. However, some of them were more reluctant to put the ethics and integrity as priority.

Our study has limitations. First, qualitative studies are prone to bias, as a different interviewer/moderator may have focus on different aspects of the participants' interventions and the authors may have analyzed the data differently. Second, all participants and moderator/interviewer were from the same research consortium, although from different countries and with different backgrounds. Nevertheless, the sharing of a professional scenario between the facilitator/interviewer and the participants could contribute to a quicker adaptation to the situation of the interview/focus group, without much effort or calculation (Criado 1998). This is a desirable scenario to engage with the participants in order to address sensitive issues, creating a space of trust and allowing them to be more open. Third, the participants were involved in research into gene therapy for orthopedic conditions, so some of the responses here may be specific

to this topic. Four, most ESRs came from the Global South, while most of experienced researchers are from the Global North. This could be another way of grouping besides career stage.

Despite its limitations, this study provides valuable information on ethics and integrity in health-related preclinical research from the perspective of scientists working in laboratories. These views help to identify key ethical challenges and, when combined with more data, ultimately lead to informed and evidence-based improvements to existing regulations.

Preclinical health-related research has an ethical dimension that impacts day-to-day work. Failure to understand the perspectives of researchers could contribute to overlooking the real needs and problems that arise in preclinical research. The more we consider this in the early stages of research, the better we can address them appropriately in the pursuit of successful science.

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PB and MW declared that they are part of the consortium. JPB, IO and EP reported.

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How to embed ethics into laboratory research

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ABSTRACT

Health-related innovation in biotechnology requires anticipating potential bioethical implications. In this article, we present a strategy to embed ethics in a group of early-stage researchers performing research in gene therapy and regenerative medicine in the laboratory phase. We conducted a series of focus group meetings with early-stage researchers who work in biotechnology laboratories. The objective was to reflect on the bioethical challenges of their own work and to promote the integration of research ethics with laboratory practice. The activity was assessed with questionnaires completed by the researchers before and after the meetings, and the analyses of the focus groups' content. As a result of the focus group series, all participants changed their perspectives about ethical issues regarding their planned research, developed the ability to reflect and debate on research ethics and had increased awareness of ethical issues in their own research activities. Half of them made changes in their research work. The study provides a concrete strategy to embed ethics and to strengthen responsibility in laboratory research. It is a strategy that allows to perform ethics reflection "on site" and in "real time" and complements the classic strategy of ethics assessment of the research protocol before starting the research procedure.

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Biotechnology; ethics; focus groups; biomedical research; research ethics

Introduction

Health-related innovation in biotechnology is a promising field but requires the anticipation of possible bioethical implications (Sugarman and Bredenoord 2020; Nuffield Council on Bioethics 2012; O'Mathúna 2007). The novelty and innovative nature of some branches of biotechnology make this anticipation challenging for various reasons (Stilgoe, Owen, and Macnaghten 2013). First, because it has cross-cutting complexity and it requires interdisciplinary and multimethod research. Second, while the translation from laboratory to clinical trials is not easy, translations to the health system and society are even more

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difficult (Jongsma and Bredenoord 2020; Torres-Padilla et al. 2020; van Delden, Bredenoord, and Solinis 2015). Moreover, health-related innovation may impact social reality on multiple levels, for instance, by changing the way society perceives and understands health, disease, prevention, and therapeutics. At the population level, health-related innovation in biotechnology may impact social inequalities and enhance discrimination or re-defined identity and other human characteristics (Jongsma and Bredenoord 2020; Torres-Padilla et al. 2020; van Delden, Bredenoord, and Solinis 2015). Thus, providing bioethics input for normative evaluation and guidance in the biotechnology development process is crucial (Bærøe, Kerasidou, Dunn, et al. 2022; Sugarman and Bredenoord 2020).

While several guidelines and normative documents on research integrity and ethics are available, there remains a gap in offering a practical approach to embedding ethics in biotechnology research (Bærøe, Kerasidou, Dunn, et al. 2022; Roje et al. 2021; McLennan et al. 2020; Pansera et al. 2020; Zwart and Ter Meulen 2019). Moreover, strategies to embed ethics in the laboratory phase need to be developed, applied, and evidenced (Bærøe, Kerasidou, Dunn, et al. 2022; Zwart and Ter Meulen 2019).

We designed and organized a strategy to embed ethics as part of a multi-sectoral and multidisciplinary European research consortium performing research in biotechnology, with a focus on gene therapy and regenerative medicine (GT&RM). We worked with early-stage researchers who are performing research in the laboratory phase. The aim of this strategy was i) to integrate ethics into laboratory research to identify bioethical problems early, ii) to create input for normative evaluation and iii) to establish a research integrity environment (ALLEA 2017). This article provides the description of the designed strategy and its effects on a group of early-stage researchers performing research during the laboratory phase.

Methods

We conducted a longitudinal series of five focus groups (FGs) between 2021 and 2022. The participants were early-stage researchers (ESRs) from a multidisciplinary European consortium performing research on gene therapy and regenerative medicine (GT&RM). To assess whether and how this strategy enables a real embedding of the ethical approach into ESRs perspectives in their work, we combined two techniques: analysis of the changes in the ESRs' method of debating ethics through the FG meetings and semi-structured questionnaires that the ESRs answered before and after the series of meetings.

Participants

All of the participants ($n = 14$) were ESRs from an established research consortium performing research in biotechnology, with a focus on

GT&RM. They came from Brazil (2), Italy, Spain, Taiwan, Germany, China, The Netherlands, Iran (2), Chile, Egypt, and India (2). Ten of them were women and four were men. They have backgrounds in chemistry, biology (3), engineering, pharmacy (2), biomedical engineering (2), drug delivery, molecular medicine, biomedical science (2), and toxicology. Their research topics relate to cell delivery and efficiency gene modulation, tissue/organ delivery tools, repair in tissue and organ culture, and in vivo imaging of regeneration and gene therapy efficacy. Currently, they are working in Finland, Switzerland (2), Romania, The Netherlands (4), Sweden (2), Germany, Portugal, and Denmark (2) in laboratory settings.

Data collection

We collected data using two different techniques: focus group discussions and survey questionnaires.

Survey questionnaires

Before we started the FG meetings (September 2021) and after we finished all the meetings (May 2022), we provided two self-administered survey questionnaires to all ESRs ($n = 14$). We elaborated both questionnaires with the aim of evaluating the focus group intervention (Creswell 2009). The questionnaires were piloted among another group of PhD students, all of them outside the project ($n = 10$), to make necessary changes and adjustments for the final versions.

The goal of the first questionnaire was to obtain initial insight into the ESR's perspective on ethics in general, and ethical challenges in GT&RM as well as to learn about their experience with ethical training. It has 4 parts and 12 questions that were a combination of open-ended and closed questions (Available in Supplementary Material).

After the FGs ended, the ESRs were provided with a second questionnaire with a set of questions similar to those on the first questionnaire and an additional section for meeting evaluations. It has 5 parts and 18 questions that were a combination of open-ended and closed questions (Available in Supplementary Material).

Using this technique allowed us to capture changes as well as assess the effects of focus group meetings. Both questionnaires were provided to the participants via an online form platform (Microsoft Forms).

Focus groups

The main technique we used was focus group meetings with workshop elements. We chose FGs as a useful tool to integrate all participants' experiences and perspectives and to introduce new concepts (Hennink 2007). FGs could be seen as an adequate setting for social interactions and to exchange

concrete experiences and conceptual abstractions regarding ethics (Timmermans et al. 2020).

– Theoretical framework

Our research strategy was based on three theoretical and practical approaches: i) Ethics Parallel Research (Jongsma and Bredenoord 2020), ii) Social Labs (Timmermans et al. 2020) and iii) the Responsible Research and Innovation framework (EC 2020).

Ethics Parallel Research (EPR) aims to ethically guide the development of biotechnology along and within the process and to provide normative evaluation. When adopting the framework, we followed the three distinctive qualities of the EPR: pragmatic, constructive, and proactive (Jongsma and Bredenoord 2020). We were pragmatic because FGs meetings were done within the ambit of biotechnology development considering the concrete aspects of GT&RM. Our approach was constructive, as we involved researchers in the ethics discussion toward better practices, and not just to point out the negative aspects without any further recommendation. And finally, it was proactive, because our intervention was done along with the researchers interwoven in the field and not at the end of the process.

Social Labs are described as tools that embed and promote social change in a particular context and with a clear focus. They are designed for work in the real world rather than with abstract ideas (Timmermans et al. 2020). FG meetings were the platform for a continuous exchange between conceptual abstractions, like RRI and concepts around ethics, and concrete experiences from laboratory practice. Social interactions within the FGs help to addressed emerging situations that happened in their research process. Actions to approach those situations were discussed and proposed.

Both Ethics Parallel Research (EPR) and Social Labs use the action research approach. This approach allows to collect scientific data, promote experiential learning/training of all stakeholders, and build theoretical and normative input as a result of the entire process (Jongsma and Bredenoord 2020; Timmermans et al. 2020). Our strategy follows the action research approach by offering training for ESRs as well as collecting data that helped us to build input regarding the ethics of biotechnology research in the laboratory phase. Thus, EPR and Social Labs guided us on how to perform a parallel investigation of the development process of GT&RM with specific normative evaluation in real-time and co-produced by all stakeholders.

Responsible Research and Innovation (RRI) is an approach that provides strategies to anticipate, assess, and improve societal engagement and identify potential implications (Burget, Bardone, and Pedaste 2017). The RRI framework aims to make the research process more inclusive and sustainable. The flagship European Commission research programs: Horizon 2020 and Horizon Europe strongly support and require the application of RRI to all research projects (EC 2020). RRI proposes six key rules to embed into

researcher methods: gender equality, open access, citizen engagement, governance, science education, and ethics. We applied all these principles in the design of the FGs.

– Intervention

We set general FGs goals in accordance with the consortium goals: i) to identify bioethical challenges of GT&RM and ii) to promote research integrity. As these goals needed to be fulfilled while the biotechnology was being developed – meaning while researchers where actually working in the laboratory – we thought that embedding ethics would be the best way to accomplish this. Using the Ethics Parallel Research approach (Jongsma and Bredenoord 2020), Social Labs (Timmermans et al. 2020), and RRI framework (EC 2020), we specified practical and specific aims for each FG (Table 1). In this way, we collected scientific data, promoted experiential learning/training of the researchers and built specific normative input for the consortium.

A guide for each FG was designed (Available on Supplementary Material), considering that we should i) explore participants' earlier experience, expectations, and perspectives on ethical issues in general and for their research projects, ii) introduce ethics research concepts applied for similar research they plan, iii) analyze researchers' biomedical techniques and ethical questions, iv) contemplate how to approach those ethical questions, and v) coproduce ideas to improve research ethics in each researcher's own environment. After each FG, and with the support of researchers outside the project's consortium (JPB and IO), we organized briefings and a short evaluation of the results obtained that were used to plan the next FG. In this way, the method used had an element of longitudinal approach in qualitative research (Koro-Ljungberg and Bussing 2013).

1st focus group (October 2021)

Following Social Labs framework, our aim for the first meeting was to start building an environment of exploration, debate, and training (Table 1). To do so, we explained that the meetings were a safe space that there are no right or wrong answers and that this is going to be useful for each of us as researchers. Next, we started exploring general group attitudes about ethics, looking at what they answered in the initial questionnaire, and recognized ethics in everyday situations. Then, we introduced basic concepts of ethics, and we reflected on them.

2nd focus group (November 2021)

Our aim for the second meeting was to strengthen this environment of exploration, debate, and training (Table 1). We started exploring general group attitudes about research ethics and research integrity, and then introducing concepts of research ethics and the Responsible Research and Innovation (RRI) framework. We used answers from the initial questionnaire as the starting point for discussion, we debated how should research ethics

Table 1. Aims of each focus group.

1st FOCUS GROUP • October 2021	
Practical aim	To start building an environment of exploration, debate, and training on ethics.
Specific aims	i) To explore general group attitudes about ethics. ii) To introduce and reflect upon basic concepts of ethics.
2nd FOCUS GROUP • November 2021	
Practical aim	To establish an environment of exploration, debate, and training on research ethics.
Specific aims	i) To explore general group attitudes about research ethics. ii) To introduce and reflect upon about basic concepts of research ethics.
Each ESR presented her/his research goal and research techniques • November 2021	
3rd FOCUS GROUP • March 2022	
Practical aim	To debate about ethical challenges in GT&RM.
Specific aims	i) To explore group attitudes about ethical challenges in GT&RM. ii) To introduce how to identify and debate about ethical challenges in biomedical research.
4th FOCUS GROUP • April 2022	
Practical aim	To debate about the ethical aspects of their research techniques and the consortium technologies.
Specific aims	i) To explore group attitudes about the ethical aspects of their own research techniques and all consortium technologies. ii) To introduce how to deliberate about ethical aspects in research techniques in biotechnologies.
5th FOCUS GROUP • May 2022	
Practical aim	To formulate recommendations for integrating ethics in laboratory phase for biotechnology research.
Specific aims	i) To formulate recommendations that ESRs could apply to integrate ethics in laboratory phase for biotechnology research. ii) To formulate recommendations that institutions should apply to integrate ethics in laboratory phase for biotechnology research.

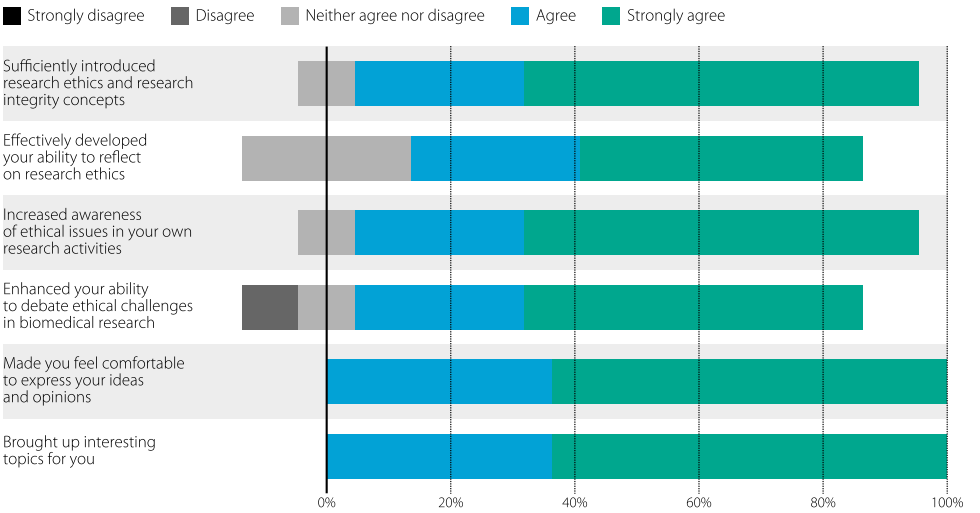

Figure 1. To what extent ESRs agree or disagree about the development and strengthening of skills after the FG process.

apply; we presented RRI principles, and we reflected on RRI keys and violations.

3rd focus group (March 2022)

Our aim for the third meeting was to debate ethical challenges in GT&RM and the consortium goal according to the EPR qualities (Table 1). We explored group attitudes about ethical challenges in GT&RM and we introduced how to identify and debate about ethical challenges in biotechnology research. In this case, we used Jamboards and in small groups we proposed to debate about the social value of the GT&RM, the consortium goal and it ethical challenges. We analyzed the GT&RM and consortium goal through the four values of RRI: open and transparent, diverse and inclusive, anticipatory and reflective, responsive and adaptive.

4th focus group (April 2022)

Our aim for the fourth meeting was to debate the ethical aspects of each ESR's research techniques and the consortium technologies (Table 1). We explored group attitudes about ethical aspects of their own research techniques and the consortium technologies. We introduced how to deliberate about ethical aspects around research techniques in the biotechnology field. We divided the ESRs according to the Work Package (WP) that they belong to: Cell delivery and efficiency gene modulation, Tissue/organ delivery tools, Repair in tissue and organ culture and In vivo imaging of regeneration and gene therapy efficacy. Using MIRO boards, each subgroup had to analyze how the WP topic could impact in various ethics areas: human agency, personal data, social well-being, health inequalities, mental health, climate change, aging population, biodiversity, and increased urbanization.

5th focus group (May 2022)

Our aim for the fifth meeting was to formulate recommendations for integrating ethics in into the laboratory phase for biotechnology research (Table 1). The recommendations were formulated according to each WP and by the same subgroup as 4th FG. Using MIRO boards, they built recommendations for integrating ethics following two perspectives: what ESRs could do/change and what could be done on an institutional level.

- Moderator- Moderator

The FGs were conducted by another ESR of the consortium (PB). She has experience conducting FGs. Moreover, before starting the FGs, we conducted a pilot FG session with participants of similar characteristics (10 ESRs working in biotechnology from different countries).

– Setting

FG meetings were conducted from October 2021 to May 2022. Every meeting lasted a maximum of 90 min. Due to COVID-19 limitations and participation of ESRs from different countries, FGs were performed online using MsTeams platform; all meetings were video recorded with adequate participant consent.

Only ESRs participated in the FGs; there were no senior researchers or supervisors who could influence the opinions of the participants. The atmosphere of the groups was relaxed, and we always ensured that the FGs were a secure place to express any thought, idea, or opinion. As was stated in the Informed Consent, ESRs were reminded that the video recordings were not going to be presented to any other person in the consortium, that all the information and discussions would only be used for research purposes, and, if published, all data would be anonymized (Sim and Waterfield 2019; Daniels et al. 2019) so there was no possibility to link opinions to any particular person from the group.

