

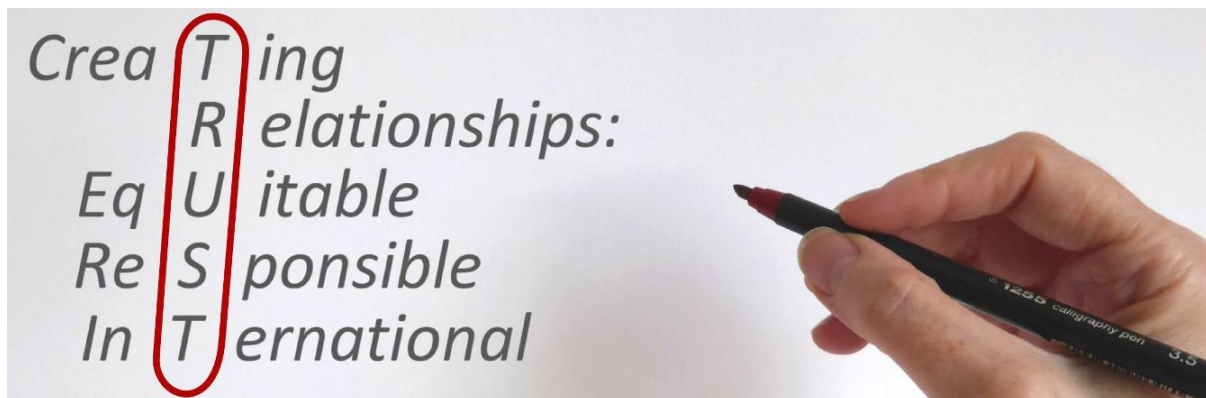


National and International Compliance Tools

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TRUST
Equitable Research Partnerships



National and International Compliance Tools

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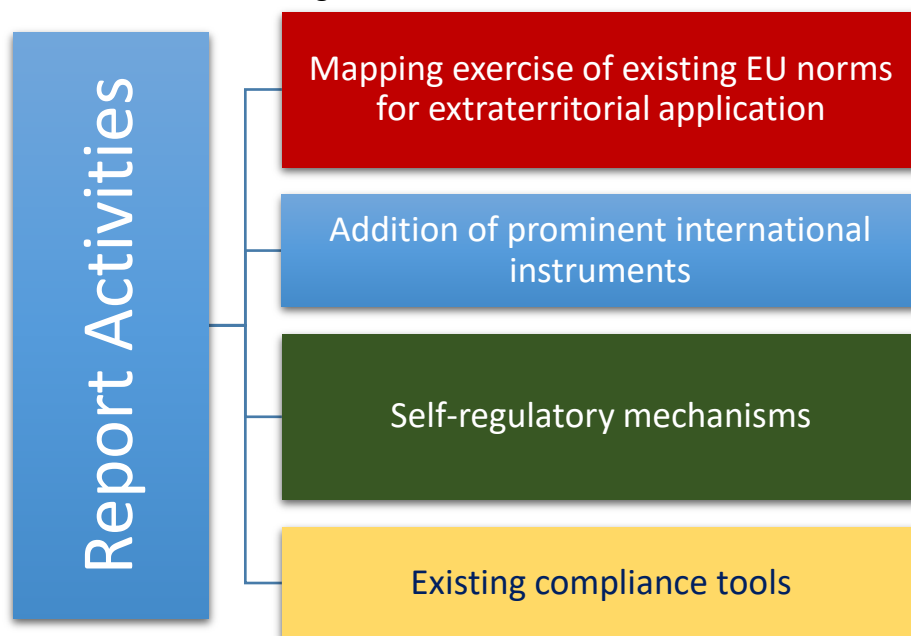
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Executive Summary

The main challenge in the governance of research at the global level is the existence of varying ethics review practices across countries.² While differences in approaches per se do not necessarily create a problem, such varying practices can lead to “ethics dumping”; the purposeful exploitation of third country research participants/resources, as well as exploitation based on insufficient ethics awareness. The TRUST project develops three tools to counter ethics dumping:

1. A Global Code of Conduct for North-South Collaboration
2. A Fair Research Contracts Webtool, and
3. A Compliance and Ethics Follow-up Tool.

This report provides the first step towards the Compliance and Ethics Follow-up Tool. It was produced based on the following activities.



The resource developed which covers the first two activities can be found on pages 18-32, structured according to the Horizon 2020 ethics review template.

An overview of self-regulatory mechanisms operated by 13 pharmaceutical companies, as presented in their public sources, can be found on pages 33-44.

An overview of existing compliance tools can be found on pages 45-54.

² Edwards et al., (2012).

Introduction

In the wake of globalization, research is increasingly conducted through collaborative initiatives with third countries. This has made the need for compliance with high ethical standards even more crucial, irrespective of where research is conducted and on what topic.

The main challenge in the governance of research at the global level is the existence of varying ethics review practices across countries.³ Diverse ethical practices can lead to tensions between universal principles and local approaches, and “ethics-free zones” that arise from severely limited or non-existent ethical oversight which in turn lead to the importation of unethical research.⁴ The European Commission (EC) has acknowledged that “due to the progressive globalisation of research activities, the risk is higher that research with sensitive ethical issues is conducted by European organisations outside the EU in a way that would not be accepted in Europe from an ethical point of view. This *exportation of non-compliant research practices is called ethics dumping.*”⁵

“Ethics Dumping”:

The term “dumping” is traditionally used to describe predatory pricing policies. Large entities can afford to undercut local competitors for a given period, to drive them out of the market. In the context of research ethics, we mean *both* purposeful exploitation of third country research participants/resources as well as exploitation based on insufficient ethics awareness.

The EC’s definition of ethics dumping is both current and relevant; our search regarding this concept in current literature has established that scholars have used the term dumping solely in the contexts of international business ethics, trade and economics, with no reference to international research partnerships.

In situations where varying ethics review practices are used, there are significant challenges in ensuring compliance with ethical standards relating to issues such as the involvement of children, patients, vulnerable populations, the use of human embryonic stem cells, privacy and data protection issues, research on animals and non-human primates.⁶ The TRUST project develops three tools to counter ethics dumping:

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This report provides the first step towards the Compliance and Ethics Follow-up Tool.

Given that ethics dumping deals with ethics matters beyond EU borders, a mapping exercise was undertaken to provide a resource of existing EU norms and rules in the field of research

³ Edwards et al., (2012).

⁴ European Commission (2009b), pp.30-32.

⁵ <https://ec.europa.eu/programmes/horizon2020/en/h2020-section/ethics>, emphasis added.

⁶ HORIZON 2020- The EU Framework Programme for Research and Innovation.

ethics related to their extraterritorial application. In addition, the resource was extended by adding prominent international instruments that have been used by EU research funders.

The resource was further strengthened by two related activities. First, by identifying relevant self-regulatory mechanisms developed for the protection of human research participants and animal welfare. Second, by providing an overview of existing compliance tools in ethics.

Conceptual framework

We used two key operational terms/concepts in the mapping exercise: “research” and “international instruments”. The first operational term, *research*, was used to determine the categorisation of relevant activities that fit within the scope of the exercise. The definition in the Organisation for Economic Co-operation and Development’s (OECD) *Frascati Manual* has been used as a standard for research and development surveys worldwide.⁷ The relevant part of the OECD’s definition of research for our purposes is “creative work undertaken on a *systematic basis* in order to increase the stock of knowledge....”⁸

According to this definition, only an activity that is designed to solve “a problem [that] is not readily apparent to someone familiar with the basic stock of common knowledge and techniques for the area concerned” qualifies as research.⁹ This definition does not however provide clear criteria for distinguishing other activities that may be related to research, and the reasons why research activities should be governed by the norms and rules that are included in this report. The following definition however, comes very close to making the much needed distinction and providing the rationale for subjecting research to ethics review:

“Research aims to generate (*new*) information, knowledge, understanding, or some other relevant cognitive good, and does so by means of a *systematic investigation*.”¹⁰

New outcomes from research may give rise to uncertainties, which can be risky, and systematic investigation may use methodologies that raise ethical issues. These two elements essentially distinguish research from other apparently similar activities that may not warrant research ethics review. We accordingly use the elements of **new outcomes** and **systematic investigation** to distinguish between research and other activities that are beyond the scope of this exercise.

The second operational term, *international instruments* also needs to be clarified. We focused on international instruments that have been used by funders and governance bodies to ensure global ethical adherence. This essentially determined the inclusion criteria for the instruments that are included in the resource. National instruments were excluded, while all international instruments that meet the inclusion criteria were included irrespective of the timeframe that they have been in existence. In summary, the following activities were undertaken for the report.

