



GLOBAL POLICY FRAMEWORK (GPF) GLOBAL STANDARD - BIOETHICS

KEY PRINCIPLES

- We operate in accordance with applicable legislation, regulations, standards and guidelines
- We are committed to patient safety
- We provide transparency to our clinical trials
- We follow appropriate informed consent procedures
- We protect the privacy of research participants
- The ethical treatment and welfare of animals is a top priority

1. WHY IT MATTERS AND TO WHOM

This Global Standard sets out the principles for a range of ethical topics that arise from the study and practices of biological and medical science that we refer to as Bioethics.

Whilst there are many separate areas within the field of Bioethics, here at AstraZeneca (AZ), we view all areas as a complete entity with shared values of putting patients first, following the science and doing the right thing.

Bioethics is central to our science under AZ's Code of Ethics, which conveys key principles for ethical application in biological and medical science.

2. WHAT YOU NEED TO KNOW AND WHY

The scope for Bioethics at AstraZeneca includes the following key areas of bioethical interest:

- Clinical Research and Patient Safety
- Privacy of Information
- Data and Artificial Intelligence
- Human Biological Samples (HBS) and Use of Genomic Information
- Genome Editing
- Genetically Modified Organisms
- Animals in Research and Development (R&D)
- Nagoya Protocol.

This Global Standard sets out the key principles and practices that apply to each of the areas. Our Bioethics Advisory Group, sponsored by the Chief Medical Officer (CMO), brings together a diverse group of experts from a wide range of disciplines to advise the Company on implementation of the principles set out in this Global Standard.

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3. REQUIREMENTS

3.1 Key Requirements of Bioethics

AstraZeneca is committed to working only with institutions, researchers, patient advocacy groups, health industry partners and other third parties, contractors, such as suppliers, joint venture or co-promotion partners, and research or licensing partners, who embrace standards of ethical behaviour that are consistent with our own. Our key requirements also include;

- We maintain a portfolio of research and development projects designed to deliver medicines that are effective, safe, differentiated and address unmet patient needs.
- We conduct clinical studies in accordance with all regulatory requirements and the recognized international quality and safety standards in all countries in which we operate.
- We ensure that the appropriate informed consent procedures are followed when conducting clinical trials, and that appropriate procedures relating to the protection of personal data are applied when we collect or access any health information.
- We make information publicly available about the registration and results of our clinical trials for all products in all phases, including marketed medicines, medicines in development and medicines whose further development has been discontinued.
- We are committed to patient safety throughout our activities.
- We use data and Artificial Intelligence (AI) systems that are private, secure, human-centric, socially beneficial, explainable, transparent, accountable and fair.
- We consider and justify all research and development involving animals, and apply the principles of the 3Rs (Replacement, Reduction and Refinement).
- We apply an internal governance process to guide the acquisition, storage, use and disposal of human biological samples and associated data.
- We comply with international standards of good practice, such as The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice and Good Laboratory Practice.
- We govern and record our utilisation of non-human genetic resources in accordance with regional and national access and benefit sharing legislation.

3.2 Clinical Research And Patient Safety

3.2.1 Dedication to Patient Safety

We are committed to detecting any adverse reactions to our investigational products and approved medicines as early as possible and to provide updated information to investigators, prescribers, consumers and research participants as appropriate.

All reports of adverse events are scrutinised by medically qualified individuals. Individual cases judged to be potential safety signals trigger further analyses of existing data and possible subsequent actions.

We regularly analyse safety data from development projects and marketed products to ensure adverse reactions and possible safety signals are identified from both clinical and non-clinical sources.

We have risk management plans for all products in Clinical Development. These documents evolve as safety data become available, so that we can minimise risk and optimise benefits for patients.

We follow defined processes aimed at ensuring all relevant safety information is incorporated in product labelling and Investigator's Brochures.

We report any adverse events we become aware of involving any AstraZeneca investigational product or approved medicine.

3.2.2 Conducting Clinical Research

We conduct clinical studies only in countries where we intend to file for approval and market the product.

We conduct clinical studies with human participants in accordance with all regulatory requirements and the recognised international quality and safety standards in all countries and territories in which we operate.

We apply quality and safety standards, including Good Manufacturing Practices, Good Laboratory Practices, Good Clinical Practices, and the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

We promote inclusion and diversity in clinical trial participants.

We adhere to the regulatory requirements of designing and delivering paediatric programs for all medicines under development.

We conduct the required package of studies and receive Executive Safety Board approval before the start of any First Time in Human (FTiH) studies.

We conduct preclinical studies to indicate the possibility of the candidate drug delivering a clinical benefit with a favourable benefit/risk ratio. A candidate drug with an acceptable safety profile may also be used to test the concept of a novel mechanism, guiding the development of future medicines or investigation in humans leading to an increased understanding of a disease and its potential treatment.