– Support materials

We used MIRO boards and Jamboards as platforms to work creatively on particular topics. The board's content was saved and used for thematic content analyses.

– Non-participants

Technical support was provided by an ESR from outside the consortium (IO) who was present at every FG.

Data analyses

FGs discussions were transcribed verbatim and pseudonymized. We analyzed qualitative data using thematic content analysis (Bergin 2018; Green and Thorogood 2018). Transcriptions were input into MAXQDA software for analysis. We re-read the transcriptions, questionnaire responses, and boards several times to become familiar with the data (IO and PB). Codes and themes were derived from the data.

Qualitative parts of the questionnaire were analyzed as described above with FG transcriptions. The quantitative parts of the questionnaire were analyzed using statistical tools in Excel. We mainly used descriptive statistics (distributions) as well as graphs to summarize the answers.

Data reporting

We use the comprehensive consolidated criteria for reporting qualitative research (COREQ) to report our research (Tong, Sainsbury, and Craig 2007) (Checklist available on Supplementary Material).

Ethical considerations

The protocol, informed consent form, General Data Protection Regulation (GDPR) form, and the information for participants' page were approved by the Bioethics Committee of Jagiellonian University, Krakow, Poland (No. 1072.6120.209.2021 – 29/09/2021). Participants were individually

informed by e-mail about the aims of the study, what their participation involved, why they were invited, the risks and benefits of their participation, and that the sessions would be videorecorded. We sent them information about the FGs, GDPR form, and the informed consent form. The dates for FGs were agreed in advance for the five meetings.

Results

Start point

In the first questionnaire, the ESRs were asked whether they thought that GT&RM could have ethical challenges. We also asked whether their research topics and methods could have potential ethical challenges. For both questions, 42.9% (6 out of 14) answered no. Moreover, only 35.7% (5 out of 14) of the participants reported to have trained or taken courses on ethics, research ethics, or research integrity before starting the FG meetings.

The FG process

We found explicit changes not only in ESRs' way of perceiving ethics, research integrity, and bioethics in GT&RM during the course of the meetings but also in their responses to the questionnaires before and after the FGs, which contained similar questions. Improvements on how participants perceive and debate about those topics were also observed during the FGs.

In general, we found that, at the beginning, participants had common and more abstract intuitions about what "ethics" is or to what it is related. The most repeated words associated with ethics were: values, norms, moral, principles, and rules. At the end, participants came up with more complex definitions of ethics. We can see differences between meetings in Table 2.

In terms of research ethics, when we began the meetings, participants were focused on the issues of animal use and manipulation of human embryos or ethical misconduct: falsification and fabrication of data. When we analyzed what had happened through the FGs and the final questionnaire, we found that the initial topics became broader and deeper. The participants also had clear thoughts about the consequences of conducting research without ethics. We can see differences between meetings in Table 3.

After the first two meetings, we talked about ethics and research ethics; we applied all this to GT&RM research techniques and work in the laboratory. We spent three meetings working on these areas (Table 1). Participants were able to reflect about their own activities in the laboratories and the methods they were using. We present some quotes according to specific topics that they came up with in Table 4.

Table 2. What ethics means for the participants.

Before the meetings	After the meetings
Set of norms that guide our conduct and actions.	For me, ethics is a way of conducting your day-to-day life. Every action involves an ethical process that every person has in their minds or has learned while growing up.
Ethics describe the way and the behavior humans interact between each other.	Ethics still means common values of good and bad that are not necessarily bound to law but are valid, nevertheless. Ethics are omnipresent and important. Ethics are not only important regarding big things, such as climate change or war and peace, but also regarding personal well-being in your job and for small things such as lab waste or who to hire for a position.
All that concerns human behavior and the morality behind people's actions.	Thinking consciously about the effect your actions have on yourself, other people, and the environment. Debating whether, when taken into account the effects, these actions should be changed or even canceled. This can range from everyday actions to bigger picture things.
Ethics, for me, are the group of moral principles that leads a person to behave a certain way. I think there are basic principles of ethics that should be followed, trying to be honest and respectful.	
Ethics, to me, is a branch of philosophy that differentiates the good and the bad through a series of understandings.	

At the final meeting, the participants explicitly expressed that they were not familiar with ethical concepts before the FGs started. When they heard the word "ethics," they never imagined it to be something that is involved in all activities of researchers specifically and people in general.

> Especially for me when I started, I had no idea about this, so … So yeah, like spread the word between our colleagues and try to make them understand how important ethics is.

They also stressed that traditional training ("sitting there, listening," as one of the participants defined it) would not allow for the full engagement of the ESRs. They appreciated that FGs were created in a way that they had the chance to contemplate things together and talk to each other, sharing questions and doubts without feeling judged.

> The good thing about our talks was that we were talking to each other, we weren't sitting here listening to you talk, so that's what helped me at least to understand. Because, ethics, like it doesn't attract people to come and listen but when you talk, when you interact with each other, it's just then that it gets really nice.

They agreed that the meetings were interesting and would have a long-lasting effect, because the mix of their backgrounds with the laboratory research activity and the ethics approach *in vivo* was a combination that they appreciated. And they expressed that this meeting should be established in all research groups.

> I think that would be making sure that in these grant applications or in these projects from EU, for example, there is that Work Package dedicated for ethics, like this. It's very difficult to have in the ethics in mind, if you have never heard about it. So I think it's very important to have that role [people that are working

Table 3. What research ethics means for the participants.

Before the meetings	After the meetings
The first example that comes to mind is performing procedures without prior consent from the test subject, for example in the case of the scientist from China "creating" CRISPR babies.	If you fabricate or falsify your results, then other people will build on that, and you will continue and continue the process of using wrong data and the wrong information to however far you go.
The publication of false data just because you need to publish something. Manipulate results in order to get funding.	We want to end up achieving something worthwhile – in our case in terms of cartilage regeneration for example. And the thing is that if you create data if you falsify the results and with that stuff, it is really difficult to achieve anything because – I think, the major problem is that sometimes the goal is confused because for some researchers the goal is just to publish because it's what it's going to give them the money [. . .] And if you systematically fabricate or falsify data and results, you're not gonna achieve anything. You may publish a lot because of what results you have, but they're not true so what are we doing in the end?
Use of animals for research.	Is it justified to let animals suffer so we can develop drugs/treatments only intended for humans? Can we weigh the lives of thousands of animals against the lives of humans? Is there a difference of worth in an animal life compared to a human?
I mainly think about people fabricating results, and maybe altering their results in such a way that it fits their expected results/story. This doesn't always have to be straight up fabrication but may also just be slight adjustments in machine settings for instance, that lead to different results.	I think also like this has great implications and not just in the frequency, but also the impact it has; for example, the falsification part where like that one guy and his colleagues published that one paper on how vaccine leads to autism, fueled all the antivaxxers. Now, we have this epidemic – sort of – antivaxxers and this could definitely be avoided if he just decided not to publish fake stuff and with bad research methods and basically falsifying his results as well.

fully on ethics] in every project, so is like these ethics training are implemented in the, you know, projects.

When we finished the FGs, to control that the results are mainly linked to the FG meetings, we determined whether the participants had participated in any organized activity regarding research integrity or ethics in the period during which our meetings were held; 57,1% (1 (8 out of 14) did not participate in any activities, while among the 42,9% (9 (6 out of 14) that had, the topics reported were risks and benefits of gene therapy, introduction to bioethics, gender bias, relationship with supervisor, tampering of data, and animal welfare.

At the end of the FG process

Development and strengthening of skills

In the post-FG questionnaire, most participants agreed that thanks to the meetings they learned about research ethics and research integrity concepts, developed the ability to reflect and debate on research ethics and had

Table 4. Participants reflections about their own research activities.

Topic	Quotes
animal welfare	For me, I think someone said in another focus group before, but to me these ethical things has [have] related in cell culture room, with serum fetal bovine, because we need to use this … yeah, this is coming from fetal, you know … and for me this is also plastic, but for me when I have to use serum, I always think in the poor fetal bovine.
	What comes to my mind is then also like animal experiments and how you can justify animals for research, that won't benefit animals in the end, but humans. And also kind of maybe thinking, OK, how many animals can I use, or can be killed, or can die for like how many people? For example, if you have like really real diseases, do you really want to … How much worse can you weigh up the worst of an animal to the people, or not.
environmental impact	Right now, I realized that like now that I started working with cells and with biological waste and with all these plastic things, I realized that's a huge thing …
	We are producing a lot of waste in our research, like biological waste but also chemicals, or plastics, which always affect the climate in some way, and also the oceans.
	The plastic that we use for experiments are not good for the environment, also, we have a lot conscious about it. Regarding toxic reagents for, that sometimes we need to use and are not always disposed properly. And always … in some experiments we need to use a lot of water and yeah, we waste a lot of.
	I would also add maybe just looking at all the plastic waste you make actually when you do pipetting and stuff like that. Sometimes I'm like OK: do I really have to change the pipette now, or … But then again also it's like always a bit of: if I don't change the pipette now, is it like affecting my experiment or not? Or is it now like in the end are they all gonna end up in the sea in the end?
use of human cells and tissue	We have to use human tissues, and sometimes especially for the intervertebral disc, which is in our case also taken from dead people which means that we are compromising their "Wholeness" [drawing a circle with her hands] – like the body wholeness – which might, for some people, also is then kind of in connection with reducing their dignity maybe.
	I use the cells in a daily basis, and I need to just stop and think that the cells that I am using are from the human.
	I also sometimes use human tissue, also from people that have died. And then to see, what kind of … at least have in mind: OK, this is now from a person that died, not for the research but in general, so that you kind of really have in mind: OK, I don't want to waste this tissue now, I really want to make use of it. Because the person also wanted to have … . Because he agreed that it can be used for research and maybe you also kind of hope, OK, maybe some results can get from that. So, kind of to have that in mind, and not just like waste it.
	It's really important for all of us ESRs to indeed be aware where tissues and cells come from as well as the agents.

(*Continued*)

Table 4. (Continued).

Topic	Quotes
health inequalities and social justice	maybe the people who are in Europe or who are richer or who are very sound enough can only afford so this can also lead to inequality if we come out with a delivery system it might be difficult to reach out to the public at large.
	This consortium is a EU-funded project, so the EU money goes into the project. And that is not – there is no guarantee that, again, this is a success. It could fail. Which means that there is also money lost actually for the society and maybe other social matters actually that might be for some people more important [. . .] could the money better go to educating about healthy food and healthy lifestyles instead of looking into what is then caused by this lack of educating people on eating healthy and exercising healthy.
	You try to create cheap and new methods for detecting cartilage defects. And for example, by using the imaging, we can avoid in the future doing surgeries or whatever, so it would be a lot cheaper to do that.
	Of course, if you're not sick, if you don't have any disease, you're fine, you can be fine also mentally. And this can have an impact also on society, due to the lower burden financially.
human health	any gene therapy approach is quite new, and then it's like: OK we don't know really what kind of side effects it might have maybe, or that it's a bit like still not very much predictable. What happens if you then really apply it even like either in animal trials or also later on humans. That might have like some side effects that we could not … maybe are not possible to foresee? And whether that's maybe ethical to actually whether yeah … it's ethical to actually do that, if we don't know like the whole extent of the consequences.
	If we can improve, we can find any good treatment, this can have an impact on an increased mobility, decreased pain, so, of course, people can be more autonomous and also this affects also the dignity. Because if you don't have to ask the others to do things, then, yeah …
	it's important to periodically keep in mind the bigger picture of the study and because it's so easy to caught up in like what is right in front of you, it becomes like a very short sighted. But in essence we are, you know, doing this to solve problems, solve big problems, basically. So always kind of have that in your mind.
gender equality within the science community	On this point then they have also … they can have a suggestion for the institutions. So what they can do. Of course they can integrate the gender equality on all levels and this in the research, so they can push to have always test on all the donors, not only male donors.
	And yeah, of course, they have to push the diversity and inclusivity to the labs.
sex of the cells	So you know that final goal is to develop some therapeutics and for this maybe we have to think also about the gender of the. in research, the donors, animal, human cells or tissue. Because now we are starting to think also about gender medicine. Because we have really a lack on this. We were testing only on men samples, so we include also these … always think about the gender of the donor that we're using.

(*Continued*)

Table 4. (Continued).

Topic	Quotes
data integrity	I also think more of the results and the way they are handled. Whether they are generated in a good and trustworthy way, as well. How much I can trust the other people as well, to have, you know, good research practice and if they thought about everything.
	Like being accurate and honest about your results, and also that like a … today there's a big pressure for significant results in the world of science. So if you don't have like significant results, it means that your research is not of good quality. Which is not true. So … Negative results are as important for science as significant results
	I think just to kind of like … ethical behavior … like in the scientific workspaces, maybe also to really maybe crosscheck also maybe now your statistics and see: OK, did I actually used to write statistics or did I just use the statistics that look nicer on my results and show like something significant which isn't there.

increased awareness of ethical issues in their own research activities (Figure 1).

Implications in GT&Rm research

In the post-FG questionnaire, all participants agreed that the GT&RM has potential ethical challenges. In this sense, when we highlighted the potential ethical challenges in their work or methods which are all part of GT&RM research, they also agreed that their research topics and methods could face potential ethical challenges.

All participants conveyed that if they could affect change, they would change things to improve their research in terms of ethics and integrity. Half of them had already made changes or taken additional actions related to research integrity or ethics in their own project, as a result of the debate during FG meetings. They reported some of these changes in the final questionnaire:

Proper disposal of plastic waste and less use of plastic during experiments.

To accept negative results, analyze carefully and rework.

Pay more attention to sex/gender of the donor I am receiving material from

Trying to keep in mind the things I have learnt, trying to be more conscious about what I am dealing with and the impact that my actions can have.

Really take animal welfare into account.

Participants' receptivity

In the post-FG questionnaire, 64,3% (9 out of 14) of the ESRs were very satisfied with the FGs, while 35,77% (5 out of 14) were satisfied. None of them reported being very dissatisfied, somewhat dissatisfied, or neither

dissatisfied nor satisfied. Moreover, all participants agreed that they felt comfortable expressing their ideas and that the topics were interesting for them (Figure).

Added value

As an added value of the FG meetings, unplanned activities were inspired by the meetings: The ESRs started a new research project on one of the topics discussed in the FGs.

Moreover, ESRs felt that the meetings were important not only to improve their research process but also to contemplate ethics in daily life. In the post-FG questionnaire, one of the participants declared:

> I just want to point out how useful and insightful these sessions have been. It was very nice to have a safe space where we could discuss everything that concerned us in our journey as PhDs and it provided us a great opportunity to understand how ethics are present in our day-to-day life, not only as scientists but as people :) Thank you!

Discussion

The FG meetings with ESRs allowed us to provide contextual and real-time ethical guidance, support good scientific practice, and recognize the social impact of biotechnologies under development. The most important dimension of this experience is inclusion and involvement of researchers who were actually working in the laboratories. This dialectical relationship between discussions in FGs and simultaneous real-time empirical research was what the ESRs most appreciated; they were also fully involved in rethinking and debating about ethics in their own research process. Implications in their laboratory practice can be clearly seen in the changes they already have made thanks to the meeting. Some of these changes are regarding animal welfare, waste disposal, deal with "negative" results, pay attention to sex of donor cells or tissue, and more consciousness that actions have impacts, among others.

There is an increasing need for better integration of ethics in multiple areas (McLennan et al. 2022; Diaz-Martinez et al. 2019). The strategy of embedding ethics is one step in this direction but still is in the process of developing clear standards of practice (McLennan et al. 2022; Plemmons et al. 2020; Diaz-Martinez et al. 2019). So far, embedding ethics has been applied in particular areas of research, mostly artificial intelligence and robotics (McLennan et al. 2022; Battistuzzi et al. 2018), biomedical research (Pansera et al. 2020; Sugarman and Bredenoord 2020), public health (Fiske et al. 2020), clinical settings (Bruce et al. 2014), and education (Langerman et al. 2020). In all cases, the authors agreed that richer descriptions of both good and bad experiences with ethics engagement are needed to help inform

the refinement of these approaches (McLennan et al. 2022; Sugarman and Bredenoord 2020).

As revealed by the results, the entire approach was effective for this group in terms of researchers not only changing their minds and becoming more aware of ethics and research integrity in a practical sense but also making changes in their work process. Moreover, and as important as the previous point, researchers were satisfied or very satisfied with the FG meetings. We highlight this point because usually ethics and research integrity are not the most popular topics for STEM scientists (Root Wolpe 2006), although this may not have to do with the topics themselves but with the way they are approached (Laas et al. 2022). Another important point of this experience was that ESRs were able to recognize not only the traditional bioethics aspects – such as risk-benefit analysis – but also the social perceptions on health, disease, justice, and the environmental impact – of GT&RM research.

To show how to promote ethical reflections for scientists and how this impacts their research is the major implication of our study. Even though there are many ethics guidelines and more awareness on research ethics, it is difficult to engage all this in day-to-day research practice, especially in laboratory settings (Laas et al. 2022; Resnik et al. 2021). FG meetings in this experience encouraged proactive discussions and facilitated the exchange of experiences, doubts, and ideas within the research process that were action oriented for those who were working in laboratory setting. The assessment of this experience indicates the benefits of integrating ethics in research consortiums such as the commitment of the researchers with ethics in relation to their work methods and research objectives, the actions they took after this intervention, and extra activities that arose from co-producing ideas and reflections.

