Global Standard: Bioethics
Bioethics refers in the broadest sense to the range of ethical issues that arise from the study and practice of biological and medical science. While there are many discrete subject matter areas within the field of bioethics, at AstraZeneca we consider them as an integrated whole considering our company values, including putting patients first, following the science, and doing the right thing.

The Bioethics Advisory Group (BAG) brings together the subject matter experts for the main areas of bioethical interest at AstraZeneca:

- Clinical Research and Patient Safety
- Privacy of Information
- Precise Genome Editing, Genomic Information and Human Biological Samples
- Genetically Modified Organisms
- Animals in Research
- Nagoya Protocol

The BAG is sponsored by the Chief Medical Officer. This Global Standard sets out the key policy principles and practices that apply to each of the subject matter areas.
Key Principles

• AstraZeneca is committed to working only with suppliers, joint venture or co-promotion partners, and research or licensing partners, who embrace standards of ethical behaviour that are consistent with our own.

• We will maintain a portfolio of research and development projects designed to deliver drugs that are effective, safe, differentiated and address patients’ needs.

• We will conduct clinical studies in accordance with all local regulatory requirements and the recognised international quality and safety standards in all countries in which we operate.

• We must ensure that the appropriate informed consent procedures are followed when conducting clinical trials, and that the procedures relating to the protection of personal data are applied when we collect or access any health information.

• We will make information publicly available about the registration and results of our clinical trials for all products in all phases, including marketed medicines, drugs in development and drugs whose further development has been discontinued.

• We will maintain our commitment to patient safety throughout our activity.

• We will carefully consider and justify all research involving animals, and we will apply the principles of the 3Rs (Replacement, Reduction and Refinement). The welfare of the animals we use is a top priority.

• We understand that use of human biological samples in research and therapy development is a potentially sensitive area. An internal global governance framework exists to guide the acquisition, storage, use and disposal of human biological samples and associated data.

• We will 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 support the general principles set forth in the Convention on Biological Diversity and the Nagoya Protocol. We govern and record our utilisation of genetic resources in accordance with regional and national access and benefit sharing legislation.
Clinical Research and Patient Safety

Maintaining Our 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 providing updated information to investigators, prescribers, consumers and research subjects as appropriate.

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

• Safety data from development projects and marketed products must be regularly analysed to ensure adverse reactions and possible safety signals are identified from both clinical and non-clinical sources.

• Research subject risk management plans must be prepared for all products in clinical development. These documents will evolve as safety data become available, so that we can minimise risk and optimise benefits.

• The safety organisation follows a defined process aimed at ensuring all relevant patient safety information is incorporated in product labelling and Investigator’s Brochures.

• All employees are required to report any adverse events they become aware of involving any AstraZeneca investigational product or approved medicine.
Conducting Clinical Research Involving Human Studies

- We will conduct clinical studies of a drug in development only in countries where we intend to file and market the product.

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

- The quality and safety standards applied include 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 are committed to determining the potential for developing paediatric indications for our products. Paediatric subjects will be included in our development programmes when it is clinically and ethically justified to assess the efficacy and safety of our products. Paediatric studies sponsored by us will meet all laws and regulations required for the study of drugs in the paediatric population.

- Before any First Time in Human (FTIH) studies, preclinical data must 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 medications or investigation in man 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 ethical. We will take active and specific steps to safeguard the interests of all participants in our clinical studies, including those subjects receiving a placebo control.

- Our informed consent process gives subjects, 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 prior to enrolment. In addition, study participants are free to withdraw at any time without any detriment to their medical care.

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

- We will design clinical programmes to maximise the exploration of potential benefits for our investigational compounds 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 will communicate our understanding of the potential benefits and risks of our investigational agents and products to the medical community through approved protocols, Investigator’s Brochures, periodic regulatory updates and the publication of clinical study results.
Clinical Trial Transparency

We are fully 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 this transparency through the timely registration of clinical studies and posting of the clinical study results on websites and/or publication in peer-reviewed journals. We fully comply with laws, regulations and specific requirements for the registration and reporting of results. Our position is:

• We register and communicate results of all AstraZeneca-sponsored clinical trials through web-based postings and, where possible, through publications.