We may engage in placebo-controlled clinical studies when judged scientifically appropriate and agreed with regulators and Ethics Committees. We take steps to safeguard the interests of all participants in our clinical studies, including those participants receiving a placebo control.

Prior to enrolment in a study, our informed consent process gives participants, parents, legal guardians and other concerned parties information about the benefits and risks of participation in the clinical study, as well as privacy, confidentiality and property rights as a clinical study participant. Study participants are free to withdraw at any time without any detriment to their medical care.

We ensure that compensation for research participants is consistent with the principle of voluntary participation in clinical studies. Payments to clinical study organisations and investigators is based on the costs incurred and the work they perform.

We design clinical programmes to explore the potential benefits of our investigational products to the clinical study participants and the intended patient populations, while minimising the risks in all clinical studies conducted by us or those acting on our behalf.

We provide timely communication of the benefits and risks of our investigational products and medicines to regulators, health care providers, investigators, patients and the public in product labelling, periodic regulatory reports, Investigator's Brochures, by posting results on all applicable global registries and by publication of clinical study results.

3.2.3 Clinical Trial Transparency

We are committed to global clinical trial transparency and believe there are important public health benefits associated with making clinical study information available to healthcare professionals and the public in a timely, accurate, meaningful and objective way.

We ensure transparency through the timely registration of clinical studies, posting of the clinical study results, easy to understand trial summaries on websites and/or publication in peer-reviewed journals, and the sharing of anonymized clinical data and documents with researchers, regulators and the public.

We comply with all global laws and regulations for study registration and reporting of results. We register and communicate results of all AstraZeneca sponsored clinical trials through appropriate digital channels and where possible through publications.

We post the research protocol (redacted for personal and confidential information) for AstraZeneca sponsored clinical trials on appropriate websites and registries.

We respond to requests for access to anonymized, patient-level data from AstraZeneca sponsored clinical trials following our internal governance process. We submit anonymized Clinical Report Packages to the European Medicines Agency and Health Canada in accordance with their policy and they make this information public.

We communicate with patients via our research sites to thank them for their participation in our trials and we provide Trial Results Summaries in lay language to study participants via www.trialsummaries.com. These will also be posted to the EU portal when it becomes available. We commit to good publishing practice and appropriate communication of information on our products and clinical studies to the international medical and scientific community.

3.2.4 Initiating Clinical Studies

Before initiating FTiH studies – a major milestone in developing new medicines – the candidate drug's characteristics must be confirmed through preclinical studies as required by the medical community, ICH and regulations.

We base decisions about participant populations for FTiH studies, which may include healthy volunteers, participant populations with a specific disease or medical condition, or participants who are at risk to develop a specific disease or medical condition, on the known risks and potential benefits to the study participants, while meeting study goals and minimising health risk.

Before commencing FTiH clinical studies, we peer-review (by an expert committee within AstraZeneca), preclinical data and proposed early clinical studies, to ensure that all safety aspects have been evaluated and that the assessment of potential risk/benefit justifies the testing of the candidate drug in the clinical setting.

We submit our clinical study protocols to external Ethics Committees and, as required, regulatory authorities in the countries where the study will take place.

3.2.5 Obtaining Informed Consent

We give those who participate in our clinical studies full, truthful and understandable information, usually in writing and orally. In accordance with the World Medical Association's Declaration of Helsinki and ICH Guidelines for Good Clinical Practice, we communicate clearly about:

- The aim of the study.
- Details of the procedures and investigational product(s), and the benefits and risks involved.
- Participants' freedom to withdraw at any time without explanation.

We ask participants or legally accepted representatives to indicate in writing their receipt of this information and their consent to be part of the study. A specific and mandatory procedure provides ethical and legal requirements for the consent process.

We communicate to regulatory authorities, investigators and Ethics Committees as appropriate and in accordance with applicable law and regulations if important new information about an investigational product becomes available during an ongoing study.

3.3 Privacy of Information

We protect the privacy of research participants by ensuring all data brought into AstraZeneca, for example, clinical, human tissue or health information, are coded, double coded or anonymised to conceal a participant's identity. When studies are performed at our own research units, information about identities is contained within those units. If any participants information is sent to AstraZeneca, it is handled in a secure and anonymised way.

We interact with patients only with their prior consent or in response to requests for potential clinical trial participation.

We work with governments and regulators to ensure standards for protecting patient privacy and confidentiality are integral to any new media, for example, Electronic Health Records or online databases, used to communicate medical data.

We are sensitive to the privacy rights of individuals who are defined to be members of small populations, such as those with rare diseases. In such situations, the 'risk of identification by association with a small population' will be assessed and managed in an appropriate manner.