Limitations

Our analysis should be interpreted in the light of the following limitations. First, the specific setting of the group and the number of the participants do not allow for generalization of our findings. Our intention is to provide information based on evidence-based practices that could be applied in similar settings. Second, FGs were performed on-line and the on-line setting could influence the way participants interact. However, the on-line setting not necessarily is a disadvantage since some studies comparing on-site and on-line FG settings show that discussions are similar, with sensitive topics being discussed more openly in online settings in some cases (Woodyatt, Finneran, and Stephenson 2016). Third, FGs depend on the dynamic and the personalities participating within FGs. For example, discussions may be dominated by three or four individuals. We tried to limit this by moderating the sessions. Fourth, the analyzing group was established beforehand. The fact that participants knew

each other previously could have resulted in the different results, for example by making the intervention more impactful.

Conclusion

In conclusion, this article provides a concrete method to embed ethics in real-time and effectively serve as a tool to strengthen responsibility in research. The contribution to a better development of scientific conduct is an objective itself, but it is also a step to achieve greater confidence in society toward scientific advances.

Considering the type of intervention and methods used, we do not pretend to generalize findings. We rather want to highlight a potential way of embedding ethics into laboratory research and present results, which should inspire more research. This eventually allows to build an evidence basis for methods and techniques on how to embed ethics into laboratory research.

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PB and MW declared that they are part of the consortium.

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Appendix 4: The PRISMA-Ethics Reporting Guideline.

Manuscript: **Bioethics of somatic gene therapy: what do we know so far?**

From:

Kahrass H, et al. PRISMA-Ethics - Reporting guideline for systematic reviews on ethics literature: development, explanations and examples. 10.31219/osf.io/g5kfb [Preprint]. Available from https://osf.io/g5kfb

No. of item		**Reported in # section (including paragraphs)**
Title		
1	**Title**: Identify the report as a systematic review.	Not reported
Abstract		
2	**Structured summary**: Provide a structured summary including, as applicable: objectives; ethics literature eligibility criteria; information sources; ethics literature appraisal and synthesis methods; included publications; synthesis of results; limitations of evidence; interpretation (conclusions and implications of key findings); funding; systematic review registration number.	Reported in a modified way with respect to journal requests for unstructured abstracts.
Introduction		
3	**Rationale**: Describe the rationale for the review in the context of existing knowledge.	Introduction (Paragraphs 1-4)
4	**Objectives:** Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction (Paragraph 5)
Methods		
5	**Eligibility criteria**: Specify the inclusion and exclusion criteria for the review (e.g., years considered, language, type of publication) and give a rationale.	Methods (Eligibility criteria)
6	**Search strategy:** Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify publications. Specify the date when each source was last searched or consulted. Provide the rationale for using the information sources and present the full search strategy, including any limits and filters used, such that it could be repeated.	Methods (Search strategy); S2 Appendix
7	**Selection process**: Specify the methods used to decide whether a publication met the inclusion criteria of the review, including how many reviewers screened each record and each publication retrieved, whether they worked independently and how disagreements were resolved, and if applicable, details of automation tools used in the process.	Methods (Selection process)
8	**Data extraction**: Indicate which sections of the publication were analysed and how were the data extracted from the publication. If	Methods (Data extraction); S3 Appendix

	applicable, state the software and details of automation tools used in the process.	
9	**Identification of codes and themes:** Explain the process of assigning the codes, themes, or items (e.g. inductive, deductive, a combination of deductive and inductive strategies), if applicable. If so, describe the process for coding of data (e.g. line by line coding to search for concepts), including how many reviewers analysed each publication. List and define all other variables for which information were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods (Identification of codes and themes)
10	**Quality appraisal:** Indicate whether a quality appraisal was performed and why, and if yes, outline the quality appraisal process and its results (e.g. how many reviewers assessed each study, did they work independently).	Methods (Quality appraisal)
11	**Synthesis methodology:** Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology (e.g. thematic analysis, content analysis, critical interpretive synthesis, grounded theory synthesis, narrative synthesis). Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods (Data extraction)
Results		
12	**Publication selection process**: Describe the results of the search and selection process, from the number of publications identified in the search to the number of studies included in the review, with a flow diagram (including reasons for exclusions at each stage).	Results (Publication selection process); Figure 1
13	**Characteristics of publications**: For each publication, included in the review, present characteristics for which data were extracted and provide the citations.	Results (Characteristics of publications); S5 Appendix; S6 Appendix
14	**Results of syntheses:** Present the results (e.g. new systematization of issues or arguments) and reference publications as evidence.	Results (Results of syntheses); S7 Appendix
15	**Quotations**: Provide original wording to illustrate themes, if applicable.	Not applicable
Discussion		
16	**Summary**: Summarize the main findings and provide a general interpretation of the results in the context of other evidence; consider their relevance to key groups (e.g. health care workers, academics, other decision maker).	Discussion (Paragraphs 2-5)
17	**Strength and limitations**: Discuss strengths and limitations of the publications included in the review and the review process itself.	Discussion (Paragraph 7)
18	**Conclusions**: Discuss implications of the results for practice, policy and/or future research.	Discussion (Paragraph 6)
Other Information		

19	**Registration and protocol**: State whether the review was registered, or state that the review was not registered. If yes, provide registration information for the review, including register name and registration number. Indicate where the review protocol can be accessed, or state that a protocol was not prepared. Describe and explain any amendments to information provided at registration or in the protocol.	Methods (Paragraph 1); S1 Appendix
20	**Support:** Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding
21	**Competing interests:** Declare any competing interests of review authors.	Disclosure statement
22	**Availability of data, code and other materials:** Report which of the following are publicly available and where they can be found: template information collection forms; information extracted from included studies; information used for all analyses; analytic code; any other materials used in the review.	-

Appendix 5: Search strategy in all databases.

Database	*Search strategy*
PubMed	("Genetic Therapy"[Mesh] OR "Gene Transfer Techniques"[Mesh]) AND ("Ethics"[Mesh] OR "Bioethics"[Mesh] OR "Morals"[Mesh] OR "Social Validity, Research"[Mesh] OR "Patient Acceptance of Health Care"[Mesh] OR "Value of Life"[Mesh] OR "ethics" [Subheading]) Filter used on Species: Humans Filter used on Languages: English and Spanish
Lilacs	"Bioetica" or "Etica" or “Moral” [Descriptor de asunto] and "Terapia Genetica" [Descriptor de asunto] or "Tecnicas de Transferencia de Genes" [Descriptor de asunto]
PhilPapers	"ethics" AND "gene" AND (transfer | therapy)
Google Scholar	Spanish search: (Etica OR Bioetica) AND (Terapia genetica OR Terapia genica OR transferencia genetica) English search: (Ethics OR Bioethics OR Ethical) AND ("Gene therapy" OR "Gene transfer") AND Research Filter used: Patents or citations not included

Appendix 6: Data extraction documents design (originally in Excel forms)

Data extraction document 1 (for article characteristics)

Article Title	**Article Type**	**Journal Title**	**Year**	**Language**	**Field**	**Authors**	**Database**	**Reference Number**

Data extraction document 2 (for article characteristics)

Article	**Author**	**Affiliation**	**Country**

Data extraction document 3 (for arguments extraction)

Category	**Argument**	**Reference Number**

Manuscript: More ethics in the laboratory, please! Scientists' perspectives on ethics in the preclinical phase

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

From:
Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007;19(6):349–357.

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the focus group/interviews?	Page 5,6
2. Credentials	What were the researcher's credentials? *E.g. PhD, MD*	Page 5,6
3. Occupation	What was their occupation at the time of the study?	Page 5,6,15
4. Gender	Was the researcher male or female?	Page 5,6
5. Experience and training	What experience or training did the researcher have?	Page 5,6
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	Page 5,6,15
7. Participant knowledge of the interviewer	What did the participants know about the researcher? *E.g. personal goals, reasons for doing the research*	Page 7
8. Interviewer characteristics	What characteristics were reported about the facilitator? *E.g. Bias, assumptions, reasons and interests in the research topic*	Page 5,6,15
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *E.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	Page 6
Participant selection		
10. Sampling	How were participants selected? *E.g. purposive, convenience, consecutive, snowball*	Page 4
11. Method of approach	How were participants approached? *E.g. face-to-face, telephone, mail, email*	Page 7
12. Sample size	How many participants were in the study?	Page 4
13. Non-participation	How many people refused to participate or dropped out? Reasons?	No one
Setting		
14. Setting of data collection	Where was the data collected? *E.g. home, clinic, workplace*	Page 4,5,6
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Page 4,5
16. Description of sample	What are the important characteristics of the sample?	Page 4

	E.g. demographic data, date	
Data collection		
17. Focus group guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Pages 4,5,6
18. Repeat interviews	Were repeat focus group/interviews carried out?	No
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Page 4,5,6
20. Field notes	Were field notes made during and/or after the focus group/interviews?	No
21. Duration	What was the duration of the focus group/interviews?	Page 4,5,6
22. Data saturation	Was data saturation discussed?	No
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	Page 5,6
25. Description of the coding tree	Did authors provide a description of the coding tree?	No
26. Derivation of themes	Were themes identified in advance or derived from the data?	Page 5,6
27. Software	What software, if applicable, was used to manage the data?	Page 5
28. Participant checking	Did participants provide feedback on the findings?	No
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? *E.g. participant number*	Results section
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Results section
31. Clarity of major themes	Were major themes clearly presented in the findings?	Results section
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Results section

More ethics in the laboratory, please! Scientists' perspectives on ethics in the preclinical phase

Focus groups guides

1st FOCUS GROUP GUIDE

---

1. Scene setting and ground rules (5 minutes)
1.a. Personal introduction:

My name is Paola, as you know, and I´m an Early-Stage Researcher in CARTHAGO project as all of you. Thank you so much for being here, and I'm looking forward to discussing and exchange ideas and thoughts with you. Ida will stay with us doing the technical support, so if you had any problems send her direct message and she will help you.

1.b. Outline of the research topic and purpose of the study:

Our meeting is part of one of the work packages of CARTHAGO: 2.5.

Work Packages 2.5 is about responsible research and innovation, following Horizon 2020 aims. The idea is to establish an educational framework towards the integration of ethics in research. Ethical issues of a novel biomedical intervention are identified and evaluated parallel to development of the field, rather than at the end-of-pipeline

The plan is to have several and periodical meetings to think, exchange ideas, debate different issues related to ethics.

1.c. Motivation to participate:

This meeting is for us, for all of us. As Work Package established, in these meetings we have to think about ethical issues on our research process, from our perspective. The important issue is that the perspective that matters is ours. And the framework that we start to build here will help us to be better scientists.
Also, what we start doing today is an innovative way of practice bioethics, so we are also being part of something kind of Avant Gard.

1.d. Ethics, confidentiality, and data process:

All these discussions were approved by the ethics committee of the Jagiellonian University Medical College, Cracow, Poland.

We will record this meeting. Recordings will be used only for research purposes. Data will be stored in safe place, following the EU General Data Protection Regulation (GDPR), as you already know after signing GDPR and inform consent form.

1.e. How to participate in the right way? Structure and rules

How our meetings will look like: This is an open discussion. I will ask questions, show you videos and pictures to start our conversation. You should feel free to say what you think, to present doubts that you may have, or to share some experiences and comments. We are on a safe environment here. It is important to know that there are no right or wrong answers. All points of view are important and welcomed. It is also important to agree or disagree with other participants because our goal is to hear as many as thoughts as possible.

Practical rules:
- Try to participate in every topic.
- Always talk to the group and not to each other in sub-groups.
- Raise virtual hand every time you want to say something - this will help us to organize the discussion better.

Do you have any doubts or questions?

---

2. Individual introductions (15 minutes – could be 5 minutes longer)

At the beginning, I'd like us to introduce ourselves. Some of us already did this, but we have new colleagues here so let's say few words about ourselves.

So, I will start – I am Paola, from Argentina, Italian citizen, a medical doctor, with a master in bioethics, and living in Krakow since April and working a lot in my PhD, which is about doing an ethical and real-time evaluation of non-viral gene therapy and orthopaedic regenerative medicine.

Could you please introduce yourself by saying your name and your field of work and background?

---

3. Discussion (50 minutes - could be 5 minutes longer)

3.1. As you know, all our meetings will be dedicated to ethics. Today I'd like to talk about your understanding of ethics and opinion about it. I'd like to start from ethics in general.

I'll show you a word cloud made from your answers about what ethics means to you.

PPT first slide: ethics word cloud

You can see your answers and what other said. Now I'd like to discuss **how you understand ethics and what meaning of this concept from the slide is closer to your understanding**.

3.1a. Would like to add anything to this slide?

3.2. What examples of ethics in daily life situations come to your mind?

3.3. Let's watch together this video: **https://www.youtube.com/watch?v=u399XmkjeXo**
What`s new for you after this video? Was there something we haven't discussed today?

---

5. Ending the discussion (1 minute)

Do you want to add something or ask any question?

Thank you so much for your engagement and your interesting thoughts in our discussion. I do appreciate it. Thank you for very useful contributions.

It will be very helpful for building a framework of good science and research. We will continue discussing about similar topics and as follow up next time.

Let me remind you that this data will be storage in a safe manner.

See you soon!

2st FOCUS GROUP GUIDE

1. Scene setting and ground rules (5 minutes)

1.a. Personal introduction:

My name is Paola, as you know, and I´m an Early-Stage Researcher in CARTHAGO project as all of you. Thank you so much for being here, and I'm looking forward to discussing and exchange ideas and thoughts with you. Ida will stay with us doing the technical support, so if you had any problems send her direct message and she will help you.

1.b. Outline of the research topic and purpose of the study:

Our meeting is part of one of the work packages of CARTHAGO: 2.5.

Work Packages 2.5 is about responsible research and innovation, following Horizon 2020 aims. The idea is to establish an educational framework towards the integration of ethics in research. Ethical issues of a novel biomedical intervention are identified and evaluated parallel to development of the field, rather than at the end-of-pipeline

The plan is to have several and periodical meetings to think, exchange ideas, debate different issues related to ethics.

1.c. Motivation to participate:

This meeting is for us, for all of us. As Work Package established, in these meetings we have to think about ethical issues on our research process, from our perspective. The important issue is that the perspective that matters is ours. And the framework that we start to build here will help us to be better scientists.
Also, what we start doing today is an innovative way of practice bioethics, so we are also being part of something kind of Avant Gard.

1.d. Ethics, confidentiality, and data process:

All these discussions were approved by the ethics committee of the Jagiellonian University Medical College, Cracow, Poland.

We will record this meeting. Recordings will be used only for research purposes. Data will be stored in safe place, following the EU General Data Protection Regulation (GDPR), as you already know after signing GDPR and inform consent form.

1.e. How to participate in the right way? Structure and rules

How our meetings will look like: This is an open discussion. I will ask questions, show you videos and pictures to start our conversation. You should feel free to say what you think, to present doubts that you may have, or to share some experiences and comments. We are on a safe environment here. It is important to know that there are no right or wrong answers. All points of view are important and welcomed. It is also important to agree or disagree with other participants because our goal is to hear as many as thoughts as possible.

Practical rules:
- Try to participate in every topic.
- Always talk to the group and not to each other in sub-groups.

- Raise virtual hand every time you want to say something - this will help us to organize the discussion better.

Do you have any doubts or questions?

---

2. Discussion (40 minutes – could be 10 minutes longer)

We will start with research ethics today, also in a general way.

2.1. What do you think, which research topics need to be ethically considered or on what elements of research process ethics should be applied? Why?

2.2. I will share with you the word cloud with your answers about ethical issues in scientific work. What meaning of the slide is closer to your understanding? Would you like to add anything to the slide?

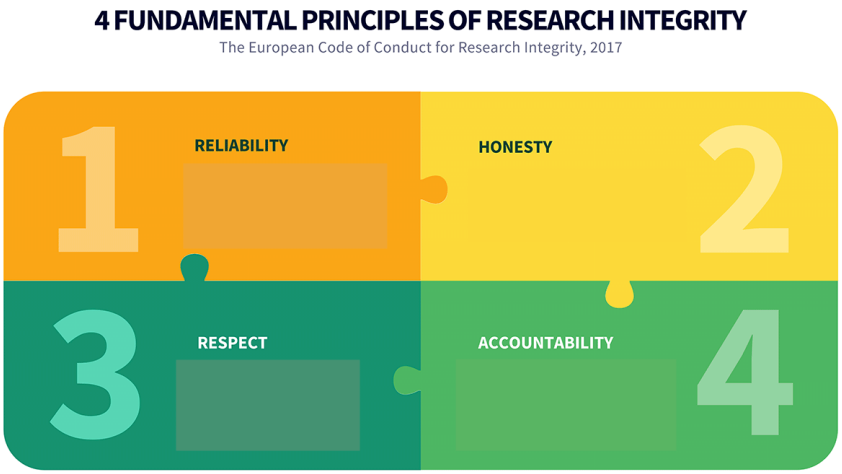
PPT first slide: research ethics word cloud

2.3. What do you know about Responsible Research and Innovation (RRI)?

2.4. Is there any relation between research ethics and RRI? Why?

2.5. Do you hear about the ALLEA (All European Academies) Code of Conduct for Research Integrity? The European Commission recognises the Code as the reference document for research integrity for all EU-funded research projects and as a model for organisations and researchers across Europe.
The European Code have stablished 4 fundamental principles of research integrity:

PPT second slide: 4 principles of RRI



Can you describe and give an example of each of them? Let's do it on Jamboards

Jamboards

Now, I will share with you the official definitions of that principles:

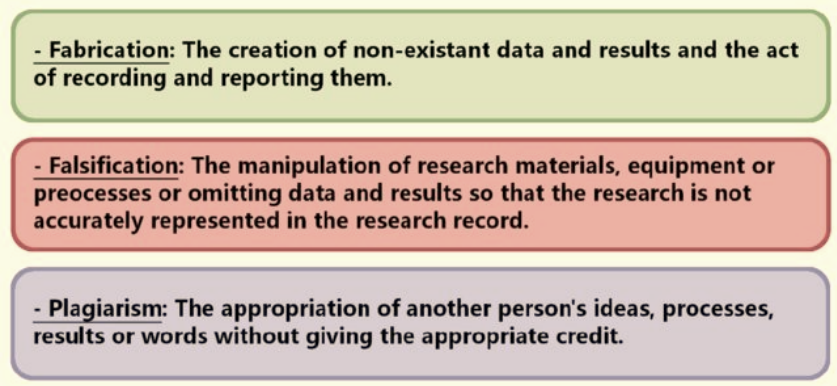
PPT third slide: definitions of 4 principles of RRI

2.6. Considering these are the principles of good practices, what do you think are the ethical violations of these principles?