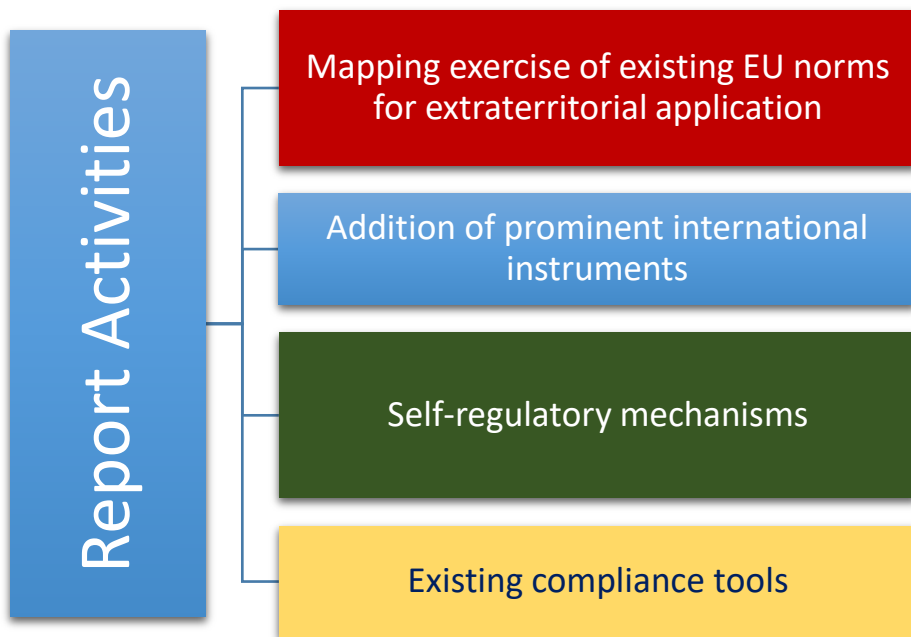
⁷ OECD, *The Frascati Manual*, 2002, p.3.

⁸ OECD, *The Frascati Manual*, 2002, p.30, emphasis added.

⁹ OECD, *The Frascati Manual*, 2002, p.34.

¹⁰ *European Textbook on Ethics in Research*, 2010:14, emphasis added.

Diagram 1 – Activities undertaken for this report:



Existing EU norms for extraterritorial application and prominent international instruments

The European Union's (EU) extraterritorial activities are governed by Article 21 of the consolidated version of the *Treaty on the European Union*:¹¹

- i. "The Union's action on the international scene shall be guided by the principles which have inspired its own creation, development and enlargement, and which it seeks to advance in the wider world... The Union shall seek to develop relations and build partnerships with third countries, and international, regional or global organisations ...
- ii. The Union ... shall work for a high degree of cooperation in all fields of international relations...
- iii. The Union shall respect the principles and pursue the objectives set out in paragraphs 1 and 2 in the development and implementation of the different areas of the Union's external action ..."

In line with Article 21, the EU has reaffirmed its commitment to adhering to its founding values and principles in the context of international cooperation. In this context, the European Commission's Directorate-General (DG) for Research and Innovation has established rules and norms to govern research funded by the EU. This makes this report relevant in an international context, since EU-specific rules and norms have taken on an extraterritorial relevance by virtue of the Horizon 2020 funding program¹².

This makes this report relevant in an international context, since EU-specific rules and norms have taken on an extraterritorial relevance by virtue of the Horizon 2020 funding program.



For the task of mapping existing EU norms for extraterritorial application as well as relevant international instruments, we focus on those that have been used within the context of EU-funded framework programmes to ensure global ethical adherence. For optimum useability for those administering and applying for Horizon 2020 funding, the thematic coverage of the Horizon 2020 ethics review table was used as a structuring tool for the resource.

The resource aims to identify possible means of mitigating and reducing the risks of ethics dumping as suggested by the EC, namely active collaboration "at multiple levels: within the EU, between the EU and other high-income countries, and between high-income and low-income countries, where the risk of dumping is higher."¹³ The suggested multiple levels of

¹¹ <http://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A12012M%2FTXT>.

¹² Horizon 2020 is the European Union's Framework Programme for Research and Innovation from 2014 to 2020.

¹³ *European Textbook on Ethics in Research*, 2010:14, emphasis added.

collaboration has in turn defined the geographical scope of this task. The resource accordingly includes rules and norms that are applicable at these multiple levels. However, it is important to supplement the resource with a narrative that points towards difficulties in maintaining European standards beyond EU borders.

European standards beyond EU borders

In theory, European standards for research apply even when research is conducted beyond the EU's borders - if it is funded by EU framework programs. In practice however, the application of EU norms and rules implies a form of external governance that may be deemed to interfere with the sovereignty of non-EU Member-States (also known as 'third countries'). This modality of governance will also not be effective in practice unless those third countries have agreed upon these rules as the normative reference point, transposed them into domestic legislation, and also applied them in administrative practice.¹⁴ In addition, even the formal adoption of such rules and norms by EU institutions may not always translate into behavioural compliance.¹⁵ And as Börzel & Risse show, the goals and content of the so-called *Europeanization beyond Europe* are of a more general character than in the case of EU-candidate countries.¹⁶

The reasons for the divides between European and third country standards include domestic obstacles (or requisites) on the part of third countries.¹⁷ Third countries may require, as outlined by Ekberg, compliance with all relevant domestic laws and regulations, as well as consistency with the norms, values, beliefs, customs and traditions of the given society.¹⁸ Some may also be wary of possible political interests influencing the decisions of foreign Research Ethics Committees (RECs). The views of local researchers may also differ from the nature and type of ethical guidelines used in international collaborative research. Applying abstract principles from existing codes may also be a challenge in practice, since history, geography, culture, gender relations and economic status can have important implications for the ways in which 'universal' ethical principles and guidelines are prioritised and applied in different contexts.¹⁹ Molyneux & Geissler suggest that ethical principles championed by the EU may also be regarded as being too detailed in terms of rules and requirements, thus hindering ethically responsible thinking in practice.²⁰ Informed consent, for example, may be seen more as a tool of protection for research organizations than a reflection of the true nature of research

Informed consent, for example, may be seen more as a tool of protection for research organizations than a reflection of the true nature of research participants' informed decisions to be involved in the research, particularly in the social sciences.



¹⁴ Lavenex & Schimmelfennig (2009).

¹⁵ Börzel & Risse (2012).

¹⁶ Ibid.

¹⁷ Schimmelfennig (2009).

¹⁸ Ekberg (2012).

¹⁹ Molyneux & Geissler (2008).

²⁰ Ibid.

participants' informed decisions to be involved in the research, particularly in the social sciences.

The priorities and concerns of research institutions in the EU may also differ from those of local communities, thus requiring the researchers to determine the appropriate order of priorities in the field. The uncritical application of the language, methods, and 'universal principles' of the modern Western philosophical framework, without taking into consideration other moral traditions whose roots and ways of thinking lie outside of Western philosophy and social theory, may also contribute to resistance by third countries. It may be regarded as a type of moral imperialism, leading to cultural invasion, and thus be seen as unethical in itself.²¹ Chattopadhyay and De Vries suggest that the EU approach should thus be seen to entail finding common ground between values across different cultures, rather than seemingly imposing an alien ethic.²² It is the responsibility of individual researchers, consortia, ethics boards and advisors to find this common ground.

Taking the above into account, in an ideal scenario of North-South collaboration in research:

- The rights and interests of all research participants are adequately protected, the research is relevant to local needs and the benefits of the research are equitably shared. The protection proviso also applies to animals used in experiments, and other third country resources (e.g. genetic materials and traditional knowledge).
- The local RECs have the necessary capacity to play an active role in ensuring that this actually happens in practice²³ and work jointly with the REC of the international research partner in providing the best possible protection.²⁴

However, this is not always straightforward. While the EU may seek to influence the nature and content of third country law, the practice of extraterritoriality is exceptional in EU law.²⁵ Thus in the event of a clash among national and EU regulations, it is important to be able to refer to the Horizon 2020 funding contracts and show that all groups who receive funding have contracted that they will accept EU legal instruments in the context of research ethics.

In the longer term, it is advisable for the EU to use its influence to foster cooperation and development of global standards.



In the longer term, it is advisable for the EU to use its influence to foster cooperation and development of global standards. In this context, the TRUST project will develop a Global Code of Conduct for North-South collaboration.

²¹ Chattopadhyay & De Vries (2008).

²² Ibid.

²³ Benatar (2002); Ekberg (2012).

²⁴ Klitzman (2012).

²⁵ Scott (2014); Lavenex (2014).

Research in low and middle income countries (LMICs)

For the previous framework program (FP7), the European Commission developed detailed guidance for the conduct of research activities in low and middle income countries (LMICs).²⁶

Three fundamental ethical considerations were identified, namely:

1. The proposed research must be responsive to the needs of the country where research is carried out (e.g. the study must be of added value for the health and welfare of the intended participants, their community, and/or their country).
2. It must be scientifically sound [... and]
3. abide by relevant EU/national legislation as well as by the relevant international guidelines.²⁷

The guidance also points out the need to take into account the *potential vulnerability* of local people i.e. the participants, the local research team and the local ethics review committee. For instance, it might be difficult for a local REC to challenge the study design or proposed methodologies when the study would result in a financial investment and improve the local research infrastructure.

Diagram 2 – Ethical Issues in LMIC according to FP7



Specific guidance is then provided on topics that are likely to create significant ethical issues in North-South collaboration, namely: benefit sharing; healthy volunteers; standard of care; ethics review process; informed consent; data protection, and animal welfare (see diagram 2).