3.4 Data and Artificial Intelligence (AI)

We follow five principles for ethical AI (private and secure, explainable and transparent, fair, accountable, and human-centric and socially beneficial), by applying the following requirements:

- We respect privacy and control, and act in a manner compatible with intended data use.
- We employ data and AI systems that are designed to be secure.
- Where data and AI is involved, humans oversee the system and are accountable for driving clear, expected benefits to people and society.
- We endeavour to use robust, inclusive datasets.
- We treat people and communities fairly and equitably in the design, process, and outcome distribution of our AI systems.

- We are open about the use, strengths and limitations of our data and AI systems.
- We ensure assumptions are clear, algorithms are appropriately documented, decisions are explainable as needed, and processes are in place to deal with unanticipated consequences.
- We apply governance proportional to the impact and risk of our data and AI systems.
- We take accountability of our use of data and AI systems throughout their life cycle, so their use is appropriate and monitored over time.

3.5 Human Biological Samples and Use of Genomic Information

We use human biological samples and genomic information, for example, from DNA, and/or RNA within human tissues and preclinical models, for research into better understanding of diseases, improved diagnosis or other improvements in healthcare and for the research and development of new medicines. Human biological samples and genomic information are also used for AstraZeneca sponsored clinical studies in the development of medicines intended for human use.

We control use of human biological samples and genomic information by application of internal standards that are consistent with relevant legal and regulatory requirements.

We provide participants with information about the nature and purpose of the studies and the use of samples through an informed consent process. We require participants to provide written consent to participate. Such consent may be part of the main study consent, for example, if the genomic information is used to select patients for therapy, or may be a separate, optional consent if genomic information is to be used for research. If consent is optional, participants can decide not to take part in the genomics research or optional samples and future use of samples and still participate in the main clinical study.

We may seek access to rare, hard to find diagnostic human biological samples where original consent for research is limited or absent. In this situation we conduct an internal review, before requesting ethical approval for use, via an appropriate external Ethics Committee.

We state in the consent if genomic data will be returned to the participant. The return of genomic data to the participant is dependent on the nature of the study and on the level of validation of the technology and reagents used to generate it. If genomic data is returned to the participant, we specify in the study protocol a detailed process for handling such findings. We communicate this process to the participants and they acknowledge their acceptance when signing the consent form.

We take rigorous measures to protect the data privacy of participants.

Human stem cells have the potential to expand understanding of the underlying causes of disease and provide options for new medicines. Differentiated cell lines derived from stem cells also have the potential to predict drug metabolism and human toxicity more accurately than existing techniques. Increasing knowledge of intracellular pathways should enable us to make different types of mature cells from pluripotent stem cells. This is used to support research on new medicines that may be able to regenerate damaged tissues and organs. For these reasons, we support investigation of human stem cell-derived cell lines for use in research and development, and we have a rigorous ethical framework that governs our work in this area.

We conduct mostly stem cell projects that aim to investigate the research potential of human induced pluripotent stem cells (hiPSC) generated by 'reprogramming' adult cells

to become more stem cell-like. hiPSC can be obtained safely from adult volunteers and do not involve embryos. We see considerable potential application of cell lines differentiated from hiPSCs in research including prediction of drug metabolism, human toxicity and as cell therapies. We use human embryonic stem cells (hESC) when there is no alternative technology that would provide the scientific information required to increase our knowledge of and develop medicines for disease.

Before initiating any new hESC research, we require a clearly defined purpose to increase knowledge about disease that cannot be obtained via the use of hiPSC and to apply such knowledge in developing medicines for disease.

We require that the hESC used must come from a fertilised egg that was created through in vitro fertilisation (IVF) but is no longer needed for reproductive purposes, with fully informed consent to donate the egg for scientific research with no financial inducements.

We only use hESC cell lines that have been accepted into a publicly recognised body or bank of registration or meeting equivalent standards. All research must be conducted in accordance with applicable legislation, regulations and guidelines.

In rare circumstances we may use human fetal tissue in research and development to advance our understanding of diseases. In such rare circumstances, we conduct an internal review of the scientific validity of the research proposal and permission to use the tissue is granted only when no other scientifically reasonable alternative is available. In order to further limit and avoid future use of human fetal tissue, we remain on the cutting-edge of scientific advancements and remain committed to implementing industry best practices.

We recognise that use of historic cell lines originally derived from hFT is widespread in research, and use of these cell lines is needed for regulatory and other scientific reasons in the development of new medicines.

We conduct internal review on use of historic cell lines originally derived from hFT that are not in widespread research use and for more recent material derived from hFT.

3.6 Genome Editing

We believe that CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and similar genome editing technologies can improve the identification and validation of new biological targets of disease and enhance testing of potential new medicines for safety and efficacy. In addition, genome editing technologies are advancing into clinical studies for the potential treatment of genetic diseases.