Wait for answers

Let's take a look on these ethical violations:

PPT fifth slide: 3 ethical violations



2.7. What's you guess – are these violations frequent or not?

2.8. Why are these actions not supposed to be done? What are the consequences of this actions?

*In case we have time:

Considering all what we have discussed today: How can we think about the relation between ethics in daily life and ethics in research?

How do you perceive relation between legal regulations or institutional norms about research and research ethics?

---

3. Ending the discussion (1 minute)

Do you want to add something or ask any question?

Thank you so much for your engagement and your interesting thoughts in our discussion. I do appreciate it. Thank you for very useful contributions.

It will be very helpful for building a framework of good science and research. We will continue discussing about similar topics and as follow up next time.

Let me remind you that this data will be storage in a safe manner.

See you soon!

3rd FOCUS GROUP GUIDE

---

1. Scene setting and ground rules (2 minutes)

Thank you so much for being here, and I'm looking forward to discussing and exchange ideas and thoughts with you. Ida will stay with us doing the technical support, so if you had any problems send her direct message and she will help you.

Our meeting is part of one of the work packages of CARTHAGO: 2.5., following Horizon 2020 aims. This meeting is for us, for all of us. As Work Package established, in these meetings we should think about ethical issues on our research process, from our perspective. And this is the most valuable thing: that is done from within the biomedical research.

All these discussions were approved by the ethics committee of the Jagiellonian University Medical College, Cracow, Poland. We will record this meeting if you all agree with that. Recordings will be used only for research purposes. Data will be stored in safe place, following the GDPR.

Remember: you should feel free to say what you think, to present doubts that you may have, or to share some experiences and comments. We are on a safe environment here. All points of view are important and welcomed. It is also important to agree or disagree with other participants because our goal is to hear as many as thoughts as possible.

Practical rules:
- Try to participate in every topic.
- Always talk to the group and not to each other in sub-groups.
- Raise virtual hand every time you want to say something - this will help us to organize the discussion better.

Do you have any doubts, comments, or questions?

---

2. Discussion

On our first meeting we talked about ethics, in a general way. On our second meeting we approached research ethics, also in a general way.

The main research topic of CARTHAGO has to do with human gene transfer and regenerative medicine for disc and joint pathology. Today, we are going to debate about the ethical aspects of the topic, to be able to know about them and work on them. This is our responsibility as WP2.5. We need to make sure that all what is being develop is ethically acceptable.

Part 1: Individual perspective (30 minutes)

So, let's visualize this:

Slide 1

Maybe you remember that you completed a questionnaire before we started this focus groups meetings. And maybe you remember that there were two questions about potential ethical challenges about non-viral gene therapy and orthopaedic regenerative medicine that. I will show you your answers:

Slide 2 and 3

2.1. It is quite balance, right? So let's talk about it. Why do you think there could be potential ethical challenges about non-viral gene therapy and why not?

2.2. Let's summarize – what ethical issues you could indicate in this case?
Slide 4 that I will complete while they talk Would you like to add something to what I wrote on the slide?

2.3. As researchers, what is your greatest worry in the development process of this topic?

2.4. What do you think, how personal or individual bias can affect the development process of this topic?

Part 2: Global perspective (40 minutes – could be 10 minutes longer)

2.5. Which do you think is the main societal value of this topic?

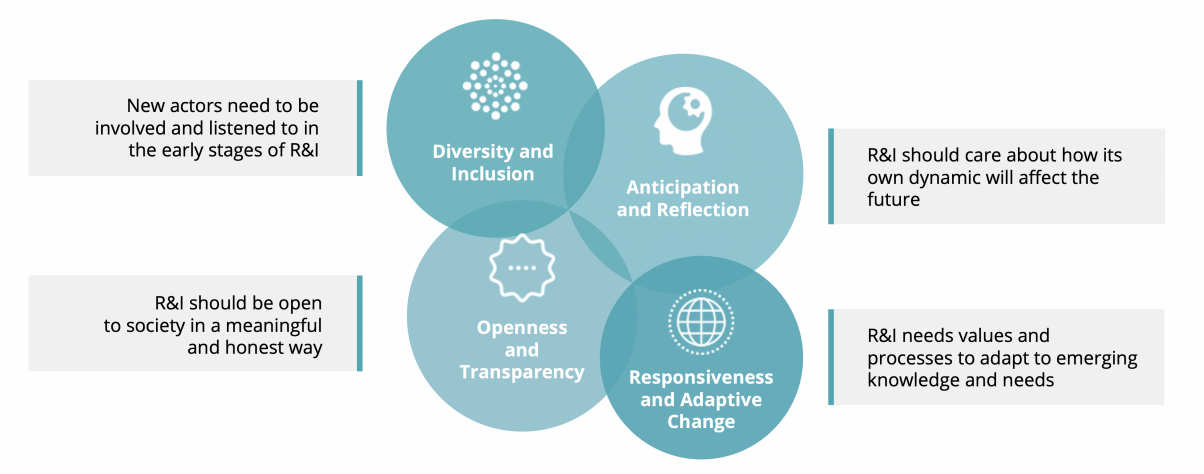
2.6. How could society be impacted by this topic?

2.5. So now I'd like to ask you to work in small groups. We are going to look CARTHAGO main goal through specifics values. Do you remember the Responsible Research and Innovation (RRI) framework? Horizon 2020 and our Work Package aims to work under. Indeed, it is the name of our WP.

Slide 5

You can see here that there is an inner circle, which is the heart of the RRI, then society actors that should be involved in RRI, and surrounding all that, there are 4 big circles of values.

Slide 6



Each group will work with one big circle of values. I'd like you to think and discuss in your group – how CARTHAGO topic (human gene transfer and regenerative medicine for disc and joint pathology) could be related to that value, in a good or bad way and then to write your ideas in the Jamboard.

You have 10-15 minutes to discuss and write your suggestions. If you have any questions you can write to me on chat.

Split groups and Jamboards

Ok, so we are back. Let's share and discuss what you have done. One per group explain and then we can make questions, comments or add other thoughts to the Jamboard.

---

3. Ending the discussion (1 minute)

Well, it has been an enriching meeting.

Do you want to add something or ask any question?

I will send you material about RRI, todays Jamboards and the one that you did in the last FG. Did you receive what I sent before?

Thank you so much for your engagement and your interesting thoughts in our discussion. I do appreciate it. Thank you for very useful contributions. See you in April!

4th FOCUS GROUP GUIDE

---

1. Scene setting and ground rules (2 minutes)

Thank you so much for being here, and I'm looking forward to discussing and exchange ideas and thoughts with you. Ida will stay with us doing the technical support, so if you had any problems send her direct message and she will help you.

Our meeting is part of one of the work packages of CARTHAGO: 2.5., following Horizon 2020 aims. This meeting is for us, for all of us. As Work Package established, in these meetings we should think about ethical issues on our research process, from our perspective. And this is the most valuable thing: that is done from within the biomedical research.

All these discussions were approved by the ethics committee of the Jagiellonian University Medical College, Cracow, Poland. We will record this meeting if you all agree with that. Recordings will be used only for research purposes. Data will be stored in safe place, following the GDPR.

Remember: you should feel free to say what you think, to present doubts that you may have, or to share some experiences and comments. We are on a safe environment here. All points of view are important and welcomed. It is also important to agree or disagree with other participants because our goal is to hear as many as thoughts as possible.

Practical rules:
- Try to participate in every topic.
- Always talk to the group and not to each other in sub-groups.
- Raise virtual hand every time you want to say something - this will help us to organize the discussion better.

Do you have any doubts, comments, or questions?

---

2. Discussion (80 minutes)

Introduction (15 minutes)

In the first meeting we focused on ethics in a general. In the second - we narrowed down our subject and approached research ethics. When met third time we debated about the ethical aspects of human gene transfer and regenerative medicine for disc and joint pathology.

Today, we are going to deepen our subject again and work on the ethics of methods used in our work packages (WP):

Slide 1
2.1. Cell delivery and efficiency gene modulation
2.2. Tissue/organ delivery tools
2.3. Repair in tissue and organ culture
2.4. In vivo imaging of regeneration and gene therapy efficacy

In the questionnaire, some of you shared that your methods could have potential ethical issues. So, for the start I'd like to ask you if or when you had a chance to think about the ethical aspects of the methods or techniques that you are using?

[GROUP DISCUSSION – 10 minutes]

Today we are going to work in small groups. Each group will have to ethically analysed each WP and it's methods and show them in a visual way using MIRO boards.

Do you have any question so far?

1st task (15 + 15 minutes = 30 minutes)

So let's start with the first board. The goal is to communicate how the WP and it's methods -the ones that you think it's important to consider- could have positive impact in some areas. I prepare for you examples of areas that may be influenced by methods of your WP:

Slide 2 and 3

- respect for human agency: autonomy and dignity
- privacy and personal information
- social well-being
- health inequalities
- mental health
- biodiversity
- climate change
- ageing population
- increased urbanization

You have 15 minutes to prepare the board in your group. Then we'll meet to briefly present what you have done – each group will have about 3 to 5 minutes for presentation and the comments from the rest of the group.

Now I'd like to ask you to click on the link on chat and go to MIRO board. When you are there, please click on the small arrow next to the name of your group. It will take you to your group board.

I will assign you to separate rooms where you can discuss. If you have any problems write on chat to Ida. See you in 15 minutes.

[TASK I – 15 minutes]

So let's start from group one…

[DISCUSSION – 15 minutes]

2nd task (20 minutes + 15 minutes = 35 minutes)

Ok, thank you for your presentations, let's go to our second task. Now I would like to ask you two things - first, think about the negative impact the methods of the methods of your WP might have. You can use the dimensions from previous task. When we get to MIRO, you will find a place to describe the negative influence.

When you finish this, I'd like to ask you to prepare second board which addresses how you can prevent this negative influence and present the possible solutions of previously mentioned problems.

For those you have 20 minutes. Then we'll meet to present what you have done. Each group will have about 3 to 5 minutes for presentation and the comments from the rest of the group.

[TASK II – 20 minutes]

So let’s start from group one…

[DISCUSSION – 15 minutes]

---

3. Ending the discussion (3 minute)

Well, it has been an enriching meeting.

Do you want to add something or ask any question?

I will send you material about what we worked on today and the posters. Did you receive what I sent before?

Thank you for very useful contributions. See you in May!

5th FOCUS GROUP GUIDE

INTRODUCTION

1. Scene setting and ground rules (2 minutes)

Ida will stay with us doing the technical support, so if you had any problems send her direct message and she will help you.

Practical rules:
- Try to participate in every topic.
- Always talk to the group and not to each other in sub-groups.
- Raise virtual hand every time you want to say something - this will help us to organize the discussion better.

Do you have any doubts, comments, or questions?

2. DISCUSSION (75 minutes)

Part 1

As this is our last focus group meeting, I prepared for you a short sum-up of what we did:

Prezi

Are there aspects which currently you see as the more important than others? Which ones? Why? Explain, please give examples.

Is there anything that you would like specially to highlight or comment?

If you have to tell someone else what was the most meaningful part of our discussions, what would you say?

+ mention that they will have a chance to write more in questionnaire

How you see the importance and role of research ethics?

Part 2

Today, we are going to formulate recommendations for integrating ethics to research in international biomedical projects.

The recommendations should lay on how to improve research from an ethical point of view and considering all the discussions that we had in all our meetings. Of course, you can also come up with something new.

The recommendations should be formulated following two perspectives:
1. What you can do: focus on what ESRs could do/change.
2. What should be done on an institutional level: focus on what the research group, PI, university, or states could do/change.

We are going to work in small groups according to the WP like last meeting.

You have 20 minutes to prepare recommendations. I prepare for you Jamboards with the name of your WP and the two perspectives of recommendation. I will assign you to separate rooms where you can discuss.

[TASK – 20 minutes]

So, let's start from group one…

[DISCUSSION – 30 minutes]

*Please comment which recommendations you find as **must** which ones are **optional**. Why these?*

With which recommendations you agree and with which you could hesitate?

How do you feel as competent in applying this ethics recommendations to the research? Are there practical? Feasible? Possible? What kind of challenges still exist? What kind? How to solve them?

---

3. CLOSE (3 minutes)

Thank you, it has been a productive meeting.

Do you want to add something or ask any question?

Ok, so this was our last meeting, I hope you enjoyed all of them, and you learn something from these meetings.

To finish this process, I will send you a post-focus group questionnaire, and there you can assess and make an opinion or critics on what we did here.

Thank you for very useful contributions. See you in Davos!

More ethics in the laboratory, please! Scientists' perspectives on ethics in the preclinical phase

Interview Guide

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1. Can you introduce yourself and explain how you are involved in gene therapy and regenerative medicine research?
2. Do you think that gene therapy and regenerative medicine could have ethical implications? Could you describe them? How should we deal with them?
3. Do you think that the ethical implications are different in the context of industry and academia? In what way?
4. In your opinion, what are the conditions under which gene therapy and regenerative medicine technologies could be used, or what limits should be in place?
5. Who should make decisions about the development and potential use of gene therapy and regenerative medicine technologies? For example, what should be the role of scientists, governments and citizens?
6. How do you think gene therapy and regenerative medicine research or technologies could impact, positively or negatively?

- Human autonomy
- Privacy and personal data
- Social well-being
- Health inequalities
- Mental health
- Biodiversity
- Climate change
- Ageing population

7. Could you describe what Responsible Research and Innovation (RRI) is?
8. How can RRI improve gene therapy and regenerative medicine research?
9. Do you apply all or some of the six keys of RRI in your work on gene therapy and regenerative medicine research? If so, how?
10. How could you improve the application of the six keys of RRI in your work on gene therapy and regenerative medicine research?
11. Are there any issues that have not been addressed that you would like to share/discuss?

UNIWERSYTET JAGIELLOŃSKI W KRAKOWIE

Komisja Bioetyczna Uniwersytetu Jagiellońskiego

OPINIA
nr 1072.6120.209.2021 z dnia 29 września 2021 roku

Na zebraniu w dniu 29 września 2021 r. Komisja zapoznała się z wnioskiem z dnia 14 września 2021 r. złożonym:
przez kierownika tematu: **dr hab. Marcin Waligóra, prof. UJ**
zatrudnionego **Zakład Filozofii i Bioetyki**
Wydział Nauk o Zdrowi UJCM
31 – 126 Kraków, ul. Michałowskiego 12

oraz jego merytorycznym uzasadnieniem dotyczącym przeprowadzenia badania pt. „Etyka w rozwoju biotechnologii/Ethics Parallel Research; Real-time ethics in development of biotechnologies".

Do wniosku dołączono:
1. Oświadczenie – badanie nie będące eksperymentem medycznym.
2. Protokół badania, wersja 1 z dnia 10.09.2021 r.
3. Informacja dla uczestnika badania, wersja 1 z dnia 10.09.2021 r.
4. Formularz świadomej zgody na udział w badaniu, wersja 1 z dnia 10.09.2021 r.
5. Formularz zgody na przetwarzanie danych osobowych, wersja 1 z dnia 10.09.2021 r.
6. Życiorys naukowy wnioskodawcy, wersja 1 z dnia 10.09.2021 r.
7. Lista piśmiennictwa, wersja 1 z dnia 13.09.2021 r.
8. Potwierdzenie złożenia dokumentacji do Komisji Bioetycznej UJ, wersja 1 z dnia 13.09.2021 r.
9. Kopia podpisanej strony umowy projektu CARHAGO, wersja 1 z dnia 25.08.2021 r.
10. Oświadczenie o realizacji badania w ramach prac badawczych UJ/UJCM.

Komisja wyraża pozytywną opinię w sprawie przeprowadzenia wnioskowanego badania - na warunkach określonych we wniosku oraz dodatkowo zastrzegając:
1/ obowiązek uzyskania pisemnej zgody każdej osoby wyrażającej wolę (gotowość) udziału w badaniu, zgodnie z obowiązującymi przepisami
2/ obowiązek przedstawienia Komisji:
- wszystkich zmian w protokole mających wpływ na przebieg oraz ocenę badania,
- zawiadomienia o przyczynach przedwczesnego zakończenia badania,
- corocznego sprawozdania z przebiegu badania,
- raportu końcowego.

Badanie może być prowadzone do dnia 5 września 2022 roku.
Skład i działanie Komisji zgodne z GCP oraz wymogami lokalnymi. Lista członków Komisji biorących udział w podjęciu uchwały stanowi załącznik do niniejszego dokumentu.

Kraków, dnia 29 września 2021 r.

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Manuscript: How to embed ethics into laboratory research

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

From:
Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007;19(6):349–357.