Whilst such guidance documents are very helpful, they do not show the complexity of dealing with individual issues in practice. The following section lists a number of challenges that can arise in research in LMICs; it is illustrative and not intended to be comprehensive.

a. The gender divide

There is a need to address the potential problem of inequity affecting women vis-à-vis the distribution of the benefits of research. Current processes of benefit sharing do not guarantee the representation and participation of women in any relevant decision-making

²⁶ http://ec.europa.eu/research/participants/data/ref/fp7/89817/international-cooperation_en.pdf.

²⁷ Ibid.

processes.²⁸ To give an example, the *Convention on Biological Diversity* makes no mention of a *mechanism* to bring about the “full participation of women at all levels of policy making and implementation for biological diversity and conservation” which is stated in its Preamble.²⁹ This omission is only ameliorated by including gender aspects in the Nagoya Protocol.³⁰

The African Union also recognizes the role played by women in the generation and conservation and sustainable use of biological diversity and associated knowledge, but again no mechanism is provided to achieve women’s participation.³¹ Whilst the European Commission has pioneered work on gender equity with its funding programs³², gender issues are not normally discussed in the context of ethics review processes. At most, gender issues may be viewed through the lens of topics that the RECs should be looking at anyway, i.e. physical/psychosocial risks; harm, abuse, exploitation.

b. Marginalisation of local researchers in collaborative partnerships

Concerns have been raised that local researchers are side-lined by their high-income country collaborators, yet they make valuable intellectual contributions to the research.³³ Being side-lined may lead to lack of involvement of the local researchers in the study design³⁴ and eventually a lack of trust:

“A disturbing issue for both [private and public] sectors is the fact [that] most trials are designed and finalised before they are brought to us, with little if any room for changing the design or inclusion/exclusion criteria. ... Really they are using us for our numbers, they are not interested in any intellectual input we make in the developing world; it is only about the number of patients we can recruit...”³⁵

c. The governance of research involving traditional medicines

North-South collaborations could include work in areas where the LMICs have a strength, for instance, in traditional medicine. In this context, Northern researchers may not be well equipped to deal with research ethics in areas that are unlike Western medical research. Tilburt & Kaptchuk have suggested a comprehensive framework for research ethics that can be used for research on traditional medicines.³⁶ One of the salient features of the framework is collaborative partnerships in terms of which “research leadership must include bilateral representation based on mutual respect between equal partners with

²⁸ Wynberg, R, Schroeder D, and Chennells R. *Indigenous peoples, consent and benefit sharing: lessons from the San-Hoodia case*. London and New York: Springer, 2009.

²⁹ <https://www.cbd.int/convention/articles/default.shtml?a=cbd-00>.

³⁰ J. Cook Lucas & F. Alvarez-Castillo (2013) Fair for Women? A Gender Analysis of Benefit Sharing, in (Schroeder, D and Cook Lucas J) (eds) : *Benefit Sharing - From Biodiversity to Human Genetics*, Berlin: Springer, pp. 129-151.

³¹ Alvarez-Castillo & Feinholz (2006).

³² <https://ec.europa.eu/programmes/horizon2020/en/h2020-section/promoting-gender-equality-research-and-innovation>

³³ Shuchman, Wondimagegn, Pain & Alem (2014), p.12.

³⁴ Lang and Siribaddana (2012).

³⁵ Professor M Tikly, quoted in Wemos foundation Report (2013), p.31.

³⁶ Tilburt & Kaptchuk (2008), pp.594-595.

community advice.”³⁷ This would ensure trustworthy collaborative partnerships particularly with LMICs, with careful attention to the following issues.³⁸

- Conservation of community indigenous knowledge and intellectual property rights
- Respect for international standards on access and benefits sharing
- Consideration of evidence of rigorous toxicological testing and safety profiles of herbal products
- Plans for benefit sharing with the community or the participants in case of commercialization

d. Ownership of data and data sharing in research

Ownership of data is usually complex in international collaborative research. For instance, a recent qualitative study³⁹ on five LMICs⁴⁰ confirmed that stakeholders in these countries freely share de-identified data for academic and public health purposes so long as anonymity of the research participants’ personal information is guaranteed, but do not do so beyond these limits.⁴¹ Data exportation and re-use for commercial purposes, on the other hand, are perceived as a threat to the local researchers and communities since there is no guarantee of local benefits⁴² and consequently a threat to the local researchers and participants.⁴³

The following statement from one of the stakeholders that was interviewed in the above study⁴⁴ highlights the main concern regarding data sharing in a manner that is beneficial to the local researchers and communities.

“... there has to be a benefit sharing component that’s in the data sharing process and the benefit sharing has to be ... done in a critical way where there is *not just benefit for the investigator who is now going to have a patent and generating billions versus the community who’s still living in poverty.*”⁴⁵

e. Benefit sharing and post-trial obligations

Most LMIC-based research institutions lack the legal resources, such as research contract offices, to ensure that the research agreements they enter into cover issues such as, *inter alia*, “...technology transfer, capacity building, intellectual property rights, and future benefit sharing”.⁴⁶ If these issues are not properly negotiated and agreed on it becomes very difficult to share benefits later, or to fulfil post-trial obligations as required by paragraph 34 of the *Declaration of Helsinki*, which provides that “sponsors, researchers and host country

³⁷ Ibid, table 1.

³⁸ Kaptue, Ngounoue & Fokunang (2014), p.111-112.

³⁹ Denny et al., (2015).

⁴⁰ India, Thailand, Vietnam, South Africa, and Kenya.

⁴¹ Denny et al. (2015), p. 294; Hate et al., (2015), p.242.

⁴² Merson et al., (2015), p.256.

⁴³ Denny et al., (2015), p.297.

⁴⁴ Denny et al., (2015).

⁴⁵ LMIC Research manager, quoted in Denny et al., 2015, p.298. Emphasis added. By equating each patent with “billions”, the quote also suggests that the management of expectations would need to be looked at, see also recommendations given in Wynberg et al. (2009) pp. 343-344.

⁴⁶ Sankor & Ijsselmuiden (2011); Sack et al., (2009).

governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial.”⁴⁷ Admittedly, the specific requirements in relation to post-trial access remain unclear to stakeholders and even to RECs.⁴⁸ Lack of clarity in this regard can lead to the exploitation of participants and research institutions in LMICs.

Non-medical research and efforts geared towards defining guidelines for application in LMICs

The current literature on research ethics in LMICs tends to focus on medical research, and there is a scarcity of literature on the ethics of non-medical research in LMICs. However, more recently profession-specific codes of ethics have been developed to govern research in particular fields. For instance, global guidelines have been developed by the International Federation of Social Workers (IFSW)⁴⁹, the World Association for Social, Opinion and Market Research (ESOMAR), and the Global Research Business Network (GRBN).⁵⁰

Both in the North and the South, concerns have been raised that social researchers have to overcome the same ethics hurdles as medical researchers, which may not be appropriate if one compares risks. It has been argued in particular that social science research protocols are often reviewed using guidelines that are intended for or derived from the biomedical research framework.⁵¹ In this context, it has even been noted that ethics review of social science research is viewed with suspicion as an unnecessary encroachment on the researchers’ academic freedom.⁵²

When faced with research in an LMIC, two hurdles must be overcome. First, the research may infringe cultural norms and thus be regarded as disrespectful. A typical example would be going straight into an indigenous community without first communicating with traditional leaders.⁵³ Whilst this hurdle is relevant to all types of research and calls for local frameworks and local codes of ethics to supplement international ones, it can be a particular issue in social science research. For instance, members of the South African San Institute, which protects the interests of the South African San people and is a partner in TRUST, have noted that most researchers who go straight to individual community members without respecting the local rules that govern research are PhD students who come with questions (i.e. who are

⁴⁷ <http://www.wma.net/en/30publications/10policies/b3/>.

⁴⁸ Sofaer et al. (2014); Mastroleo (2016).

⁴⁹ Global guidance on the working environment for social work (2012), available at <http://ifsw.org/policies/effective-and-ethical-working-environments-for-social-work-the-responsibilities-of-employers-of-social-workers-3/>

⁵⁰ ESOMAR/GRBN Online Research Guideline, available at <https://www.esomar.org/uploads/public/knowledge-and-standards/codes-and-guidelines/ESOMAR-GRBN-Online-Research-Guideline-October-2015.pdf>

⁵¹ Wassenaar (2007), p.65

⁵² Mutenherwa & Wassenaar (2014), p.118.

⁵³ See also, TRUST videos at <https://www.youtube.com/channel/UClivLKhGDPW2mu5wn7zw7qw>.

undertaking social science research).⁵⁴ Ethics codes developed by indigenous peoples have a prominent role to play in the setting up of culturally sensitive rules.

An example of an indigenous ethics code is *Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research*.⁵⁵ Additionally, TRUST is assisting SASI and the South African San Council to develop a San Code of Ethics.