• We post the research protocol (redacted for personal and confidential information) for AstraZeneca-sponsored clinical trials on appropriate websites when a manuscript has been published in a peer-reviewed journal.

• We are committed to responding to requests for access to de-identified, individual patient-level data from AstraZeneca-sponsored clinical trials. We consider requests on a case-by-case basis in the context of evolving best practice and relevant legal, data privacy and patient confidentiality requirements.

• We submit anonymised Clinical Report Packages to the European Medicines Agency 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 are committed to good publishing practice and appropriate communication of information on our products and clinical studies to the international medical and scientific community.
Initiating Clinical Studies

Before initiating FTiH studies – a major milestone in developing new medications – the characteristics of the investigational compound must be confirmed through preclinical safety, toxicology and development studies as required by the medical community, ICH and local regulations.

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

- Before FTiH clinical studies commence, preclinical data and proposed early clinical studies must be peer-reviewed by an expert committee within AstraZeneca to ensure that all safety aspects have been evaluated and that the assessment of potential risk/benefit justifies the testing of the new agent in the clinical setting.

- Following the internal review, our clinical study protocols must be submitted externally to ethical committees and as required regulatory authorities in the countries where the study will take place.

Obtaining Informed Consent

We must 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.

Participants and, for minors, their legally accepted representatives are asked to indicate in writing their receipt of this information and their consent to be part of the study. A specific and mandatory Standard Operating Procedure aims to ensure that ethical and legal requirements for the consent process are met.

If important new information about an investigational product becomes available during an ongoing study, we will communicate this to investigators, ethics committees and participants as appropriate in each situation, and in accordance with applicable law and regulations.
Privacy of Information

- We must protect the privacy of research participants by ensuring all data brought into AstraZeneca (e.g. clinical, human tissue, health information etc.) are coded, double coded or anonymised to conceal a subject’s identity. When studies are performed at our own research units, information about identities must be contained solely within those units. If any research subject information is sent to AstraZeneca, it will be handled in a secure and anonymised way.

- We will communicate directly with individuals only with their prior consent or in response to requests from prospective volunteers.

- We will work with governments and regulators to ensure standards for protecting patient privacy and confidentiality are integral to any new media (e.g. Electronic Health Records, online databases etc.) used to communicate medical data.

- We recognise that we must also be 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.
Precise Genome Editing, Genomic Information and Human Biological Samples

Precise Genome Editing

- We believe that CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and similar technologies represent the next generation of genome engineering and are opening new and exciting doors to drug discovery and development, as well as to the role that genes play in disease pathology. In practice, these technologies are enabling us to accelerate and improve the drug discovery and development process, specifically in the identification and validation of new targets and in our ability to test potential new therapies for safety and efficacy.

- Genome editing technologies offer the potential for the treatment of genetic diseases in the future. The development of such medicines requires the establishment of methods to enable the efficient modification of the target gene with no effects elsewhere in the genome. We are developing methods to improve the efficiency and specificity of precise genome editing to minimise off-target effects.

- We support the general principle of cell and gene therapies in human somatic cells, but we are aware of risks due to: unwarranted on-target effects; possible off-target effects; unwanted germline (i.e. sperm, egg or embryo) modification. Any possible future pre-clinical or clinical work in this regard would be subject to existing AstraZeneca standards with respect to their biosafety and safety and be subject to ethical review.

- We neither practice nor 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.