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the focus group?	PB (page 8)
2. Credentials	What were the researcher's credentials? *E.g. PhD, MD*	MD, MA
3. Occupation	What was their occupation at the time of the study?	ESR (page 8)
4. Gender	Was the researcher male or female?	Page 8
5. Experience and training	What experience or training did the researcher have?	Page 8
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	Page 8
7. Participant knowledge of the interviewer	What did the participants know about the researcher? *E.g. personal goals, reasons for doing the research*	Page 8
8. Interviewer characteristics	What characteristics were reported about the facilitator? *E.g. Bias, assumptions, reasons and interests in the research topic*	Page 8
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *E.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	Page 4
Participant selection		
10. Sampling	How were participants selected? *E.g. purposive, convenience, consecutive, snowball*	Page 3
11. Method of approach	How were participants approached? *E.g. face-to-face, telephone, mail, email*	Page 10
12. Sample size	How many participants were in the study?	Page 3
13. Non-participation	How many people refused to participate or dropped out? Reasons?	No one (page 3)
Setting		
14. Setting of data collection	Where was the data collected? *E.g. home, clinic, workplace*	Page 3
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Page 8
16. Description of sample	What are the important characteristics of the sample? *E.g. demographic data, date*	Page 3
Data collection		

17. Focus group guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Yes (page 8)
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	No
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Yes (page 8)
20. Field notes	Were field notes made during and/or after the interview or focus group?	No
21. Duration	What was the duration of the focus group?	Yes (page 8)
22. Data saturation	Was data saturation discussed?	No
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	Page 9
25. Description of the coding tree	Did authors provide a description of the coding tree?	No
26. Derivation of themes	Were themes identified in advance or derived from the data?	Page 9
27. Software	What software, if applicable, was used to manage the data?	Page 9
28. Participant checking	Did participants provide feedback on the findings?	No
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? *E.g. participant number*	Results section
30. Data and findings consistent	Was there consistency between the data presented and the findings?	Results section
31. Clarity of major themes	Were major themes clearly presented in the findings?	Results section
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Results section

Introduction

Hello! As you know, I am one of the ESRs in CARTHAGO and I am working on the ethical issues in our MSCA-ITN project.

Part of that work is performing a focus group with you, as described in the CARTHAGO research proposal. Before we meet, I would like to ask you a few questions about your experience with ethics topics / concepts. This will help me to prepare our future meetings.

It is important to know that there are no wrong answers. Everything you think about it is necessary to improve our research process. Your answers will be kept confidential. If we publish the results, your personal data will not be revealed.

If, at any stage of this process, you feel uncomfortable, please let me know: I will try to adjust it according your preferences.

Thank you so much!

Paola

PART 1: ETHICS

1. Describe what ethics, in general, means to you.

2. When you hear about ethical issues in scientific work, what comes to mind?

PART 2: KNOWLEDGE SOURCES

2. Have you ever had courses or training on research integrity?
    a. Yes
    b. No = go to Q4

3. Describe the topics.

PART 3: YOUR RESEARCH

5. How would you describe what are you working on?

6. Which particular research methods are you using?

7. Do you think there could be potential ethical challenges about your work or methods?
    a. Yes
    b. No = go to Q9

8. Describe these potential ethical challenges concisely.

PART 4: THE RESEARCH CONSORTIUM

9. Do you think there could be potential ethical challenges about non-viral gene therapy?
    a. Yes
    b. No = go to Q11

10. Describe these potential ethical challenges concisely.

11. Do you think there could be potential ethical challenges about orthopaedic regenerative medicine?
    a. Yes
    b. No = go to end

12. Describe these potential ethical challenges concisely.

Thank you for your time!

INTRODUCTION

We finished our Focus Groups meetings.

Now, as our last activity, I would like to ask you some questions and give you the opportunity to express an opinion about this experience.

Thank you so much!

Paola

PART 1: ETHICS

1. Describe what ethics, in general, means to you.

2. When you hear about ethical issues in scientific work, what comes to your mind?

PART 2: KNOWLEDGE SOURCES

3. Did you participate in any courses (or any other organised activities i.e., trainings, workshops, lectures) on research integrity or ethics during the period of our meetings (from October 2021 to May 2022) besides of our focus group meetings?

a. Yes
b. No = go to Q5

4. Describe the topics of the courses / trainings / workshops.

5. Did you use any sources of knowledge on research integrity or ethics during the period of our meetings (October 2021 to May 2022) other than those provided with our focus group meetings?

a. Yes
b. No = go to Q7

6. What sources of knowledge on research integrity or ethics did you use?

PART 3: YOUR RESEARCH

7. How would you describe what are you working on?

8. Do you think there could be potential ethical challenges about your work or methods?

a. Yes
b. No = go to Q10

9. Describe these potential ethical challenges concisely.

10. During the period of our meetings (October 2021 to May 2022), did you make any changes or took additional actions related to research integrity or ethics as part of your CARTHAGO project?

a. Yes
b. No = go to Q12

11. Describe these changes or actions concisely.

12. If you had a chance, what changes - related to research integrity or ethics - would you like to do in your project or research environment?

PART 4: THE RESEARCH CONSORTIUM

13. Do you think there could be potential ethical challenges about non-viral gene therapy?

a. Yes
b. No

14. Do you think there could be potential ethical challenges about orthopaedic regenerative medicine?

a. Yes
b. No

15. Describe these potential ethical challenges concisely.

PART 5: THE FOCUS GROUPS MEETINGS

16. Please judge to what extent do you agree or disagree that our meetings:

Please use the scale from 1 to 5 where 1 – Strongly disagree, 2 – Disagree, 3 Neither agree, nor disagree, 4 – Agree, 5 – Strongly agree

1	Sufficiently introduced research ethics and research integrity concepts	1	2	3	4	5
2	Developed your ability to reflect on research ethics	1	2	3	4	5
3	Increased awareness of ethical issues in your own research activities	1	2	3	4	5
4	Promoted your ability to debate ethical challenges in biomedical research	1	2	3	4	5
5	Made you feel comfortable to express your ideas and opinions	1	2	3	4	5
6	Brought up interesting topics for you	1	2	3	4	5

17. Please assess to what extent are you satisfied about participation in our focus group meetings:

18. If you have any comments about our focus groups meetings, please write it here.

Thank you for your time!

Appendix 14: Details of the articles included in the systematic review.

ID	Authors	Title	Year	Journal	Database	Language	Field
1	Traulsen JM, Bjornsdóttir I, Almarsdóttir AB	'I'm Happy if I Can Help'. Public views on future medicines and gene-based therapy in Iceland	2008	Community Genetics	PubMed	English	Genetics
2	Addison C, Lassen J	"My whole life is ethics!" Ordinary ethics and gene therapy clinical trials	2017	Medical Anthropology	PubMed	English	Social Sciences
3	Gaspar HB, Swift S, Thrasher AJ	"Special exemptions": should they be put on trial?	2013	Molecular Therapy	PubMed	English	Biotechnology
4	Barns I, Schibeci R, Davison A, Shaw R	"What do you think about genetic medicine?" Facilitating sociable public discourse on developments in the new genetics	2000	Science, Technology, & Human Values	PubMed	English	Science
5	Carmen IH	A death in the laboratory: the politics of the Gelsinger aftermath	2001	Molecular Therapy	PubMed	English	Biotechnology
6	Hughes JJ	A defense of limited regulation of human genetic therapies	2019	Cambridge Quarterly of Healthcare Ethics	PubMed	English	Bioethics
7	Riva L, Petrini C	A few ethical issues in translational research for gene and cell therapy	2019	Journal of Translational Medicine	PubMed	English	Medicine
8	Steele FR	A matter of trust	2000	Molecular Therapy	PubMed	English	Biotechnology
9	Bonatti J, Haeusler C, Klaus A, Fink M, Hammerer-Lercher A, Laufer G	Acceptance of gene therapy by the heart surgery patient	2002	European Journal of Cardio-thoracic Surgery	PubMed	English	Surgery
10	Ledley FD	After gene therapy: issues in long-term clinical follow-up and care	1995	Advances in Genetics	PubMed	English	Genetics
11	Holtug N	Altering humans — The case for against human gene therapy	1997	Cambridge Quarterly of Healthcare Ethics	PhilPapers	English	Bioethics
12	Baird PA	Altering humans genes: social, ethical, and legal implications	1994	Perspectives in Biology and Medicine	PubMed	English	Medicine
13	Kim SY, Schrock L, Wilson RM, Frank SA, Holloway RG, Kieburtz K, de Vries RG	An approach to evaluating the therapeutic misconception	2009	IRB: Ethics and Human Research	PubMed	English	Bioethics
14	Podhajcer O, Pitossi F, Boyesen McReddie C	Aspectos eticos de la terapia genica	1998	Medicina	LILACS	Spanish	Medicine
15	Sturgis P, Cooper H, Fife-Schaw C	Attitudes to biotechnology: estimating the opinions of a better-informed public	2005	New Genetics and Society	PubMed	English	Genetics
16	Kimmelman J	Beyond human subjects: risk, ethics, and clinical development of nanomedicine	2012	Journal of Law, Medicine & Ethics	PubMed	English	Bioethics

17	Freire JE, Medeiros SC, Lopes Neto AV, Monteiro Júnior JE, Sousa AJ, Rocha AJ, Menezes LM	Bioethical conflicts of gene therapy: a brief critical review	2014	Revista da Associação Médica Brasileira	LILACS	English	Medicine
18	Swazo NK	Calculating Risk/Benefit in X-Linked Severe combined immune deficiency disorder (X-SCID) gene therapy trials: the task of ethical evaluation	2006	Journal of Medicine and Philosophy	PubMed	English	Bioethics
19	Walter JJ	Catholic reflections on the human genome	2003	The National Catholic Bioethics Quarterly	PubMed	English	Bioethics
20	Fischer A	Cautious advance. Gene therapy is more complex than anticipated	2000	EMBO Reports	PubMed	English	Biology
21	Pepper MS, Alessandrini M, Pope A, Van Staden W, Green RJ	Cell and gene therapies at the forefront of innovative medical care: implications for South Africa	2018	South African Medical Journal	PubMed	English	Medicine
22	Ledley FD	Clinical considerations in the design of protocols for somatic gene therapy	1991	Human Gene Therapy	PubMed	English	Genetics
23	Friedmann T	Clinical gene therapy: lessons from the ether dome	2004	Molecular Therapy	PubMed	English	Biotechnology
24	Lowenstein PR	Clinical trials in gene therapy: ethics of informed consent and the future of experimental medicine	2008	Current Opinion in Molecular Therapeutics	PubMed	English	Biotechnology
25	Moseley R	Commentary: maintaining the somatic/germ-line distinction: some ethical drawbacks	1991	Journal of Medicine and Philosophy	PubMed	English	Bioethics
26	King NM, Henderson GE, Churchill LR, Davis AM, Hull SC, Nelson DK, Parham-Vetter PC, Rothschild BB, Easter MM, Wilfond BS	Consent forms and the therapeutic misconception: the example of gene transfer research	2005	IRB: Ethics and Human Research	PubMed	English	Bioethics
27	Campbell A, Glass KC, Charland LC	Describing our "humanness": can genetic science alter what it means to be "human"?	1998	Science and Engineering Ethics	PhilPapers	English	Bioethics
28	Tauer CA	Does human gene therapy raise new ethical questions?	1990	Human Gene Therapy	PubMed	English	Genetics
29	Scully JL	Drawing a line: situating moral boundaries in genetic medicine	2001	Bioethics	PubMed	English	Bioethics
30	Kimmelman J, Levenstadt A	Elements of style: consent form language and the therapeutic misconception in phase 1 gene transfer trials	2005	Human Gene Therapy	PubMed	English	Genetics

31	King N, Cohen-Haguenauer O	En route to ethical recommendations for gene transfer clinical trials	2008	Molecular Therapy	PubMed	English	Biotechnology
32	Nicholson S, Pandha HS, Harris JD, Waxman J	Ethical and regulatory issues in gene therapy	1995	British Journal of Urology	PubMed	English	Urology
33	Levin AV	Ethical considerations in gene therapy	2016	Ophthalmic Genetics	PubMed	English	Ophthalmology
34	Flotte TR	Ethical implications of the cost of molecularly targeted therapies	2015	Human Gene Therapy	PubMed	English	Genetics
35	Fletcher JC	Ethical issues in and beyond prospective clinical trials of human gene therapy	1985	Journal of Medicine and Philosophy	PhilPapers	English	Bioethics
36	Penticuff J	Ethical issues in genetic therapy	1994	Journal of Obstetric, Gynecologic & Neonatal Nursing	PubMed	English	Nursing
37	Shannon TA	Ethical issues in genetics	1999	Theological Studies	PubMed	English	Theology
38	Fost N	Ethical issues in genetics	1992	Pediatric Clinics of North America	PubMed	English	Pediatrics
39	Bernstein M, Bampoe J, Daar AS	Ethical issues in molecular medicine of relevance to surgeons	2004	Canadian Journal of Surgery	PubMed	English	Surgery
40	Zhang X	Ethical reflection on human gene therapy in the Chinese context	2008	Journal International de Bioéthique	PubMed	English	Bioethics
41	Haan EA	Ethics and the new genetics	1990	Journal of Paediatrics and Child Health	PubMed	English	Pediatrics
42	Kimmelman J	Ethics, ambiguity aversion, and the review of complex translational clinical trials	2012	Bioethics	PubMed	English	Bioethics
43	Valenzuela CY	Etica cientifica de la terapia genica de individuos. Urgencia de la cirugia genica del ADN	2003	Revista Medica de Chile	LILACS	Spanish	Medicine
44	Fletcher JC	Evolution of ethical debate about human gene therapy	1990	Human Gene Therapy	PubMed	English	Genetics
45	Nevin NC	Experience of gene therapy in the United Kingdom	1998	Annals of the New York Academy of Sciences	PubMed	English	Science
46	Kaji EH, Leiden JM	Gene and stem cell therapies	2001	JAMA	PubMed	English	Medicine
47	Goering S	Gene therapies and the pursuit of a better human	2000	Cambridge Quarterly of Healthcare Ethics	PubMed	English	Bioethics
48	Drugan A, Müler O, Evans M	Gene therapy	1987	Fetal Therapy	PubMed	English	Obstetrics
49	Bertolaso M, Olsson J, Picardi A, Rakela J	Gene therapy and enhancement for diabetes (and other diseases): the multiplicity of considerations	2010	Diabetes/Metabolism Research and Reviews	PubMed	English	Endocrinology
50	Royal Commission on New Reproductive Technologies	Gene therapy and genetic alteration	1994	Human Gene Therapy	PubMed	English	Genetics

51	Kaspar RW, Wills CE, Kaspar BK	Gene therapy and informed consent decision making: nursing research directions	2009	Biological Research for Nursing	PubMed	English	Nursing
52	Danks DM	Gene therapy and related novel forms of treatment	1993	The Medical Journal of Australia	PubMed	English	Medicine
53	Dimichele D, Miller FG, Fins JJ	Gene therapy ethics and haemophilia: an inevitable therapeutic future?	2003	Haemophilia	PubMed	English	Hematology
54	Giangrande PLF	Gene therapy for hemophilia? No	2004	Journal of Thrombosis and Haemostasis	PubMed	English	Hematology
55	Dimichele D	Gene therapy for hemophilia? The debate reframed	2005	Journal of Thrombosis and Haemostasis	PubMed	English	Hematology
56	Friedmann T, Roblin R	Gene therapy for human genetic disease?	1972	Science	GS English	English	Science
57	Anderson WF, Fletcher JC	Gene therapy in human beings: when is it ethical to begin?	1980	The New England Journal of Medicine	GS English	English	Medicine
58	Hoshino K	Gene therapy in Japan: current trends	1995	Cambridge Quarterly of Healthcare Ethics	PubMed	English	Bioethics
59	Weatherall DJ	Gene therapy in perspective	1991	Nature	PubMed	English	Science
60	Ashcroft RE	Gene therapy in the clinic: whose risks?	2004	Trends in Biotechnology	PubMed	English	Biotechnology
61	Robinson KD, Abernathy E, Conrad KJ	Gene therapy of cancer	1996	Seminars in Oncology Nursing	PubMed	English	Nursing
62	Wolf SM, Gupta R, Kohlhepp P	Gene therapy oversight: lessons for nanobiotechnology	2009	Journal of Law, Medicine & Ethics	PhilPapers	English	Bioethics
63	Spink J, Geddes D	Gene therapy progress and prospects: bringing gene therapy into medical practice: the evolution of international ethics and the regulatory environment	2004	Gene Therapy	PubMed	English	Genetics
64	Roth RI, Fleischer NM	Gene therapy: applications to pharmacy practice	2002	Journal of the American Pharmaceutical Association	PubMed	English	Pharmacy
65	Mavilio F	Gene therapy: back on track?	2010	EMBO Reports	PubMed	English	Biology
66	Rabino I	Gene therapy: ethical issues	2003	Theoretical Medicine	PubMed	English	Medicine
67	Jin X, Yang YD, Li YM	Gene therapy: Regulations, ethics and its practicalities in liver disease	2008	World Journal of Gastroenterology	PubMed	English	Gastroenterology
68	Cohen-Haguenauer O	Gene therapy: regulatory issues and international approaches to regulation	1997	Current Opinion in Biotechnology	PubMed	English	Biotechnology
69	Hillman AL, Brenner MK, Caplan AL, Carey J, Champey Y, Culver KW, Drummond MF, Freund DA, Holmes EW, Kelley WN, Kolata G, Levine	Gene therapy: socioeconomic and ethical issues. A roundtable discussion	1996	Human Gene Therapy	PubMed	English	Genetics