The second hurdle is that local frameworks and codes of ethics have to be made operationally useful for local RECs. For instance, Onuoha developed an ethical framework which is based on an African worldview and embraces three main African values of humanity, community and morality.⁵⁶ However, Mutenherwa & Wassenaar have observed that this framework is “yet to be operationalised in a way that will guide researchers and RECs in their normative application to social science (and other) studies”.⁵⁷

TRUST is assisting the South African San Institute and the South African San Council to develop a San Code of Ethics.



Often non-medical research that is conducted in LMICs is distinguished by its interdisciplinary nature. A clear understanding of the principles and values that should govern research in such contexts is critical for the implementation of “standardised approaches to designing, planning, conducting and administering research”.⁵⁸

Legal instruments relevant to research ethics

International and regional organisations have issued codes and legal instruments over the years, with the aim of addressing the major ethical issues earlier referred to, thus contributing to ensuring compliance with ethical standards. One can distinguish between the following main types in relation to ethics:

- Treaties (also known as Conventions) are international legal instruments, agreed to by sovereign states. Treaties are binding. An example that is relevant to research ethics is the *Convention on Biological Diversity* with its provisions on benefit sharing in international research.⁵⁹
- Within Europe, Directives are a legal act of the European Union that requires member states to achieve a particular state of affairs, without prescribing how to achieve it. The *European Data Protection Directive* is an example relevant to research ethics.⁶⁰
- Non-binding international ethics guidelines. An example relevant to research ethics is UNESCO’s 2009 *Universal Declaration on Bioethics and Human Rights*.⁶¹

⁵⁴ Personal communication from Andries Steenkamp, former Chair of the South African San Council, a statement which will also appear in a future film on the TRUST YouTube channel.

⁵⁵ <https://www.nhmrc.gov.au/guidelines-publications/e52>

⁵⁶ Onuoha (2007).

⁵⁷ Mutenherwa & Wassenaar (2014), p.123.

⁵⁸ Rossouw, Van Zyl & Pope (2014).

⁵⁹ <https://www.cbd.int/convention/text>

⁶⁰ <http://ec.europa.eu/justice/data-protection/>

⁶¹ http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html

- Non-binding community-specific codes of ethics. An example cited earlier is *Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research*.⁶²
- Non-binding professional ethics codes with global applicability.

Diagram 3 – Types of legal instruments relevant to research ethics



The key challenges in relation to the above-mentioned legal instruments can be summarized as follows:

a. Lack of comprehensive guidance on which instruments to apply to which type of research

This is particularly problematic in cross-jurisdictional research since local guidelines and laws can, and do, clash with international guidance. The 2002 report by the Nuffield Council on Bioethics was intended to help bridge this gap. It sought to address the absence of consistent ethical guidance for those involved in externally-sponsored research. The Council proposed an ethical framework consisting of four principles, namely the duty to alleviate suffering; the duty to show respect for persons; the duty to be sensitive to cultural differences; and the duty not to exploit the vulnerable.⁶³

b. Varying status of the existing guidelines.

Some legal instruments are legally binding (e.g. a treaty), whilst other have a mere advisory status, for instance, the 2002 Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.⁶⁴ Others are binding on members of a particular profession only, for instance: the International Federation of Social Workers (IFSW).

⁶² <https://www.nhmrc.gov.au/guidelines-publications/e52>

⁶³ Nuffield Council on Bioethics, *The ethics of research related to healthcare in developing countries* (2002).

⁶⁴ http://www.cioms.ch/publications/guidelines/guidelines_nov_2002_blurb.htm

- c. **Significant variation between countries on the establishment and operation of RECs**
In international research, it is not always clear which local REC is the most appropriate to approve a research study. In addition, funding bodies too, may have their own requirements and guidance both for researchers and research ethics reviews. An example of a funding body that has developed guidelines on North-South collaboration is the Wellcome Trust.⁶⁵ An example of a funding body which operates its own ethics review system is the European Commission within its Horizon 2020 program.
- d. **Scarcity of structures that are equipped to deal with non-medical research**
As already noted, local RECs in LMICs are more likely to be familiar with medical research than non-medical research. In this context, it was also noted that lack of specialized ethics training for REC members on how to deal with vulnerable persons in the context of research is a concern.⁶⁶

Resource - Existing EU norms for extraterritorial application and prominent international instruments

The following pages list the diverse legal instruments and ethics guidelines that are relevant to North-South collaboration from the perspective of the Horizon 2020 ethics review.

⁶⁵ *Guidance notes on research involving people in low and middle income countries*, available at <http://www.wellcome.ac.uk/About-us/Policy/Policy-and-position-statements/WTD015295.htm>

⁶⁶ Edwards et al, 2012.

Clinical trials

There are no Treaties governing clinical trials.

Issuing body/institution	Legislation, Regulations ⁶⁷ /Directives ⁶⁸	Guidelines
World Health Organization		<i>Ethical Issues in Patient Safety Research: Interpreting Existing Guidance</i> (2013)
World Health Organization		<i>Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants</i> (2011)
World Health Organization		<i>Operational Guidelines for Ethics Committees that Review Biomedical Research</i> (2000)
The Joint United Nations Programme on HIV/AIDS (UNAIDS)		<i>Good Participatory Practice: Guidelines for Biomedical HIV Prevention Trials</i> (2011)
The Joint United Nations Programme on HIV/AIDS (UNAIDS)		<i>Ethical Considerations in Biomedical HIV Prevention Trials</i> (2012)
World Medical Association		<i>The Declaration of Helsinki</i> (2013)
Council for International Organizations of Medical Sciences (CIOMS)		<i>International Ethical Guidelines for Biomedical Research Involving Human Subjects</i> (2002)
The European Parliament and the Council	<i>Directive 2001/83/EC</i> of 6 November 2001 On The Community Code Relating To Medicinal Products For Human Use	
The European Parliament and the Council	<i>Directive 2002/98/EC</i> of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC	
The European Parliament and the Council	<i>Directive 2004/24/EC</i> of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use	

⁶⁷ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a regulation shall have general application. It shall be binding in its entirety and directly applicable in all Member States.'

⁶⁸ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.'

The European Parliament and the Council	<i>Directive 2004/27/EC</i> of 31 March 2004 amending <i>Directive 2001/83/EC</i> on the Community code relating to medicinal products for human use	
The Commission of European Communities	<i>Commission Directive 2005/28/EC</i> of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products	
The Commission of European Communities	<i>Commission Directive 2006/17/EC</i> of 8 February 2006 implementing <i>Directive 2004/23/EC</i> of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells	
The European Parliament and the Council	<i>Clinical Trials Regulation No. 536/2014</i> of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing <i>Directive 2001/20/EC</i> ⁶⁹	

⁶⁹ This became applicable on 28 May 2016.

Research involving human participants

There are no Regulations or Directives governing research involving human participants

Issuing body/institution	Treaties	Guidelines
World Medical Association		<i>The Declaration of Helsinki (2013)</i>
World Health Organization		<i>Operational Guidelines for Ethics Committees that Review Biomedical Research (2000)</i>
World Health Organization		<i>Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants (2011)</i>
World Health Organization		<i>Ethical Issues in Patient Safety Research: Interpreting Existing Guidance (2013)</i>
World Health Organization		<i>Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation (2005)</i>
World Health Organization (WHO)		<i>Operational Guidance: Information Needed to Support Clinical Trials of Herbal Products (2005)</i>
WHO – International Clinical Trials Registry Platform		<i>Resolution WHA 58.34 (2005), which called upon ‘the global scientific community, international partners, the private sector, civil society, and other relevant stakeholders, as appropriate...[to inter alia] provide support for a substantive and sustainable programme of health-systems research aligned with priority country needs and aimed at achieving the internationally agreed health-related development goals.’</i>
Office of the United Nations High Commissioner for Human Rights (OHCHR)	<i>International Covenant on Civil and Political Rights (1976), Article 7</i>	
United Nations Educational, Scientific, and Cultural Organization, Bioethics Program (UNESCO)		<i>Universal Declaration on Bioethics and Human Rights (2005)</i>
United Nations General Assembly		<i>Universal Declaration of Human Rights (1948)</i>
Council for International Organizations of Medical Sciences (CIOMS)		<i>International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)</i>

The Council of Europe	<i>The European Convention on Human Rights (1950)</i> ⁷⁰	
The Council of the European Union	<i>Convention on Human Rights and Biomedicine (Convention of Oviedo, 1997)</i>	
The Council of the European Union	<i>Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research, CETS No. 195 (2005)</i>	
The Council of the European Union	<i>The European Charter of Fundamental Rights (2000)</i>	
The Council of the European Union	<i>Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (1997)</i>	

⁷⁰ The latest amendment to the Convention was by the provisions of Protocol No. 14 (CETS no. 194), which came into force on 1 June 2010.