- We develop methods to improve efficient modification of the target gene and minimise off-target effects elsewhere in the genome.
- We support the general principle of cell and gene therapies in human somatic cells and pluripotent stem cells. We recognise risks due to: unwarranted on-target effects, possible off-target effects, and unwanted germline, that is, sperm, egg or embryo modification.
- We neither practice or endorse human gene therapies which target the germline at this time. The ethical and scientific risks inherent in such practice are a topic of intense global discussion and deemed illegal in many countries.
- We follow closely developments in therapeutic gene editing and commit to active participation in the debate around its use.

3.7 Genetically Modified Organisms

Through genetic engineering, we produce Genetically Modified Organisms (GMOs) for research and development of new medicines. All GMO work (including work carried out by third parties on our behalf) is risk assessed, appropriately classified and carried out under appropriate levels of biosafety containment and in compliance with local and relevant international environmental, health and safety laws and regulations. We use genetically modified micro-organisms (GMMOs), for example, animal and human cells, bacteria and viruses and genetically modified animals.

- We provide appropriate training in GMO regulations, risk assessment and handling GMOs inside containment.
- We risk assess all work and take a precautionary approach in case of uncertainty of risk.
- We classify the GMOs correctly and work in facilities designed to provide appropriate containment.
- We support transparency and openness about our use of GMOs.
- We treat waste streams containing GMOs appropriately to prevent or minimize loss of containment.
- We report and investigate GMO incidents in accordance with our safety, health and environmental Global Standards.

3.8 Animals in Research and Development (R&D)

The responsible use of animals is a vital part of biomedical research and product safety testing, where suitable alternatives are not available. We undertake studies involving animals to discover and develop new medicines, to increase our understanding of biology and disease, and to meet the requirements of international regulators. We apply the following principles to all animal studies we conduct ourselves or by third parties acting on our behalf, and to the breeding and supplying of animals for use in such studies.

We adopt a humane approach in the care and treatment of all animals, and the greatest consideration is given to their health and welfare, consistent with meeting the necessary scientific objectives.

We commit to the principles of the 3Rs; Replacement, Reduction and Refinement.

We carefully consider and justify all animal studies to ensure that: the study is scientifically necessary; there is no reasonably practicable alternative to the use of animals (Replacement); only the minimum number of an appropriate species of animal is used to achieve the scientific objectives (Reduction); and that the study is designed and undertaken to minimise pain and distress to the animals involved (Refinement).

We commit to sharing knowledge of good practices and 3Rs achievements both throughout AstraZeneca and the wider scientific community.

We ensure that our own facilities and animal welfare programmes, as well as those of third parties who conduct animal studies on our behalf, comply with our policies. All animal studies are undertaken in compliance with all relevant local and national laws and regulations, and with the principles of the "Guide for the Care and Use of Laboratory Animals" 8th Edition (Institute for Laboratory Animal Research). Wherever possible, we work with third parties accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

We ensure the timely notification of any situations where: there may be non-compliance with our policies; standards of ethical behaviour may not have been met; or other significant events may have actual or potential impact to our animal programs. Formal arrangements must be put in place to satisfy this requirement, whether the work is carried out in our own facilities or by third parties acting on our behalf.

We do not conduct or resource work using wild-caught nonhuman primates or great ape species. In the rare case where there is no credible alternative model to develop a treatment for disease, exceptions may be considered. The decision to progress requires rigorous secondary ethical and scientific review to challenge the need for the study, followed by Board-level approval.

3.9 Nagoya Protocol

A co-ordinated effort is required on the part of communities, governments and businesses to conserve global biodiversity. We support the objectives set forth in both the Convention on Biological Diversity and the Nagoya Protocol, which together govern the conservation of biodiversity and the fair and equitable return for use of its components. We use non-human, for example, plant, animal, and viral genetic resources in the research and development of new medicines.

We assess whether (non-human) genetic resources we intend to access are within scope of the Nagoya Protocol. We obtain genetic resources in accordance with regional and national access legislation, where such laws and regulations exist. Consequently, where appropriate, we ensure that genetic resources are accessed with the prior informed consent of the country of origin, with a contract of mutually agreed terms in place to ensure the fair and equitable sharing of benefits arising from the utilisation of the materials. These benefits may be monetary or non-monetary, as determined on a case-by-case basis. We then use these materials in accordance with any mutually agreed conditions.

When sourcing materials within the scope of the Nagoya Protocol, we take all reasonable steps to ensure that we demonstrate appropriate due diligence and comply with all relevant access legislation.

We seek to keep relevant information relating to the genetic resources we use. We make available due diligence statements to appropriate authorities as required and at designated checkpoints throughout the research and development of any medicine that emerges.