- As a global pharmaceutical company, we remain committed to active participation in the precise genome editing debate.
Genomic Information

- We use genomic information (e.g. from DNA, and/or RNA within human tissues and preclinical models) and human biological samples obtained for research into better understanding of diseases, improved diagnosis or other improvements in healthcare and for the discovery and development of new treatments or drugs. Genomic information and human biological samples are also used for AstraZeneca sponsored clinical programmes in the development of pharmaceuticals intended for human use.

- Our use of genomic information and human biological samples is controlled by application of internal standards that are consistent with relevant legal and regulatory requirements.

- Subjects will be given information about the nature and purpose of the investigations, use of samples and are asked to provide 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, subjects can decide not to take part in the genomics research or optional future use of samples and still participate in the main clinical study.
Human Biological Samples

- Following internal review, 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 will request ethical approval for use via an appropriate external Research Ethics Committee.

- The genomic data may or may not be returned to the subject depending on the nature of the investigation and on the level of validation of the technology and reagents used to generate it. This will be clearly stated in the consent. If the data is returned to the subject we will specify, in the study protocol, a detailed process for handling such findings. We will communicate in this process to the subjects, and they will acknowledge their acceptance when signing the consent form.

- As with all clinical research, we take rigorous measures to protect the data privacy of subjects aiming to minimise the risk of their re-identification when processing the data.

- Human stem cells have the potential to expand understanding of the underlying causes of serious disease and provide options for therapeutic intervention. In the laboratory setting, differentiated cell lines derived from stem cells also have the potential to predict drug metabolism and human toxicity more accurately that existing techniques. Increasing knowledge of intracellular pathways should enable us to make different types of mature cells from pluripotent stem cells. This is being used to support discovery of new drugs 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 the laboratory, and we have a rigorous ethical framework that governs our work in this area.
• Most of our stem cell projects 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 drug discovery including prediction of drug metabolism and human toxicity. 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 serious disease.

• Before initiating any hESC research, there must be a clearly defined purpose to increase knowledge about serious disease that cannot be obtained via the use of hiPSC and to apply such knowledge in developing treatments for serious disease.

• 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 will only use hESC cell lines that have been accepted into a publicly recognised body or bank of registration. All research must be conducted in accordance with applicable local, national and international legislation, regulations and guidelines.

• In rare circumstances we may use human fetal tissue in research to advance our understanding of serious medical disorders. In such rare circumstances, an internal review of the scientific validity of the research proposal will be conducted and permission to use the tissue will be 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.
Genetically Modified Organisms

Through genetic engineering, we produce Genetically Modified Organisms (GMOs) for the discovery, development and manufacture of new medicines. All GMO work (including work carried out by third parties on our behalf) must be conducted under appropriate levels of biosafety containment and in compliance with relevant environmental, health and safety laws and regulations. The GMOs we use include genetically modified animal and human cells, viruses, extrachromosomal DNA (plasmids) and genetically modified micro-organisms (GMMs, for example bacteria) and genetically modified animals.

Accordingly, we will:

• Subject all work to prior risk assessment and apply a precautionary approach to uncertainty.
• Conduct all research and development in facilities designed to provide appropriate containment.
• Support transparency and openness about our use of GMOs.
• Treat waste streams containing GMOs to minimise or prevent discharge into the environment.
We consider the responsible use of animals to be ethically appropriate in biomedical research and product safety testing, where suitable alternatives are not available. The following principles apply 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.

• A humane approach must be adopted 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 are committed to the principles of the 3Rs; Replacement, Reduction and Refinement.

• We must 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 will be 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 are committed to sharing of knowledge of good practices and 3Rs achievements both throughout AstraZeneca and the wider scientific community.

• We must 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 must be 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, our preference is to work with third parties accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

• 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 serious 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.
We believe that a coordinated effort is required on the part of communities, governments and businesses to conserve global biodiversity. We support the general principles 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 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 will 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 said materials. These benefits may be monetary or non-monetary, as determined on a case-by-case basis. We will then use these materials in accordance with any mutually agreed conditions of use.

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

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