Human genetic material and biological samples

Issuing body/institution	Treaties	Legislation, Regulations ⁷¹ /directives ⁷²	Guidelines
WHO			<i>Guidelines for the Safe Transport of Infectious Substances and Diagnostic Specimens (1997)</i>
WHO			<i>Guideline for Obtaining Informed Consent for the Procurement and Use of Human Tissues, Cells, and Fluids in Research (2003)</i>
UNESCO			<i>Universal Declaration on the Human Genome and Human Rights, 2005</i>
UNESCO			<i>International Declaration on Human Genetic Data (2003)</i>
The European Parliament and the Council		<i>Directive 2004/23/EC of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells</i>	
The Council of the European Union	<i>Convention on Human Rights and Biomedicine (Convention of Oviedo, 1997)</i>		Recommendation Rec (2006) 4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin (2006)
The Council of the European Union	<i>Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research (2005)</i>		
The Commission of European Communities		<i>Commission Directive 2006/86/EC of 24 October 2006</i>	

⁷¹ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a regulation shall have general application. It shall be binding in its entirety and directly applicable in all Member States.'

⁷² In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.'

		implementing <i>Directive 2004/23/EC</i> of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells	
The Commission of European Communities		<i>Commission Directive 2012/39/EU</i> of 26 November 2012 amending <i>Directive 2006/17/EC</i> as regards certain technical requirements for the testing of human of human tissues and cells	
European Commission: European Group on Ethics in Science and New Technologies		<i>Directive 2004/23/EC</i> on Setting Standards of Quality and Safety for the Donation, Procurement, Testing, Processing, Preservation, Storage, and Distribution of Human Tissues and Cells	
International Society for Biological and Environmental Repositories			<i>Best Practices for Repositories I: Collection, Storage and Retrieval of Human Biological Materials for Research (2012)</i>

Research on human embryos, embryonic stem cells and cloning

Issuing body/institution	Treaties	Legislation, Regulations ⁷³ /directives ⁷⁴	Guidelines
The Council of the European Union	<i>Convention on Human Rights and Biomedicine</i> (Convention of Oviedo, 1997)		
The Council of the European Union	<i>Additional Protocol on Prohibition of Human Cloning</i> , ETS No. 168 (1998)		
European Group on Ethics in Science and New Technologies			<i>Statement of the Commission Related to Research Activities Involving Human Embryonic Stem Cells</i> (2013)
European Group on Ethics in Science and New Technologies			Opinion No. 22 - The Ethics Review of hESC FP7 Research Projects (2007)
International Society for Stem Cell Research			<i>Guidelines for the Conduct of Human Embryonic Stem Cell Research</i> (2006)

⁷³ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a regulation shall have general application. It shall be binding in its entirety and directly applicable in all Member States.'

⁷⁴ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.'

Animal experimentation

Issuing body/institution	Treaties	Legislation, Regulations ⁷⁵ /directives ⁷⁶	Guidelines
The European Parliament and the Council		<i>Directive 2003/65/EC</i> of 22 July 2003 amending Council <i>Directive 86/609/EEC</i> on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes	
”		<i>Directive 2010/63/EU</i> of 22 September 2010 on the protection of animals used for scientific purposes	
The Council of the European Union	<i>Convention ETS 123</i> on the protection of animals used for experimental and other scientific purposes (1986).		<i>Guidelines for accommodation and care of animals</i> (Appendix A of <i>Convention ETS 123</i>), 2006

⁷⁵ In terms of Article 288 of the *Treaty on the Functioning of the European Union* ‘a regulation shall have general application. It shall be binding in its entirety and directly applicable in all Member States.’

⁷⁶ In terms of Article 288 of the *Treaty on the Functioning of the European Union* ‘a directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.’

Data protection

Issuing body/institution	Treaties	Legislation, Regulations ⁷⁷ /directives ⁷⁸	Guidelines
World Medical Association			<i>Declaration on Ethical Considerations Regarding Health Databases (2002)</i>
World Medical Association			<i>Declaration of Helsinki (2013), paragraph 24</i>
The European Parliament and the Council		<i>Directive (EU) 2016/680 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data by competent authorities for the purposes of the prevention, investigation, detection or prosecution of criminal offences or the execution of criminal penalties, and on the free movement of such data⁷⁹</i>	
The European Parliament and the Council		<i>Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)⁸⁰</i>	
The Council of the European Union	<i>Convention for the Protection of individuals with regard to Automatic processing of personal data (1981)</i>		<i>Recommendation No. R (97) 5 on the Protection of Medical Data (1997)</i>

⁷⁷ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a regulation shall have general application. It shall be binding in its entirety and directly applicable in all Member States.'

⁷⁸ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.'

⁷⁹ The Directive repealed Council Framework Decision 2008/977/JHA. It entered into force on 5th May 2016 and EU Member States have to transpose it into their national law by 6th May 2018, see http://ec.europa.eu/justice/data-protection/reform/index_en.htm

⁸⁰ The Regulation entered into force on 24th May 2016 but shall apply from 25 May 2018, see http://ec.europa.eu/justice/data-protection/reform/index_en.htm

Third countries

There are no Regulations or Directives governing research involving third countries.

Issuing body/institution	Treaties	Guidelines
The Council of the European Union	<i>The Charter of Fundamental Rights of the European Union</i>	
European Commission: European Group on Ethics in Science and New Technologies (EGE):		<i>Ethical Aspects of Clinical Research in Developing Countries (2003)</i>
The World Conference on Science		<i>Declaration on Science and the Use of Scientific Knowledge (1999)</i>

Environment and Safety

Issuing body/institution	Treaties	Legislation, Regulations ⁸¹ /directives ⁸²	Guidelines
The United Nations Environment Programme (UNEP)	<i>The Convention on Biological Diversity (1992)</i>		
UNEP	<i>The Cartagena Protocol on Biosafety to the Convention on Biological Diversity (2000)</i>		
UNEP	<i>The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (2010)</i>		
UNEP	<i>Basel Convention on the control of transboundary movements of hazardous wastes and their disposal (1989)</i>		
UNEP	<i>Bamako Convention on the Ban of the Import into Africa and the Control of Transboundary Movement and Management of Hazardous Wastes within Africa (1991)</i>		
UNEP	<i>Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (1998; revised in 2013)</i>		
United Nations	<i>Convention on the Prohibition of Military or</i>		

⁸¹ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a regulation shall have general application. It shall be binding in its entirety and directly applicable in all Member States.'

⁸² In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.'

General Assembly	<i>any Other Hostile Use of Environmental Modification Techniques (1976)</i>		
United Nations General Assembly	<i>United Nations Framework Convention on Climate Change (1992)</i>		
International Labour Organisation (ILO)	<i>Safety and Health in Agriculture Convention, 2001 (No. 184)</i>		<i>Protection of Workers' Health Recommendation, 1953 (No. 97)</i>
ILO			<i>Safety and Health in Agriculture Recommendation, 2001 (No. 192)</i>
ILO	<i>Working Environment (Air Pollution, Noise and Vibration) Convention, 1977 (No. 148)</i>		<i>Working Environment (Air Pollution, Noise and Vibration) Recommendation, 1977 (No. 156)</i>
UNESCO	<i>World Heritage Convention Concerning the Protection of the World Cultural and Natural Heritage (1972)</i>		
Food and Agriculture Organisation of the United Nations (FAO)	<i>International Treaty on Plant Genetic Resources for Food and Agriculture (2001)</i>		
The European Parliament and the Council		<i>Regulation (EU) No 511/2014 of 16 April 2014 on compliance measures for users from the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization in the Union</i>	
The European Parliament and the Council		<i>Directive 2001/18/EC of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Declaration (OJ L 106)</i>	
The European Parliament		<i>Directive 2009/41/EC of 6 May 2009 on the contained use of</i>	

and the Council		genetically modified micro-organisms.	
The European Parliament and the Council		<i>Regulation EC No 1946</i> of 15 July 2003 on transboundary movements of genetically modified organisms	
The European Parliament and the Council		<i>Directive 2008/56/EC</i> Council of 17 June 2008 establishing a framework for community action in the field of marine environmental policy (Marine Strategy Framework Directive)	
The European Parliament and the Council		<i>Directive 92/43/EEC</i> of 21 May 1992 on the conservation of natural habitats and of wild fauna and flora aims to promote the maintenance of biodiversity	
The European Parliament and the Council		<i>Directive 79/409/EEC</i> of 2 April 1979 on the conservation of wild birds	
The European Parliament and the Council		<i>Council Regulation EC No 338/97</i> of 9 December 1996 on the protection of species of wild fauna and flora by regulating trade therein	
The European Parliament and the Council		<i>Directive 2000/54/EC</i> of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work	
The European Parliament and the Council		<i>Directive 98/24/EC</i> of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work	
The Council of the European Union	<i>The Charter of Fundamental Rights of the European Union</i>		
The World Conference on Science			<i>Declaration on Science and the Use of Scientific Knowledge</i> (1999)

Dual use⁸³

Managing body/institution	Treaties	Legislation, Regulations ⁸⁴ /directives ⁸⁵	Guidelines
WHO			<i>Biorisk management: Laboratory biosecurity guidance (2006)</i>
WHO			<i>Laboratory Biosafety Manual (2004)</i>
International Atomic Energy Agency (IAEA)	<i>The Convention on the Physical Protection of Nuclear Material (1980)</i>		<i>Nuclear Security Culture - Implementing Guide (2008)</i>
IAEA	<i>Treaty on the Non-Proliferation of Nuclear Weapons (1968)</i>		
United Nations Office for disarmament affairs	<i>The Biological Weapons Convention: Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (1972)</i>		
Organisation for the Prohibition of Chemical Weapons	<i>Chemical Weapons Convention (1994)</i>		<i>The Hague Ethical Guidelines (2015)</i>
The Preparatory Commission for the Comprehensive Nuclear-Test-Ban Treaty Organization (CTBTO)	<i>The Comprehensive Nuclear Test Ban Treaty (1996) - not yet in force</i>		
The Council of the European Union		<i>Council Regulation (EC) No 428/2009 of 5 May 2009 setting up a Community regime for the control of exports, transfer,</i>	

⁸³ Thanks to Dr Johannes Rath for comments on this section.