	MN, Levy E, Schondelmeyer SW, Velu T, Wilson JM.						
70	Smith KR	Gene therapy: theoretical and bioethical concepts	2003	Archives of Medical Research	PubMed	English	Medicine
71	Hoose B	Gene therapy: where to draw the line	1990	Human Gene Therapy	PubMed	English	Genetics
72	Fuchs M	Gene therapy. An ethical profile of a new medical territory	2006	The Journal of Gene Medicine	PubMed	English	Medicine
73	Amor D	Gene therapy. Principles and potential applications	2001	Australian Family Physician	PubMed	English	Medicine
74	McKenny GP, Aguilar-Cordova E	Gene transfer for therapy or enhancement	1999	Human Gene Therapy	PubMed	English	Genetics
75	Farrelly C	Genes and equality	2004	Journal of Medical Ethics	PubMed	English	Bioethics
76	Cole-Turner R	Genes, religion and society: the developing views of the churches	1997	Science and Engineering Ethics	PubMed	English	Bioethics
77	Fost N	Genetic diagnosis and treatment. Ethical considerations	1993	The American Journal of Diseases of Children	PubMed	English	Pediatrics
78	Churchill LR, Collins ML, King NM, Pemberton SG, Wailoo KA	Genetic research as therapy: implications of "gene therapy" for informed consent	1998	Journal of Law, Medicine & Ethics	PubMed	English	Bioethics
79	Chadwick R, Levitt M	Genetic technology: A threat to deafness	1998	Medicine, Health Care and Philosophy	PubMed	English	Medicine
80	Friedmann T	Genetic therapies, human genetic enhancement, and ... eugenics?	2019	Gene Therapy	PubMed	English	Genetics
81	Gustafson JM	Genetic therapy: ethical and religious reflections	1992	Journal of Contemporary Health Law and Policy	PubMed	English	Law
82	Ramón JR	Genetica y bioetica: lo posible y lo deseable	2005	Revista de la Academia Canaria de Ciencias	GS Spanish	Spanish	Science
83	Williams ED	Genetics and bioethics: the current state of affairs	2002	Revista Latinoamericana de Bioética	PubMed	English	Bioethics
84	Kaplan JC, Junien C	Genomics and medicine: an anticipation. From Boolean Mendelian genetics to multifactorial molecular medicine	2000	Comptes rendus de l'Academie des Sciences	PubMed	English	Science
85	Gage JL	Government regulation of human gene therapy	1987	Jurimetrics Journal	PubMed	English	Law
86	Costea I, Isasi R, Knoppers BM, Lillicrap D	Haemophilia gene therapy: the patients-perspective	2009	Haemophilia	PubMed	English	Hematology
87	Savulescu J	Harm, ethics committees and the gene therapy death	2001	Journal of Medical Ethics	PubMed	English	Bioethics
88	Editorial	Hasty compassion	1993	The Lancet	PubMed	English	Medicine

89	Health Department of the United Kingdom Gene Therapy Advisory Committee	Guidance on making proposals to conduct gene therapy research on human subjects	2001	Human Gene Therapy	PubMed	English	Genetics
90	Wirth T, Parker N, Ylä-Herttuala S	History of gene therapy	2013	Gene	PubMed	English	Genetics
91	Messer N	Human cloning and genetic manipulation: some theological and ethical issues	1999	Studies in Christian Ethics	PubMed	English	Bioethics
92	McGleenan T	Human gene therapy and slippery slope arguments	1995	Journal of Medical Ethics	PubMed	English	Bioethics
93	Larson EJ	Human gene therapy and the law: an introduction to the literature	1990	Emory Law Journal	PubMed	English	Law
94	Launis V	Human gene therapy and the slippery slope argument	2002	Medicine, Health Care and Philosophy	PubMed	English	Medicine
95	Carmen IH	Human gene therapy: a biopolitical overview and analysis	1993	Human Gene Therapy	PubMed	English	Genetics
96	Holtug N	Human gene therapy: down the slippery slope?	1993	Bioethics	PubMed	English	Bioethics
97	Walters L	Human gene therapy: ethics and public policy	1991	Human Gene Therapy	PubMed	English	Genetics
98	Krimsky S	Human gene therapy: must we know where to stop before we start?	1990	Human Gene Therapy	PubMed	English	Genetics
99	Anderson WF	Human gene therapy: scientific and ethical considerations	1985	Journal of Medicine and Philosophy	GS English	English	Bioethics
100	Leiden JM	Human gene therapy: the good, the bad, and the ugly	2000	Circulation Research	PubMed	English	Hematology
101	Anderson WF	Human gene therapy: why draw a line?	1989	Journal of Medicine and Philosophy	PubMed	English	Bioethics
102	Patel PI	Identification of disease genes and somatic gene therapy: an overview and prospects for the aged	1993	Journal of Gerontology	PubMed	English	Gerontology
103	Ellliot R	Identity and the ethics of gene therapy	1993	Bioethics	PubMed	English	Bioethics
104	Kahn J	Informed consent in human gene transfer clinical trials	2008	Human Gene Therapy	PubMed	English	Genetics
105	Zänker KS, Huber HP	Interdisciplinary forum: from genetic diagnosis to gene therapy in oncology	1997	Journal of Cancer Research and Clinical Oncology	PubMed	English	Oncology
106	Macer DR, Akiyama S, Alora AT, Asada Y, Azariah J, Azariah H, Boost MV, Chatwachirawong P, Kato Y,	International perceptions and approval of gene therapy	1995	Human Gene Therapy	PubMed	English	Genetics

	Kaushik V, Leavitt FJ, Macer NY, Ong CC, Srinives P, Tsuzuki M						
107	Richter G, Bacchetta MD	Interventions in the human genome: some moral and ethical considerations	1998	Journal of Medicine and Philosophy	PubMed	English	Bioethics
108	Editorial	Keeping faith in gene manipulation	1996	Nature	PubMed	English	Science
109	Fitzgerald KT	Knowledge without wisdom: human genetic engineering without religious insight	2002	Christian Bioethics	PubMed	English	Bioethics
110	Ruiz-Perez G	La terapia genetica: observaciones para una perspectiva etica	1993	Scripta Theologica	GS Spanish	Spanish	Theology
111	Casanova Perdomo AR	Las tecnologias de manipulacion de genes humanos como imperativo tecnologico: analisis desde la optica del principalismo bioetico y el principio de responsabilidad	2011	Revista Latinoamericana de Bioética	GS Spanish	Spanish	Bioethics
112	Green RM	Last word: imagining the future	2005	Kennedy Institute of Ethics Journal	PubMed	English	Bioethics
113	Dickens BM	Legal and ethical challenges in gene therapy	1996	Transfusion Science	PubMed	English	Hematology
114	Areen J, King P	Legal regulation of human gene therapy	1990	Human Gene Therapy	PubMed	English	Genetics
115	Wilson JM	Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency	2009	Molecular Genetics and Metabolism	GS English	English	Genetics
116	Robin SS, Markle GE, Curd M, Duster T, Lappé M, Mazur A	Let no one split asunder: controversy in human genetic engineering	1987	Politics and the Life Sciences	PubMed	English	Politics
117	Palmer JG	Liability considerations presented by human gene therapy	1991	Human Gene Therapy	PubMed	English	Genetics
118	Nunes FA, Raper SE	Liver-directed gene therapy	1996	Medical Clinics of North America	PubMed	English	Medicine
119	Neel JV	Looking ahead: some genetic issues of the future	1997	Perspectives in Biology and Medicine	PubMed	English	Medicine
120	Barreiro AJ	Los delitos relativos a la manipulacion genetica en sentido estricto	1999	Anuario de derecho penal y ciencias penales	GS Spanish	Spanish	Law
121	Baramt M	Making clinical trials safer for human subjects	2001	American Journal of Law & Medicine	PubMed	English	Law
122	Crisp R	Making the world a better place: genes and ethics	1995	Science and Engineering Ethics	PubMed	English	Bioethics
123	Gafo J	Manipulacion genetica	2000	Almogaren. Revista del Centro Teológico de Las Palmas	GS Spanish	Spanish	Theology
124	Friedmann T	Medical ethics. Principles for human gene therapy studies	2000	Science	PubMed	English	Science
125	Swiss Academy of Medical Sciences	Medical-ethical guidelines for somatic gene therapy in humans	1999	Schweiz Med Wochenschr	PubMed	English	Medicine

126	Winter SF, Roger HD	Medical, ethical and legal aspects of somatic gene therapy	1995	European Journal of Health Law	PubMed	English	Law
127	Bruce DM	Moral and ethical issues in gene therapy	2006	Human Reproduction & Genetic Ethics	PubMed	English	Bioethics
128	Stahl D	Moral evaluations of genetic technologies. The need for catholic social doctrine	2015	The National Catholic Bioethics Quarterly	PhilPapers	English	Bioethics
129	Fletcher JC	Moral problems and ethical issues in prospective human gene therapy	1983	Virginia Law Review	PubMed	English	Law
130	Turriff A, Blain D, Similuk M, Biesecker B, Wiley H, Cukras C, Sieving PA	Motivations and decision making processes of Men with X-linked retinoschisis considering participation in an ocular gene therapy trial	2019	American Journal of Ophthalmology	PubMed	English	Ophthalmology
131	Lenk C, Biller-Andorno N	Nanomedicine–emerging or re-emerging ethical issues? A discussion of four ethical themes	2007	Medicine, Health Care and Philosophy	PhilPapers	English	Medicine
132	Ebbesen M, Jensen TG	Nanomedicine: techniques, potentials, and ethical implications	2006	Journal of Biomedicine and Biotechnology	GS English	English	Biotechnology
133	Scully JL, Rippberger C, Rehmann-Sutter C	Non-professionals' evaluations of gene therapy ethics	2004	Social Science & Medicine	PubMed	English	Social Sciences
134	Benjaminy S, Bubela T	Ocular gene transfer in the spotlight: implications of newspaper content for clinical communications	2014	BMC Medical Ethics	PubMed	English	Bioethics
135	Miller HI	Overregulation is an unnecessary hindrance to human gene therapy	1995	Human Gene Therapy	PubMed	English	Genetics
136	Cohen-Haguenauer O	Overview of regulation of gene therapy in Europe: a current statement including reference to US regulation	1995	Human Gene Therapy	PubMed	English	Genetics
137	Steele F	Painful lessons	2000	Molecular Therapy	PubMed	English	Biotechnology
138	Brooks SP, Benjaminy S, Bubela T	Participant perspectives on a phase I/II ocular gene therapy trial	2019	Ophthalmic Genetics	PubMed	English	Ophthalmology
139	Aiyegbusi OL, Macpherson K, Elston L, Myles S, Washington J, Sungum N, Briggs M, Newsome PN, Calvert MJ	Patient and public perspectives on cell and gene therapies: a systematic review	2020	Nature	PubMed	English	Science
140	Konduros J	Patient testimonial: my experience on a gene therapy trial	2019	Transfusion and Apheresis Science	PubMed	English	Hematology
141	King WD, Wyatt GE, Liu H, Williams JK, DiNardo AD, Mitsuyasu RT	Pilot assessment of HIV gene therapy-hematopoietic stem cell clinical trial acceptability among minority patients and their advisors	2010	Journal of the National Medical Association	PubMed	English	Medicine

142	Dettweiler U, Simon P	Points to consider for ethics committees in human gene therapy trials	2001	Bioethics	PubMed	English	Bioethics
143	Gansbacher B	Policy statement on the social, ethical and public awareness issues in gene therapy	2002	The Journal of Gene Medicine	PubMed	English	Medicine
144	Robillard JM, Roskams-Edris D, Kuzeljevic B, Illes J	Prevailing public perceptions of the ethics of gene therapy	2014	Human Gene Therapy	PubMed	English	Genetics
145	Górecki DC	Prospects and problems of gene therapy: an update	2001	Expert Opinion on Emerging Drugs	GS English	English	Pharmacy
146	Shalala D	Protecting research subjects--what must be done	2000	The New England Journal of Medicine	PubMed	English	Medicine
147	Kimmelman J	Protection at the cutting edge: the case for central review of human gene transfer research	2003	Canadian Medical Association Journal	PubMed	English	Medicine
148	Pattee SR	Protections for participants in gene therapy trials: a patient's perspective	2008	Human Gene Therapy	PubMed	English	Genetics
149	Delhove J, Osenk I, Prichard I, Donnelley M	Public acceptability of gene therapy and gene editing for human use: a systematic review	2020	Human Gene Therapy	PubMed	English	Genetics
150	Horst M	Public expectations of gene therapy: scientific futures and their performative effects on scientific citizenship	2007	Science, Technology, & Human Values	GS English	English	Science
151	Zallen DT	Public oversight is necessary if human gene therapy is to progress	1996	Human Gene Therapy	PubMed	English	Genetics
152	Sato H, Akabayashi A, Kai I	Public, experts, and acceptance of advanced medical technologies: the case of organ transplant and gene therapy in Japan	2006	Health Care Analysis	PhilPapers	English	Health Care Sciences
153	Kimmelman J	Putting the shoe on the wrong foot: a reply to Ponder and Srivastava	2008	Haemophilia	PubMed	English	Hematology
154	Kimmelman J	Recent developments in gene transfer: risk and ethics	2005	BMJ	PubMed	English	Medicine
155	Anderson FW	Reflections: of hope and of concern	1991	Human Gene Therapy	PubMed	English	Genetics
156	Areen J	Regulating human gene therapy	1985	West Virginia Law Review	PubMed	English	Law
157	Leavitt WJ	Regulating human gene therapy: legislative overreaction to human subject protection failures	2001	Administrative Law Review	PubMed	English	Law
158	Black J	Regulation as facilitation: negotiating the genetic revolution	1998	The Modern Law Review	PubMed	English	Law
159	Cornetta K, Smith FO	Regulatory issues for clinical gene therapy trials	2002	Human Gene Therapy	PubMed	English	Genetics

160	Cornetta K	Regulatory issues in human gene therapy	2003	Blood Cells, Molecules and Diseases	PubMed	English	Hematology
161	Orkin SH, Motulsky AG	Report and recommendations of the panel to assess the NIH investment in research on gene therapy	1995	National Institutes of Health (not journal)	GS English	English	Science
162	Committee	Report of the Committee on the Ethics of Gene Therapy	1992	Human Gene Therapy	PubMed	English	Genetics
163	Priest SH	Risk communication for nanobiotechnology: to whom, about what, and why?	2009	Journal of Law, Medicine & Ethics	PhilPapers	English	Bioethics
164	Ragni MV	Safe passage: a plea for safety in hemophilia gene therapy	2002	Molecular Therapy	PubMed	English	Biotechnology
165	Temin HM	Safety considerations in somatic gene therapy of human disease with retrovirus vectors	1990	Human Gene Therapy	GS English	English	Genetics
166	Lagay FL	Science, rhetoric, and public discourse in genetic research	1999	Cambridge Quarterly of Healthcare Ethics	PubMed	English	Bioethics
167	Lebo RV, Golbus MS	Scientific and ethical considerations in human gene therapy	1991	Bailliere's Clinical Obstetrics and Gynaecology	PubMed	English	Obstetrics
168	Weatherall DJ	Scope and limitations of gene therapy	1995	British Medical Bulletin	PubMed	English	Medicine
169	Anderson WF	September 14, 1990: the beginning	1990	Human Gene Therapy	PubMed	English	Genetics
170	Nelles M, Stieger K, Preising MN, Kruse J, Lorenz B	Shared decision-making, control preferences and psychological well-being in patients with RPE65 deficiency awaiting experimental gene therapy	2015	Ophthalmic Research	PubMed	English	Ophthalmology
171	Motulsky AG	Societal problems in human and medical genetics	1989	Genome	PubMed	English	Genetics
172	Ledley FD	Somatic gene therapy for human disease: a problem of eugenics?	1987	Trends in Genetics	PubMed	English	Genetics
173	Ledley FD	Somatic gene therapy in gastroenterology: approaches and applications	1992	Journal of Pediatric Gastroenterology and Nutrition	PubMed	English	Gastroenterology
174	Kimmelman J	Stable ethics: enrolling non-treatment-refractory volunteers in novel gene transfer trials	2007	Molecular Therapy	PubMed	English	Biotechnology
175	Lyngstadaas A	Status and potential of gene therapy in clinical medicine. Assessment of an emerging health technology through systematic survey of clinical gene therapy protocols and published results	2002	International Journal of Technology Assessment in Health Care	PubMed	English	Health Care Sciences