⁸⁴ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a regulation shall have general application. It shall be binding in its entirety and directly applicable in all Member States.'

⁸⁵ In terms of Article 288 of the *Treaty on the Functioning of the European Union* 'a directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, but shall leave to the national authorities the choice of form and methods.'

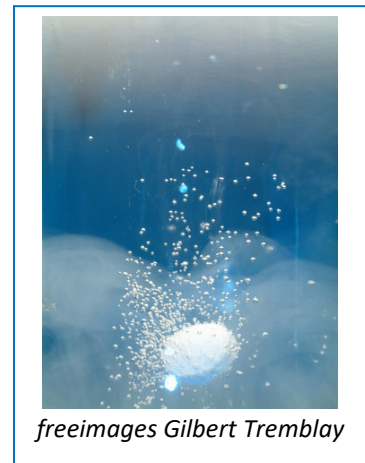
		brokering and transit of dual-use items	
The European Parliament and the Council		<i>Regulation (EU) No 388/2012 of 19 April 2012 amending Council Regulation (EC) No 428/2009 setting up a Community regime for the control of exports, transfer, brokering and transit of dual-use items</i>	
Multilateral export control regime		<i>Wassenaar Arrangement on Export Controls for Conventional Arms and Dual-Use Goods and Technologies (1996)</i>	
United Nations		<i>Security Council Resolution 1540 (2004)</i>	

Within Europe many of the safety provisions (e.g. physical security, containment) are also relevant in a security context. Therefore, implementation of adequate safety legislation is also considered relevant in the context of dual use.

Overview of self-regulatory mechanisms

Self-regulatory mechanisms are usually found in industry and business as part of corporate responsibility tools designed to manage social and environmental impacts.⁸⁶ Self-regulation usually entails “...a group of persons or bodies, acting together, [to perform] a regulatory function in respect of themselves and others who accept their authority.”⁸⁷ Accordingly, self-regulation is “the practice of industry taking initiative to formulate and enforce rules and codes of conduct with no government involvement, or with such involvement taking a very limited form, for example as observer or advisor.”⁸⁸

The self-regulatory mechanisms described here are based on a review⁸⁹ of the policies and guidelines of 14 pharmaceutical and chemical companies; AstraZeneca, BASF, Bayer, GlaxoSmithKline, Johnson & Johnson, Merck & Co, Merck KGaA, Monsanto, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi and Syngenta.



The review considered the policies that are mentioned on these companies’ websites by comparing and contrasting the positions they take in relation to three issues:

1. monitoring and auditing practices,
2. issues relating to informed consent, and
3. post-trial access to medicines.

Diagram 3 - Scope of review



Monitoring and auditing practices are relevant because this report is about compliance mechanisms, of which monitoring and auditing are one example (see also the last section of this report). Informed consent was chosen as the ethical cornerstone of modern clinical trials. And post-trial access to successfully tested medicines was chosen as a yet unachieved aspiration of the *Declaration of Helsinki*.⁹⁰

Although the review was intended to provide an overview of some of the dimensions associated with these issues, there are some limitations. First, the data for this comparison

⁸⁶ Laura Albareda, (2008) "Corporate responsibility, governance and accountability: from self-regulation to co-regulation", *Corporate Governance: The international journal of business in society*, Vol. 8 Iss: 4, pp.430 – 439.

⁸⁷ Black (1996), 27.

⁸⁸ Black (1996), 27.

⁸⁹ The review was conducted by Klaus Leisinger with support from the SCORE team University of Basel (Zinette Bergman, Lena Berger, Ann-Kathrin Hess, Laura Lämmli, Manfred Max Bergman).

⁹⁰ Art 34, *Declaration of Helsinki* (2013), “In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial.”

was collected from the companies' websites and from public documents made available on these websites. Therefore this is not a census or a review of all of the relevant policies and documents from these companies since the data collection was limited by public availability. Furthermore, because this review was based on the documents and statements made publicly available by these companies, it was not possible to verify whether or not they actually comply with these standards or – if the position is different – what their actual practices are. The review is based on what these 14 companies publicly present as their positions.

In addition, it is worth quoting GSK's approach to undertaking clinical trials in LMICs, which acknowledges that more and more trials are moving to the South. The introduction to their position paper on "Clinical Trials in the Developing World" is reproduced in Box 1.

Box 1: Statement from GSK on Clinical Trials in the Developing World⁹¹

"Historically, the majority of patients recruited into clinical trials for medicine development have been from Western Europe and the US. However, clinical trials are increasingly recruiting patients from other countries, including developing countries. This shift in focus is questioned by some. They argue that industry is using some of the world's poorest populations as "guinea pigs" for developed world diseases and acting in an unethical way that fails to reflect the standards applied in the developed world. This paper describes our approach to addressing these concerns and sets out the philosophy underpinning the conduct of GSK clinical research wherever it takes place."

⁹¹ <http://www.gsk.com/media/280806/clinical-trials-in-the-developing-world-policy.pdf>

An overview of company policies

The 14 companies on which this review is based make use of a wide variety of policies. Table 1 provides an overview of the policies referred to on websites and/or public documents:

Table 1 – Overview of company policies

Company	Codes on interaction with healthcare professionals	UN Global Compact	Guide for the care and use of laboratory animals	Guidelines for good clinical practice (ICH)	Declaration of Helsinki
AstraZeneca	✓	✓	✓	✓	✓
BASF		✓	✓		
Bayer	✓	✓	✓	✓	✓
GSK *	✓	✓	✓	✓	✓
J&J +	✓	✓	✓	✓	✓
Merck&Co.	✓	✓	✓	✓	✓
Merck KGaA	✓	✓	✓	✓	✓
Monsanto		✓			
Novartis	✓	✓	✓	✓	✓
Novo Nordisk	✓	✓		✓	✓
Pfizer	✓	✓	✓	✓	✓
Roche		✓	✓	✓	✓
Sanofi	✓	✓	✓	✓	✓
Syngenta		✓			

* GlaxoSmithKline, + Johnson & Johnson

Company	International ethical guidelines for biomedical research involving human subjects (CIOMS & WHO)	Nagoya Protocol	Principles for responsible clinical trial data sharing (PhRMA & EFPIA)	Responsible Care Global Charter
AstraZeneca		✓	✓	
BASF				✓
Bayer		✓	✓	✓
GSK *		✓	✓	
J&J +			✓	
Merck&Co.	✓		✓	
Merck KGaA	✓	✓	✓	✓
Monsanto			✓	✓
Novartis		✓	✓	
Novo Nordisk			✓	
Pfizer	✓		✓	
Roche		✓	✓	✓
Sanofi	✓	✓	✓	✓
Syngenta				

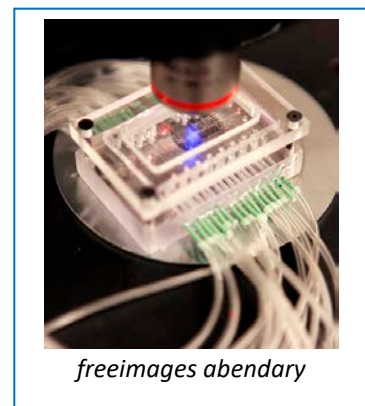
As the table illustrates, all 14 companies are signatories of the *UN Global Compact*,⁹² while nearly all state that they comply with the *Guide for the Care and Use of Laboratory Animals*, the *Guidelines for Good Clinical Practice (ICH)*, the *Declaration of Helsinki*, the *Principles for Responsible Clinical Trial Data Sharing (PhRMA & EFPIA)*, and the *Code on Interactions with Healthcare Professionals*. Less frequently, companies also indicate their compliance with the *Nagoya Protocol*⁹³, and the *Responsible Care Charter*.

Is there compliance monitoring and/or auditing in place?

Clinical trials involving human participants

Regulations and guidelines for the monitoring and auditing of clinical trials are described in many of the codes and conventions the 14 companies refer to. These include, but are not limited to, the *Declaration of Helsinki (2013)*, the *International Conference on Harmonisation (ICH)*, the *Council for International Organizations of Medical Sciences (2002)*, the *Pharmaceutical Research and Manufacturers of America (2009)*, and the *World Health Organization (WHO)*.