176	Kimmelman J	Staunch protections: the ethics of haemophilia gene transfer research	2008	Haemophilia	PubMed	English	Hematology
177	Glass KC, Weijer C, Cournoyer D, Lemmens T, Palmour RM, Shapiro SH, Freedman B	Structuring the review of human genetics protocols, part III: gene therapy studies	1999	IRB: Ethics and Human Research	PubMed	English	Bioethics
178	Norfolk, Gallagher JC, Jessiman I	Submission to the Committee on the Ethics of Gene Therapy	1990	The Linacre Quarterly	PubMed	English	Theology
179	Bayertz K, Paslack R, Schmidt KW	Summary of "gene transfer into human somatic cells. State of the technology, medical risks, social and ethical problems: a report"	1994	Human Gene Therapy	PubMed	English	Genetics
180	Xiang L, Xiao L, Gou Z, Li M, Zhang W, Wang H, Feng P	Survey of attitudes and ethical concerns related to gene therapy among medical students and postgraduates in China	2015	Human Gene Therapy	PubMed	English	Genetics
181	Risco DL	Terapia genica e investigacion con celulas madre en la legislacion española	2006	Derecho y Salud	GS Spanish	Spanish	Law
182	Espin-Villacres V, Andrade-Vera K, Espin-Mayorga V	Terapia genica en medicina	2001	Boletín Médico del Hospital Infantil de México	LILACS	Spanish	Pediatrics
183	Rodriguez Yunta E	Terapia genica y principios eticos	2003	Acta Bioethica	LILACS	Spanish	Bioethics
184	Agudelo Vélez CA, Martínez Sánchez LM	Terapia génica: una opción de tratamiento y una controversia ética	2013	Salud Uninorte	GS Spanish	Spanish	Medicine
185	Smith RS, Piras BA, Smith CJ	The bioethics of gene therapy	2010	The National Catholic Bioethics Quarterly	PhilPapers	English	Bioethics
186	Pace A	The catholic theology of genetic manipulation	2004	The Linacre Quarterly	PubMed	English	Theology
187	Ledley FD, Brody B, Kozinetz CA, Mize SG	The challenge of follow-up for clinical trials of somatic gene therapy	1992	Human Gene Therapy	PubMed	English	Genetics
188	Wilson RF	The death of Jesse Gelsinger: new evidence of the influence of money and prestige in human research	2010	American Journal of Law & Medicine	PubMed	English	Law
189	Walters LR	The ethics of human gene therapy	1986	Nature	GS English	English	Science
190	Kimmelman J	The ethics of human gene transfer	2008	Nature	PubMed	English	Science
191	Dyer AR	The ethics of human genetic intervention: a postmodern perspective	1997	Experimental Neurology	PubMed	English	Neurosciences
192	McDonough PG	The ethics of somatic and germline gene therapy	1997	Annals of the New York Academy of Sciences	PubMed	English	Science
193	Bunch WH, Drennan JC	The ethics of the introduction of gene therapy into orthopaedic practice	2000	Clinical Orthopaedics and Related Research	PubMed	English	Orthopaedics
194	Friedmann T	The evolving concept of gene therapy	1990	Human Gene Therapy	PubMed	English	Genetics

195	Farrelly C	The genetic difference principle	2004	The American Journal of Bioethics	PubMed	English	Bioethics
196	Nycum G, Reid L	The harm-benefit tradeoff in “bad deal” trials	2007	Kennedy Institute of Ethics Journal	PubMed	English	Bioethics
197	Fletcher JC	The long view: how genetic discoveries will aid healthcare reform	1998	Journal of Women's Health	PubMed	English	Medicine
198	Kraj T	The magisterium and modern genetics	2002	The National Catholic Bioethics Quarterly	PubMed	English	Bioethics
199	Sadler TD, Zeidler DL	The morality of socioscientific issues: construal and resolution of genetic engineering dilemmas	2004	Science Education	GS English	English	Education
200	Juengst ET	The NIH "Points to Consider" and the limits of human gene therapy	1990	Human Gene Therapy	PubMed	English	Genetics
201	Kong WM	The regulation of gene therapy research in competent adult patients, today and tomorrow: implications of EU Directive 2001/20/EC	2004	Medical Law Review	PubMed	English	Law
202	Karpati G, Lochmüller H	The scope of gene therapy in humans: scientific, safety and ethical considerations	1997	Neuromuscular Disorders	PubMed	English	Neurosciences
203	Walter JJ	Theological issues in genetics	1999	Theological Studies	PubMed	English	Theology
204	Henderson GE, Easter MM, Zimmer C, King NM, Davis AM, Rothschild BB, Churchill LR, Wilfond BS, Nelson DK	Therapeutic misconception in early phase gene transfer trials	2006	Social Science & Medicine	PubMed	English	Social Sciences
205	Kimmelman J, Palmour N	Therapeutic optimism in the consent forms of phase 1 gene transfer trials: an empirical analysis	2005	Journal of Medical Ethics	PubMed	English	Bioethics
206	Kimmelman J	Tomorrow, interrupted? Risk, ethics, and medical advance in gene transfer	2009	Molecular Therapy	PubMed	English	Biotechnology
207	Gilbert S	Trials and tribulations	2008	Hastings Center Report	PubMed	English	Bioethics
208	Kass LR	Triumph or tragedy? The moral meaning of genetic technology	2000	The American Journal of Jurisprudence	PubMed	English	Law
209	Henderson GE, Davis AM, King NM, Easter MM, Zimmer CR, Rothschild BB, Wilfond BS, Nelson DK, Churchill LR	Uncertain benefit: investigators' views and communications in early phase gene transfer trials	2004	Molecular Therapy	PubMed	English	Biotechnology
210	Teichler Zallen D	US gene therapy in crisis	2000	Trends in Genetics	GS English	English	Genetics
211	Anderson WF	Uses and abuses of human gene transfer	1992	Human Gene Therapy	PubMed	English	Genetics

212	Robillard JM, Whiteley L, Johnson TW, Lim J, Wasserman WW, Illes J	Utilizing social media to study information-seeking and ethical issues in gene therapy	2013	Journal of Medical Internet Research	PubMed	English	Medicine
213	Stockdale A	Waiting for the cure: mapping the social relations of human gene therapy research	1999	Sociology of Health & Illness	GS English	English	Social Sciences
214	Ponder KP, Srivastava A	Walk a mile in the moccasins of people with haemophilia	2008	Haemophilia	PubMed	English	Hematology
215	Chapman CR, Moch KI, McFadyen A, Kearns L, Watson T, Furlong P, Bateman-House A	What compassionate use means for gene therapies	2019	Nature Biotechnology	PubMed	English	Biotechnology
216	Porter J	What is morally distinctive about genetic engineering?	1990	Human Gene Therapy	PubMed	English	Genetics
217	Keenan JF	What is morally new in genetic manipulation?	1990	Human Gene Therapy	PubMed	English	Genetics

Appendix 15: Descriptive figures of the cohort of articles.

Figure 1. Numbers of articles per year.

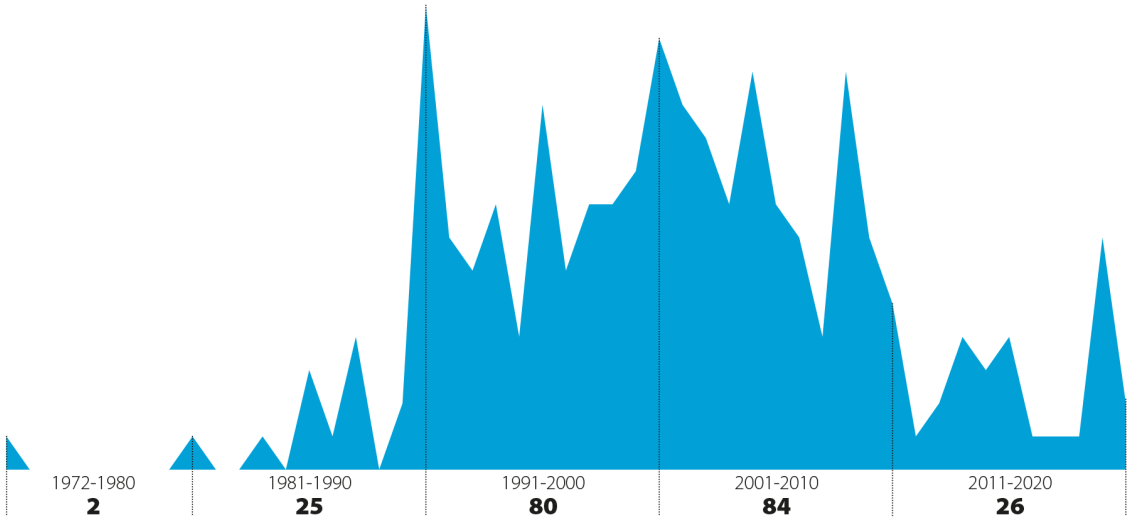


Figure 2. Types of articles.

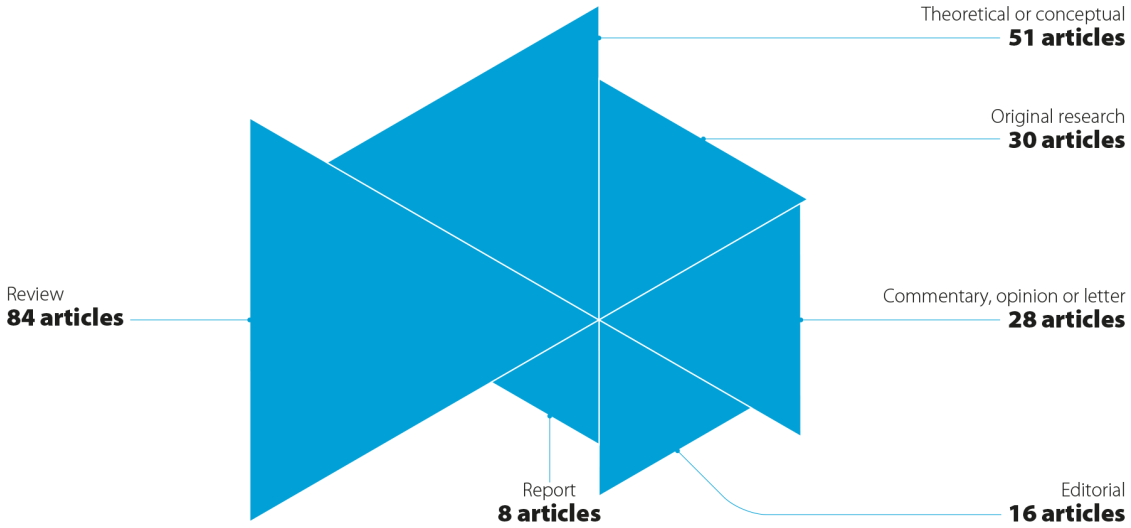


Figure 3. Country affiliation of all authors of included articles.

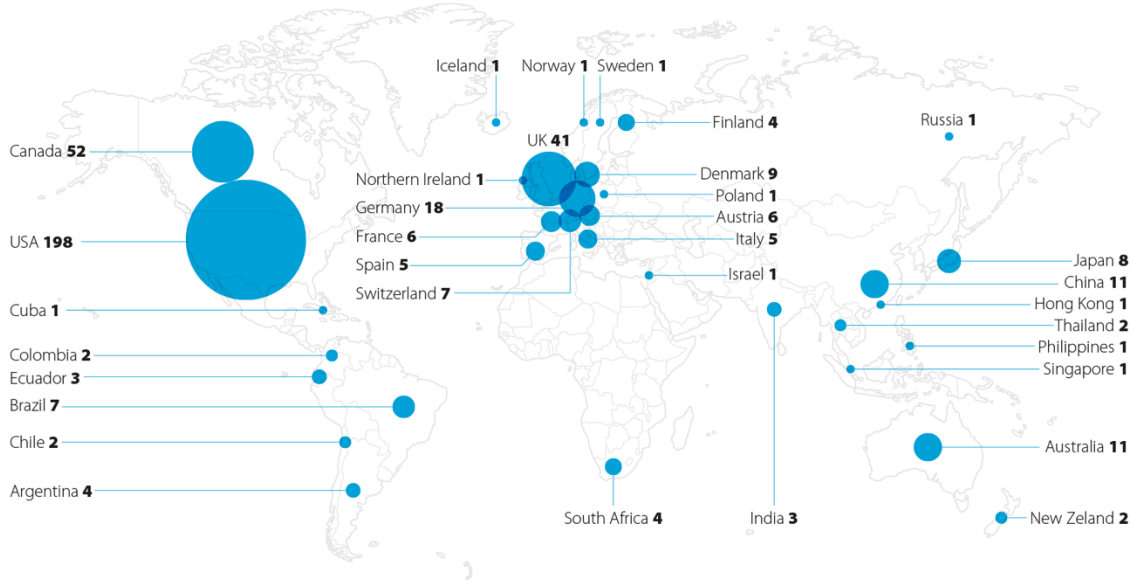


Figure 4. Journals in which articles have been published.

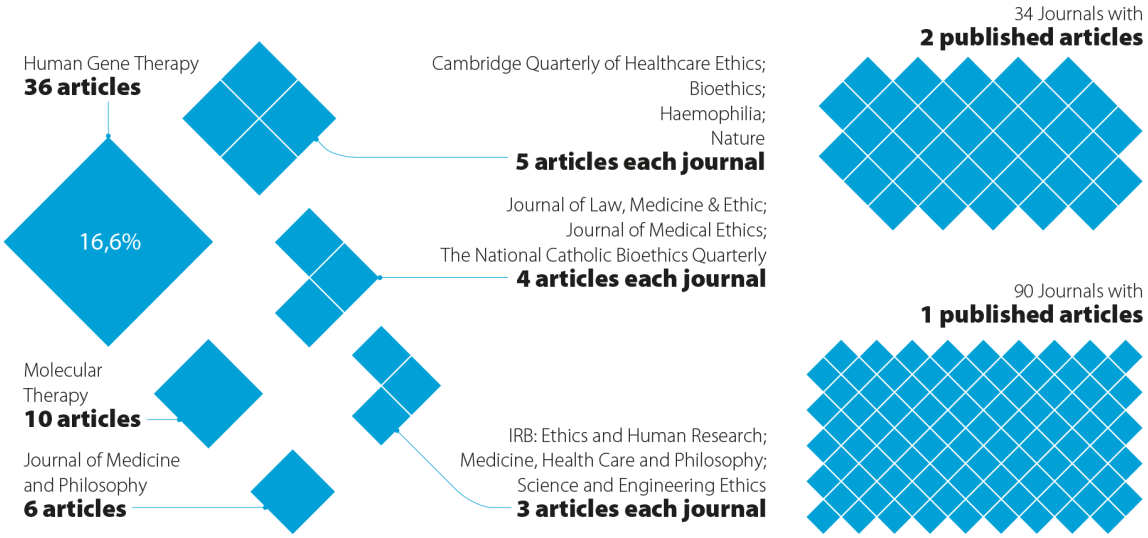
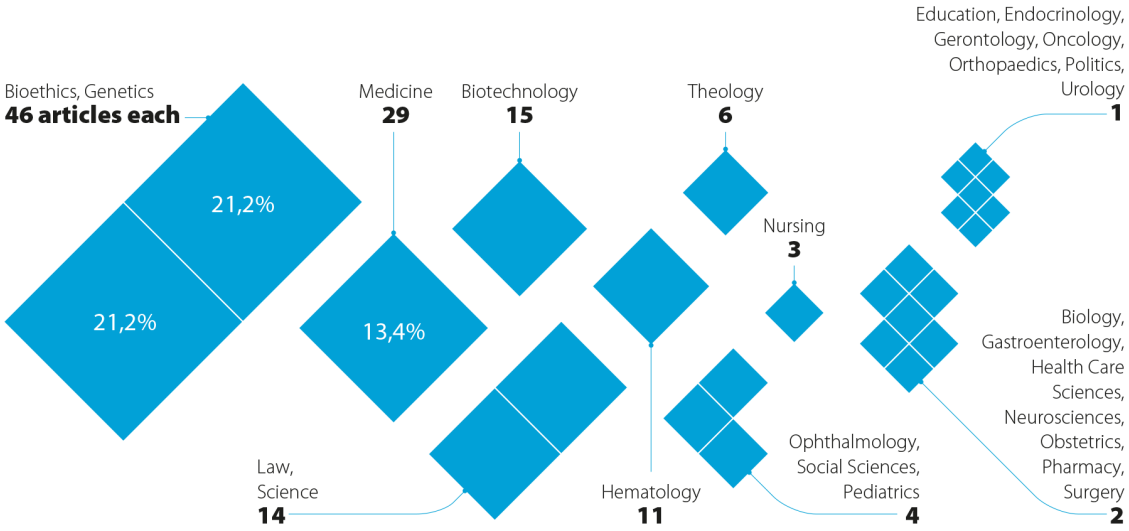


Figure 5. Academic fields (according to Journal Citation Report (JCR)) of the journals in which articles were published.



Appendix 16: Research-related arguments (Table 1) and society-related arguments (Table 2).

Table 1: Research-related arguments.

Category	Arguments	ID/s of article/s where the argument was/were extract
Pre-clinical stage	need for animal testing to evaluate safety, efficacy and long-term effects	31, 35, 52, 56, 57, 59, 71, 97, 99, 100, 117, 123, 124, 155, 189, 191, 214
	it is not always possible to extrapolate directly from animal experiments to human studies	7, 10, 17, 18, 22, 64, 88, 154, 161, 189, 209
	difficulty in establishing causality in disease occurrence and basic studies of pathophysiology are needed it	10, 45, 110, 161, 184, 189
	genetic therapies should take into account environmental effects on genes	4, 47, 49, 50
Clinical trials	delay in initiating trials could be harmful to people who are suffering	31, 81, 97, 104, 113, 143, 211
	adverse results do not invalidate gene therapy as is experimental	38, 124, 154, 174
	there are no reports of major adverse reactions in the last gene therapy clinical trials	45, 175
	need for public input in the research process	5, 10, 16, 53, 62, 66, 81, 136, 139, 141, 148, 149, 150, 151, 152, 184, 210, 213
	gene therapy trials are new and could have high/uncertain risks	10, 18, 22, 28, 32, 40, 41, 68, 90, 102, 104, 114, 117, 136, 174, 175, 121
	many gene therapy trials lack adequate statistical power to make valid conclusions about possible racial or ethnic differences	141
Selection of participants	participation in gene therapy trials can be beneficial for people both in developing and developed countries	214
	could be justified in life-threatening diseases without any therapeutic alternative	55, 56, 57, 72, 74, 89, 100, 101, 110, 123, 158, 162, 183
	genetic education can foster participant engagement	166
	society's ethical commitments to people living today should be prioritized over those who may benefit in the future from gene therapy	176
	the good of society should not come at the expense of individual persons	193, 200
	there is a risk of exploitation related to what we call collateral affective benefits (hope and altruism) for research participants	196

	the “terminally” of a participant situation should not be used to justify the “higher risk” than is permitted for a non-terminal participant	196
	there is pressure to recruit a record number of human subjects to a record number of trials	207
	it is unethical to recruit subjects from economically disadvantaged countries because they may not have access to gene therapy	214
	difficult to ensure fairness in the selection of subjects	7, 22, 31, 33, 40, 55, 64, 83, 97, 117, 129, 153, 176, 192, 200
Decision making and informed consent	informed consent could require a different strategy than usual to guarantee genuine decisions	51, 70, 81, 125, 138, 142, 148, 149, 189
	the consent form is an influential component to the consent process	196, 209
	problems with understanding the nature of the intervention and risks for participants	1, 14, 42, 51, 104, 114, 149, 152, 165, 184, 201, 213
	participants may decide based on the hope that they will benefit themselves	28, 31, 32, 35, 51, 60, 66, 69, 104, 117, 130, 213
	concerns about subjects’ overestimate benefits and provide invalid informed consent	174, 176, 200, 204, 205, 209
	confusions between research and therapy intensify extant problems of informed consent	26, 31, 36, 40, 78, 174, 196, 201, 204, 205, 209
	should be clear that personal benefit does not overlap with the scientific purpose of the study	9, 13, 89, 95, 117, 122, 209
	benefits to participants should be distinguished from benefits to society	19, 174
	it is important to give very detailed information to patients participating in gene therapy trials to prevent unrealistic hopes	170, 196
	risks should be communicated even if they are unlike to happen	8, 12, 18, 46, 50, 51, 159, 160, 214
	gene therapy could be irreversible so the right to revoke one's consent is less meaningful than for continuing medical treatment	50
	receiving insufficient information about the treatment is a main concern	144
	participants prefer to wait for strong evidence before considering enrolling in a clinical trial	8, 73, 86
	informed consent should inform participants, no protect the institutions	151
Confidentiality	difficulties in protecting the privacy and confidentiality	4, 12, 36, 47, 64, 97, 162, 171, 187, 197, 198, 217
	information obtained during gene therapy trials may adversely affect individuals receiving treatment or their families	50, 171, 187, 197, 198, 217

Review and monitoring	somatic gene therapy arises similar ethical issues than other medical technologies/treatments	4, 6, 12, 18, 19, 22, 28, 32, 37, 38, 41, 44, 50, 63, 65, 66, 69, 70, 71, 72, 73, 76, 77, 78, 85, 93, 94, 96, 100, 102, 105, 111, 114, 122, 124, 126, 128, 143, 158, 162, 168, 171, 173, 175, 178, 179, 181, 185, 191, 216
	no need for special evaluation of gene therapy protocol because it is similar to other biotechnologies	100, 107, 173, 216
	there are specific bioethical implications for gene therapy and must be carefully considered	5, 16, 20
	gene therapy has very specific and unique ethical complexities comparing to other medical practices	2, 39, 46, 71, 90, 119, 190, 208
	need for public involve in the review and monitoring protocols	127
	a worldwide accepted and controlled bioethics convention is need it for gene therapy	126
	need for special evaluation and audit of protocols	11, 35, 40, 45, 57, 62, 81, 100, 113, 118, 121, 124, 131, 150, 154, 159, 160, 188, 190, 192, 200, 202, 210, 213
	the ethical complexity of gene therapy should not be approach only with ethics committee	2, 147, 151, 154, 158, 159, 160, 162
	the protocol should be strictly followed and any changes in the protocol should be documented	110, 115, 62, 89, 115, 137, 145, 187, 188
	should be effective means of control and discipline after the protocol is approved	162
	any adverse event must be reported	46, 62, 89, 115, 145
	there is an obligation to avoid harm	19, 40, 87
	security issues should not be confused with ethical issues	32
Risk/benefit ratio	should be treated as a conventional medical therapy in determining risk/benefit ratios	85, 192
	beneficence hinges on the potential for net benefit in the whole population while doing minimal harm to the individual	32, 81
	there could be subtle benefits of gene therapy	88, 100, 125
	non-viral vectors could be safer but still not efficient	17, 39, 62, 67, 70, 73, 131
	long term transgene expression is limited	142
	need for a distinction between medical benefits and collateral benefits	196
	difficulties in risk/benefit balance because the risks are uncertain and cannot be reduced to one utility	176, 193

	difficulties in risk/benefit balance related to how potential social benefits should be balanced against individual risks	196, 201
	difficult in balance benefits and risks compared to the burden and prognosis of the disease	18, 34, 40, 41, 48, 63, 95, 100, 104, 114, 121, 125, 190
	probabilities and outcomes for adverse events relating to gene therapy are difficult to define	7, 10, 18, 22, 40, 42, 51, 63, 67, 104, 114, 117, 165, 184, 190
	new materials have novel properties that may affect humans in unpredictable ways	7, 16, 61, 63, 64, 70, 90
	could produce serious and/or irreversible side effects	10, 17, 18, 23, 43, 50, 54, 60, 64, 69, 71, 85, 86, 88, 90, 100, 101, 114, 126, 167, 176, 183, 192
	could happen an unintentional modification of the germinal cells	31, 54, 64, 67, 85, 88, 107, 114, 117, 125, 126, 164, 175, 177, 180, 202
	could produce immune responses generated against both the vector and the transgene	54, 62, 118, 161, 164, 165, 168, 169, 175, 176, 177, 194, 196, 202, 213
	the gene vector could either activate an oncogene or inactivate a tumour-suppressor gene	164, 169
	possible risks are transfer of an unwanted gene, administration of replication competent virus and bacterial contamination of the vector	177, 196, 202
	concerns about the long-term safety and efficacy	12, 16, 17, 31, 40, 41, 45, 59, 60, 61, 63, 64, 67, 69, 76, 77, 89, 90, 105, 123, 166, 175, 182
	technical issues in terms of the quality and stability of the transgene expression	17, 31, 41, 59, 70, 85, 90, 110, 161, 168, 183, 184, 192, 196, 200, 202, 213
	viral vectors are still not quite safe	17, 39, 61, 62, 64, 70, 71, 73, 90, 99, 100, 110, 118, 131, 142, 161, 165, 167, 183, 187, 196, 202, 213
Conflicts of interest	difficulties in management of conflicts of interest	33, 39, 40, 53, 77, 85, 93, 100, 102, 121, 124, 115, 145, 146, 188, 207, 213
	conflicts of interest could be financial and personal	207
	important stakeholders have deep interests in gene therapy	127, 155
	clinical investigators should not have personal financial relationship with companies that may benefit with results	46
	due to the great investments, there is a big pressure for success on the scientists	4, 53, 117, 121
	overlapping roles could lead to potential conflicts in the recruitment of subjects	104
Regulations	regulatory system is likely to be challenged by gene therapy	6, 21, 22, 31, 45, 67, 66, 68, 69, 121, 136, 159, 160, 190, 201

	gene therapy research is highly regulated and is affected by overregulation and bureaucracy	65, 68, 135, 179, 207
	gene therapy regulation cannot be a broad “blanket”, but each type needs to be assessed on its own merits and risk analysis	149
Research priorities and limits	gene therapy should be used in diseases evaluated in advance	71, 85, 101, 125
	the boundaries for what should be the therapeutic objective have to be established	175
	neither scientists or pharmaceutical companies should not control or decide alone about gene therapy limits	4, 156
	if gene therapy would be determined by market forces, this would lead to the development of genetic technology for enhancement	4, 191
	need to redefine rights and responsibilities of all actors involved	14, 17, 109, 117, 150, 152, 155, 184, 210, 213
	human gene pools are a collective property, so a public debate is needed about gene therapy	50
	the need for public participation in the ethical, social and policy discussion around gene therapy	4, 50, 53, 58, 200
	could be difficult to design regulation considering political and cultural differences	17, 62, 60, 63, 64, 68, 75, 76, 83, 85, 120, 127, 136, 152, 201
	it is no longer gene therapy per se being debated, but its application to particular diseases or particular patients	179, 193, 216
	should be more efforts to prevent diseases rather than treat	4
	gene therapy should not be a "first line" of defence therapy as long as an alternative is available	18
Unproven use	use of unproven gene therapy could apply to rare diseases	3
	potentially high prices or limited availability of approved gene therapy may patients to seek unproven use	215
Long term implications	need to consider the long-term implications (specially the absence of vertical transmission)	4, 154, 162, 164, 187
	need an adequate follow-up and to provide ongoing care for participants	10, 22, 54
	several factors work against achieving follow-up of patients participating in gene therapy trials	187

Table 2: Society-related arguments.

Category	Arguments	ID/s of article/s where the argument was/were extract
Human identity	human identity is under constant redefinition in biomedicine	76, 91, 105
	humanity's identity is more than a pool of genes	127, 216
	gene therapy could modify human identity, humanness, or personal perception	11, 19, 27, 47, 69, 79, 101, 103, 109, 123, 131, 133, 191, 199, 212, 216
	effort is part of what makes us appreciate our lives, so we do not have to eliminate all the pain or suffering	47
	we could lose our caring characteristics	47
	could threaten human dignity	208
	gene therapy involves causing particular human individuals to cease to exist	4, 103
	the body could be perceived as an enemy or as a source of weakness perfectible by technology	133
	gene therapy will reshape ideas on how best to live	2
	gene therapy should not be used to change human traits	162
Conceptual redefinitions	there are no ethical differences between germline and somatic gene therapy	25, 29
	we are not conceptually forced to allow all kinds of gene therapy once we allow one	96
	biotechnology highlights moral problems but not creates them	44
	research in somatic gene therapy cannot be considered eugenics	172
	could create a need for a new disease/illness, prevention, and treatment concepts	11, 14, 49, 81, 110, 113, 122,126, 133, 208
	enhancement or eugenic therapy could be captured as a therapy of human genetic disease	167
	could be difficult to difference enhancement from treatment	11, 14, 29, 44, 47, 64, 66, 72, 74, 80, 81, 85, 94, 96, 97, 101, 102, 109, 110, 113, 114, 120, 122, 126, 132, 179, 185
Disabilities and diverse functions	is not necessary to overcome every human "limitation"	4, 47, 79, 81, 83, 91, 103, 105
	disability could be an integrated aspect of a person's identity	133
	diverse functions or bodies that do not imply disabilities to prevent or treat (like deafness)	47

	gene therapy could impact on the social attitudes on disability	133
	the possibility of pursuing a better human could lead to more discrimination to disable people	47
	gene therapy will not increase discrimination, it will make us aware of it	6, 81
	instead of working on solutions based on social bias we need to think again about our social values	47
Biodiversity concerns	gene therapy will replace the animal tissue culture used in current treatments	164
	there seems to be little concern in the impact of gene therapy on biodiversity	4
	gene therapy manufacturing could be dangerous to the environment	1, 136
	failure to treat ourselves as part of the environment of which we are part	4
Population impact	gene therapy research is a significant step on science evolution, and therefore, for humanity's well-being	40, 65, 67, 69, 70, 72, 74, 76, 78, 83, 105, 106, 107, 118, 124, 126
	not affect human evolution	165
	gene therapy of one person could have bad repercussions on others	16, 27, 37, 44, 70, 77, 82, 85, 90, 93, 97, 114, 121, 126, 157, 200
	could modify human evolution	37, 43, 76, 77, 81, 82, 91, 93, 94, 96, 101, 109, 122, 123, 126, 157, 167, 183, 184, 212, 217
	could increase the possibility of developing other new technologies with undesirable effects	4, 35, 71, 72, 80, 93, 94, 96, 97, 101, 106, 122, 123, 128, 165, 183, 191, 199
	genetic diseases could become more prevalent in each generation after the somatic gene therapy	37, 43, 202
	could eventually lead us to accept eugenic goals	4, 49, 52, 74, 81, 85, 94, 96, 157, 172, 208, 217
	could lead us to modify the colour of the skin or change our personality based on social stereotypes	167, 171
	new approaches have novel properties that may affect humans in unpredictable ways	142
	longevity could provoke loneliness, and overpopulation, despite of improving quality of life	1
	might cause harmful or unacceptable genetic alterations or lead to social abuses	158
	could turn social problems into genetic problems	4, 29, 85, 93
	gene therapy arises the issues of fairness, justice, or equity in access to therapy	69, 67, 75, 81
	gene therapy could reduce personal privacy, lead to genetic discrimination, and cause population aging	180
	if we accept somatic gene therapy, we are logically committed to accepting germ-line therapy	44, 72, 122, 208

	the need to consider broad and long-range research consequences: the public health, environmental, and evolutionary concerns	200, 201
	genetic technology is offered with the focus on individual patient choice	70, 72, 79
	could motivates/deepen conflicts between values	17, 35, 101, 107, 121, 152, 163
	"bad" genes are needed from the viewpoint of the species	106
Social justice	gene therapy could be cost-effective when compared with current therapies	50, 53, 55, 69, 143, 162, 164, 189, 202, 215
	possibility of gene therapy reinforces the need for universal access to health care	86, 197
	debates about genetics and justice should take seriously the fact of scarcity	195, 197
	could be only available in countries/people with high income	1, 14, 17, 21, 33, 34, 36, 76, 77, 79, 90, 96, 101, 102, 183, 189, 197
	could be discriminatory to people who do not have access to gene therapy	11, 28, 36, 63, 81, 84, 101, 123, 185, 198, 212
	it may relegate funding from other areas of healthcare	4, 21, 32, 34, 36, 38, 61, 64, 69, 83, 75, 77, 79, 85, 112, 119, 125, 197, 202
	economic inequities could impact human biology	112
Public perception	there is a high public support for the use of gene therapy to cure serious diseases but not to enhancement	9, 19, 45, 50, 61, 63, 66, 67, 73, 74, 81, 85, 90, 97, 101, 106, 107, 113, 144, 167, 180, 212
	gene therapy is viewed by the majority as a desirable extension to the range of medical options available	179
	in regard to therapeutic means, the Church is receptive and encouraging, so long as proper precautions are taken	186, 198
	lay people are interested in knowing about gene therapy	212
	guarantee sound research in general and patients' safety in particular is crucial to public support and recruiting	146
	ambivalence about genetic technology	208
	gene therapy has a long way to go before gaining widespread acceptance among medical students	180
	lay people think that is a risky procedure	127
	there is no public trust in gene therapy	4, 8, 127
	people are unaware of "gene therapy" term and its availability	69, 86, 97, 126
	the possible consequences of manipulating genes or design humans arise fear	9, 15, 60, 86, 93, 97, 98, 101, 105, 106, 126, 212
	the most frequent reasons for not accepting GT were fears of adverse effects, high cost and a belief that it went against nature	180, 216
	concerns about the political uses of gene technology, genetic discrimination, and misuses of power	180, 208

	genetic manipulation leads to a touchy issue about alteration of the soul, and therefore the Church wants to proceed slowly	186
	could provoke negative emotional reactions because of the stories of deaths	23, 62, 121, 131, 150, 163, 165, 210
Human health	could be the only type of treatment for particular diseases	11, 23, 31, 43, 50, 60, 62, 68, 70, 110, 111, 123, 128, 175, 179, 181, 182, 183, 185, 192
	has many potential applications, other than only in monogenetic diseases	59, 62, 64, 69, 70, 73, 145, 161, 175, 181
	could prevent/treat serious diseases that make humanity suffer and improve quality of life	60, 64, 68, 69, 73, 74, 80, 83, 84, 133, 140, 143, 169, 182, 185, 192, 199, 211
	progress in genetic research is clearly relevant to women's health for understanding and treating common diseases	197
	“therapeutic abortion” could be rare if genetic diseases could be treated	53, 129
	gene therapy could avoid anxiety associated with the life-threatening nature of the underlying disease	53
	gene therapy also holds the promise of preventing diseases	155
	gene therapy may provide a curative rather than a symptomatic approach to diseases	143
	the treatment objective of gene therapy is not always curative, but rather aims at restoring function than eliminating the cause	175
	there is a moral obligation to develop gene therapy if we consider it is the only treatment for particular diseases	12, 19, 33, 36, 76, 125, 129, 194
Implementation	gene therapy requires specific cooperation between healthcare workers and scientists	64
	gene therapy will create a need for specific standard operational procedures	64
	could set up problems in its implementation into the practice of medicine	38, 59, 66, 67, 68, 131, 159, 165, 193, 194, 213
	genetic diagnoses are needed before the therapy, so it should be already available	56, 81, 84, 123, 189
	analogous to present medical practices, therapeutic manipulation objectifies the disease in the person rather than the person	217
	if alternative treatment exists, use of gene therapy will depend on its efficiency, costs, and level of discomfort to patients	59
Communication to people	the term "gene therapy" use in research does not reflect whether is a therapy or research	50, 53, 54, 89, 93, 95, 104, 107, 113, 117, 124, 150, 161, 201, 204, 213
	terminology has been shown to influence risks and benefit perception	205, 209
	public opinion should be adequately informed about gene therapy	81

	scientists need to spend proper time in communicating science to media	8, 137, 149, 212
	need for public trust on the basis on proper knowledge and transparency on research process	14, 15, 17, 62, 68, 66, 81, 84, 90, 100, 108, 150, 152, 161, 163, 165, 184, 213
	there is a tendency to exaggerate potential benefits and minimize potential risks	68, 66, 78, 124, 134, 190, 202, 216
	gene therapy research could evoke unrealistic expectations more than other areas of medical research	66
	it is an emotionally volatile topic and if no patient is helped the negative reaction could provoke a society slowdown	155, 169
Playing God	we are not playing God with gene therapy as science is a human activity	127
	there may be both proper and improper ways of playing God	203
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