These codes and conventions describe monitoring guidelines in relation to pre-trial practices, the monitoring of trials while they are being conducted, and special regulations for exceptional contexts. In terms of pre-trial practices, monitoring guidelines focus primarily on stipulating ethical review standards and regulations. These relate to who should undertake ethical reviews of clinical trials, what must be submitted for review, including what research protocols should contain, what should be evaluated, and how this should be evaluated. In terms of monitoring clinical trials during the research phase, companies frequently report details regarding their internal monitoring and auditing practices, which include the committees and codes of conduct they have in place, as well as descriptions of other external and independent monitoring committees. Finally, the codes and conventions also describe monitoring and auditing practices from a global perspective. This relates either to how monitoring and auditing standards can be applied and verified through third party research networks or how monitoring standards can be implemented in low and middle income country contexts that often lack the infrastructure, resources, or qualified personnel to do so.



In addition to monitoring and auditing of clinical trials, regulations extend to the monitoring of products already in use through post-marketing safety studies, monitoring the implementation of emerging technologies, monitoring of access to data, and the monitoring of stem cell research and other genetic resources.

⁹² *The United Nations Global Compact* is a voluntary initiative based on company commitments to implement 10 principles in the areas of human rights, labour standards, environmental protection and anti-corruption.

⁹³ *The Nagoya Protocol on Access and Benefit Sharing* is a 2010 supplementary agreement to the 1992 *Convention on Biological Diversity* governing access to non-human genetic resources and traditional knowledge.

Research involving animals

In contrast to the wide-ranging auditing and monitoring committees in place to regulate clinical trials involving humans, research involving animals seems to be more standardized across the 14 companies. This is because the companies report compliance with, and use of, only a small number of policies. Twelve out of 14 companies, for example, reported that the auditing and monitoring of their research and research facilities are based on the *Guide for the Care and Use of Laboratory Animals* (2011), while many of them are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC). Other policies mentioned are the *Swiss Charter on Animal Welfare* (Roche), the 3Rs (Reduce, Refine, Replace) (Roche, Novo Nordisk), and the Institutional Animal Care and Use Committee (IACUC) (Roche). For an example, see Box 2.

Box 2: Statement from Merck KGaA (2015: 74)

“To demonstrate that we adhere to the highest international animal welfare standards, it is our goal to have all our laboratory animal facilities at Merck Serono accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) by the end of 2015. The AAALAC accreditation factors in national laws and guidelines while also taking into account the high international quality standards of the "Guide for the Care and Use of Laboratory Animals" from the Institute for Laboratory Animal Research (ILAR). Our two laboratory animal facilities in Darmstadt, Germany were successfully reaccredited in 2013 and 2014. The Grafing site in Germany was accredited at the beginning of 2015. The U.S. facility in Billerica, MA was AAALAC-accredited in 2012 and is preparing for reaccreditation in 2015”.

Monitoring and auditing guidelines mentioned by these companies tend to describe the ethical clearance process which needs to be put in place prior to conducting research, and more general specifications on the types and frequency of reviews required from monitors, which includes internal as well as external monitoring practices, the required training of research and monitoring staff, details about animal welfare and research facilities, the use of specific animals, and third party contracting.

To give an example for the ethical review of animal experimentation as documented on a company website: in order to guarantee high and uniform standards of animal welfare worldwide, Bayer has established a global Corporate Animal Welfare Committee. This committee reports directly into the Corporate Center of the Bayer Holding Board. The Head of the Corporate Animal Welfare Committee meets regularly with animal welfare experts from all sites at which animal studies are conducted to ensure that animal welfare is high on the agenda and improving.⁹⁴

⁹⁴ Source: <http://www.animalstudies.bayer.com/en/bayer-principles.aspx>.

In the context of North-South collaborations, policies on third party contracting may be relevant. To give an example, according to their website Novo Nordisk operate a monitoring and audit process on the use of animals at external contractor facilities to ensure that all external contractors comply with Novo Nordisk's global standards and principles on the use of animals. The company visits, monitors and approves all external contractors prior to initiation of a project in order to review conditions and procedures (Novo Nordisk, 2015b: 6).



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Informed consent

As one of the benchmarks for the ethical conduct of trials, it is interesting to see what the 14 selected companies report in public sources about informed consent. With the exceptions of BASF, Monsanto, and Syngenta, informed consent is a topic mentioned by all companies in a number of statements and policies. Despite the considerable number of sources used, there seems to be a general consensus on what informed consent is and how it should be obtained. Particularly relevant in the context of North-South collaborations and the potential for ethics dumping are efforts at achieving and maintaining global standards of informed consent as opposed to double standards, depending on the strength of local ethics oversight.

Global standards of informed consent

Global standards of informed consent are often mentioned in terms of the legal and regulatory frameworks in place to guide these standards. Examples of legal specifications include explanations of how informed consent does not waive the legal rights of research participants, or how participants have the right to abstain or withdraw from a study at any time, whether such legal provision is part of the national law in the host country or not. Legal provision is also made for instances when minors, vulnerable groups, or illiterate participants are involved, as well as special legislation for the use of genetic resources.

Some examples: Pfizer's clinical trial standards provide that the permission of a legally-acceptable representative, in accordance with international guidelines and applicable local law, is required for members of vulnerable populations who are not capable of giving informed consent (e.g., paediatric participants). Such study participants must be afforded the opportunity to provide or withhold their assent, unless the relevant ethics committee has waived assent requirements in accordance with applicable local laws.⁹⁵

At times, global standards are extended or adapted to local contexts. Obtaining informed consent for clinical trials in contexts such as these should, according to these standards, respect the local laws, customs, culture, and traditional knowledge of indigenous people. This applies to both participation in clinical trials and the use of genetic resources.⁹⁶

⁹⁵ Source: http://www.pfizer.com/research/research_clinical_trials/global_clinical_trial_standards.

⁹⁶ See *Nagoya Protocol*, Article 7 on access to traditional knowledge associated with genetic resources.

In cultures other than those in Western society, additional measures may often be needed to ensure the objectives of informed consent are met. While still complying with ethical and legal requirements, additional steps are therefore taken to match the objectives of informed consent to local cultures. For example, local leaders and/or family members may need to be involved. Where formal written informed consent from the participant is not possible in a GSK sponsored trial (due, for example, to poor literacy) investigators will work with independent witnesses to document a verbal consent process. They will formally verify that the purpose of the trial has been explained to the participant and he/she has understood what is proposed and involved (GSK, 2011: 4).

In the context of the provision of human materials, it is also noted that the informed consent document alone can never take the place of an interactive dialogue between research staff and research participants. Researchers are thus encouraged to focus on enriching the informed consent process itself, in addition to ensuring that the informed consent document includes all of the ethically relevant information. The informed consent process can be enhanced in the following ways, to give an example from Johnson & Johnson (2006: 10):



- i. Whenever possible, the person conducting the informed consent dialogue should have no vested interest in the research protocol. If members of the research team participate in the informed consent process, their role must be disclosed and care must be taken to ensure that information is provided in a transparent and accurate manner.
- ii. Empirical research has shown that informed consent is most effective as a dynamic, interactive, and evolving process as opposed to a static, one-time disclosure event. Thus, researchers should provide ample opportunities for providers of human materials to discuss their involvement in the research protocol.
- iii. Counselling services should be made available upon request to any providers of human materials prior to procurement.

In exceptional cases, additional informed consent must be obtained from trial participants. This might happen, for example, when patients are offered previously untested medication or if new information fundamentally alters the nature of the clinical trial. GSK's guidelines provide that

“where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, reestablishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be

recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed” (GSK, 2002: 4).

The most frequently occurring issue in both the global standards as well as the procedure of informed consent relates to the voluntariness of participation. All documents on informed consent clarify that research participation is voluntary and that research participants are free to withdraw at any time.⁹⁷

Is there post-trial access to medicines (especially for chronic diseases)?

There seems to be no consensus on the role and responsibilities of companies in relation to post-trial access to successfully tested medicines, even though this is part of the *Declaration of Helsinki* (2013, Art 34).

Information on post-trial access to medicine provided by the 14 companies can be sub-divided into three main areas. First, at a global level, there are policies and guidelines that set out the goals of what post-trial access should ideally include. Second, policies and guidelines consider the specific levels of what post-trial access to medicines should entail. Finally, different dimensions of the actual implementation, including of who is responsible, for post-trial access to medicines are also described.

The general consensus is that it is the responsibility of local or national authorities to provide post-trial access to medicines.



Global policies and guidelines for post-trial access to medicines

In their policies on post-trial access to medicines, as outlined on public sources, it is clear that companies would like to achieve post-study care that conforms to international standards and that are responsive to the health needs and priorities of the local contexts within which clinical trials are conducted.⁹⁸ For example:

- Pfizer’s research, like that undertaken by other pharmaceutical companies, “complies with international standards, regardless of where the trial site is located, usually under global protocols, under the oversight of multiple regulators, and without exploitation. Its Policies and Processes require that informed consent, independent ethics review, post-study care, and the use of placebos conform to established international ethical standards. It doesn’t pay patients to enrol in clinical trials and doesn’t use placebo-controls, or withhold life-saving drugs, in any study where doing so would harm the participants” (Pfizer, 2009: 1).

⁹⁷ See WHO (1995): 11; *Declaration of Helsinki* (2013), Article 27; ICH (1996): 5, 9 and 16.

⁹⁸ A disclaimer, especially for this section. We investigated the positions of 13 pharmaceutical companies on a number of issues relevant in North-South collaborations, as publicized through public sources. We did not undertake a check of whether they adhere to what they promise on their websites and in related documents.

- Merck expects its clinical trials to be responsive to the health needs and priorities of the populations and communities in which they are carried out. This includes consideration to making any intervention or product developed, or knowledge generated as a result of clinical trial research, reasonably available for the benefit of that population or community⁹⁹ (Merck & Co., 2012: 3).

Specific considerations of post-trial access to medicines

The *Declaration of Helsinki*, Art. 22, requires that “in clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.”¹⁰⁰ The following could be gleaned from documents available to the public.

- “The issue of post-trial treatment is, where appropriate, addressed in pre-trial agreements, the trial protocol and as part of the informed consent process. Factors to be considered include the disease and the type of medicines used in the study (e.g. preventative, palliative, acute treatment, the availability and affordability of the medicines) and whether post trial access might constitute undue inducement for patients to participate in the study” (GSK, 2011: 6).
- “The protocol must clearly define the appropriateness, relevance, and feasibility of providing investigational product and/or alternative therapies to study participants at the conclusion of the study, or other necessary follow-up care (e.g., unresolved adverse events). This determination may include consideration of local availability of the treatment and alternative treatments, the development stage of the investigational product, the seriousness of the disease being treated, the global results of the research program, the overall safety and benefit/risk ratio of the investigational product, local laws/regulations, as well as the individual study participant’s results.”¹⁰¹



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Post-trial access to medicine: Who is responsible?

Phase III clinical trials are designed to assess the effectiveness of a new medicine and its value in clinical practice. One has to distinguish between medicines for infectious diseases and medicines for chronic diseases. Simplified, infectious diseases can be cured whilst chronic diseases can only be managed to a certain degree. Clinical trial participants living in absolute poverty and suffering from chronic diseases can end up in a difficult situation. They participated in a trial, which was successful. The relevant company makes the drug “commercially available” or offers it to national health institutions. In both cases the prices may be too high for the patient (who is often uninsured) as well as the government of a low- or even middle income country. In practice this means that the patients – who felt the positive

⁹⁹ In line with CIOMS Guideline 10.

¹⁰⁰ <http://www.wma.net/en/30publications/10policies/b3/>.

¹⁰¹ Source: http://www.pfizer.com/research/research_clinical_trials/global_clinical_trial_standards.

impact of the innovative medicine – end up without access to the drug they need, even though they contributed to bringing it to market.

Thousands of clinical trials are conducted world-wide every year and a major concern is to ensure that patients who have benefitted from the trials can continue to do so after the trial has come to an end and before the product is made available in that country. The following excerpt from Roche encapsulates the general position held by most companies:

- “Patients receive state-of-the-art care and free treatment as participants in any of the more than 2,000 Roche-sponsored clinical trials per year. The success of our clinical trials is fundamental to the success of our business. No matter where a Roche clinical trial is conducted or who conducts it, it is essential that we carefully manage all related issues and risks to ensure that:
 - the safety, well-being, legal rights and ethical concerns of those taking part is addressed
 - patients who have benefited from a trial can still access treatment once the trial is complete, even although the tested product may still be awaiting regulatory approval
 - products are made available in all countries where participants live once the product has been approved....
 - We do not perform trials in countries where we do not plan to market the medicine being tested”.¹⁰²

A comparison of the various references these companies make to who is responsible for providing this care shows that the general consensus is that it is the responsibility of local or national authorities to provide post-trial access to medicines. Here, ‘national authorities’ refers mostly to national governments, but may also include health ministries, local health authorities, investigators, as well as local scientific and ethics groups. Most commonly, it is argued that the provision of medicines falls within the domain of national health care programmes and, as a consequence, post-trial access to medicine ostensibly is the responsibility of national authorities. In relation to newly-developed medicines, companies argue that it is the local governments’ responsibility to ensure national licencing of new products and to make them available to patients. Many companies also state that they will not conduct clinical trials unless this national infrastructure is available, and that post-trial care will be secured before a trial commences. Prior to clinical trials, companies prefer to secure a written agreement to confirm that national authorities will take responsibility for post-trial care. For example:

The general consensus is that it is the responsibility of local or national authorities to provide post-trial access to medicine



- “Before commencing a Roche Sponsored Clinical Trial in a low or middle income country, Roche will ensure that a description of post trial drug supply is written and

¹⁰² Source:

http://www.roche.com/research_and_development/who_we_are/how_we_work/clinical_trials/global_standards.htm.

incorporated into the protocol and patient informed consent forms. The preferred route is a written agreement obtained by the national health system assuring continuous medication and eligibility of all patients within national treatment systems, post completion of the Roche Sponsored Clinical Trials” (Roche, 2008: 1).

Although the option of national authorities taking responsibility for post-trial access to medicine is the preferred route, there are exceptional circumstances when this is not possible. In these instances, pharmaceutical companies may take on the responsibility of providing post-trial care. Two such exceptions, as illustrated by the examples below, are when a medicine may not yet be funded through normal health care infrastructure, or when a patient’s illness is life-threatening or seriously debilitating, and no alternative treatments are available.

- “In exceptional circumstances, if nationally licensed medicines used during a trial are not funded through the normal healthcare infrastructure, post trial provision of the medicines may be funded by GSK. Such circumstances include those in which individual patients have received measurable medical benefits from nationally licensed medicines during the study and where patients are unlikely to benefit from alternative nationally funded licensed medicines. This commitment is made pending the medicine being made available through the normal healthcare infrastructure or until the patient no longer requires it” (GSK, 2011: 6).
- “There are certain circumstances when, for the well-being of patients participating in a trial, continued access to the Roche investigational medicinal product is necessary. Examples are serious, life- threatening or disabling diseases such as HIV/AIDS, cancer, or lupus, when no alternative treatment is commercially available. In these situations, following termination of the Roche Sponsored Clinical Trial, an adequate supply of treatment will be assured for all the Roche Sponsored Clinical Trial participants until the Roche investigational medicinal product becomes available commercially in their country, provided participants continue to receive medical benefit from that medication and the benefit-risk ratio for the product continues to support such use” (Roche, 2008: 1).

An alternative approach, usually employed in contexts with limited infrastructure or resources, consists of companies explicitly negotiating the extent of their responsibility on a case by case basis. The following example illustrates this approach:

- “When clinical trials are carried out in countries or communities with limited resources, the sponsor must determine the appropriate standard of care to be provided to clinical trial participants, including determining whether or not an investigational agent will be made available after the clinical trial to trial participants, and determining whether or not other services provided during a clinical trial will continue after the trial, and under what circumstances. This also applies to investigation of new indications for licensed medicines” (Merck & Co., 2012: 3).

Defining the nature and the scope of these responsibilities can also be a cause for concern for companies:

- “GSK strongly supports the goal of improving access to medicines and we recognise our responsibility for helping to improve access to our products worldwide. GSK is however, concerned by the suggestion that research sponsors should be routinely obliged to provide treatments to participants post trial” (GSK, 2011: 6).

“GSK is however, concerned by the suggestion that research sponsors should be routinely obliged to provide treatments to participants post trial.”



In 2015, SOMO (a Dutch NGO which specializes in critical independent research on multinationals) published a study on “Post-Trial Access to Treatment Corporate- Best Practices”, in which Sanofi provided almost half of all submitted good practice case studies (SOMO: 2015, 9). Whilst Sanofi emphasized that a company cannot replace a national health-care system (ibid. 7), they will look at post trial access on a disease-by-disease, compound-by-compound and study-by-study basis and also have a range of policies to avoid the inclusion of vulnerable research participants who depend on researchers for post trial access (ibid. 9)

In summary, most of the leading international pharmaceutical or agrochemical companies have self-regulatory ‘soft law’¹⁰³ to which they publicly commit themselves. This in principle is a good sign with regard to the level of awareness that there are areas where existing law does not suffice to make a legal action legitimate. The content of this soft law comprises, in most cases, the necessary substance. Therefore, if and when corporate soft law is audited as if it were ‘hard law’ most of the ethical risks could be mitigated – this, however, is not always the case.¹⁰⁴

¹⁰³ "Soft law" refers to instruments which are not legally binding, as opposed to "hard law", which always is.

¹⁰⁴ In future reports, we are likely to argue that pre-trial due diligence undertaken by pharmaceutical researchers is an important prerequisite to avoid the exploitation of LMIC research participants and resources

Overview of existing compliance tools

Throughout most of the history of ethics review, ethics approvals have been obtained once, and no further questions asked. It is only recently that follow-up and compliance mechanisms in ethics review have achieved prominence in high income countries. For instance, it was only in 2006 that UK Research Councils added requirements for a complaints' procedure and ad hoc audits, as well as institutional monitoring, to their ethics standards.¹⁰⁵ Compliance and follow-up are complementary concepts. Compliance, i.e. the adherence to legal instruments and agreed guidelines, is desired, and follow-up tools are used to increase the likelihood of compliance. Example tools are represented in diagram 4.

Diagram 4 – Example Compliance Tools



This section gives examples of regulatory compliance mechanisms already in use in research ethics.

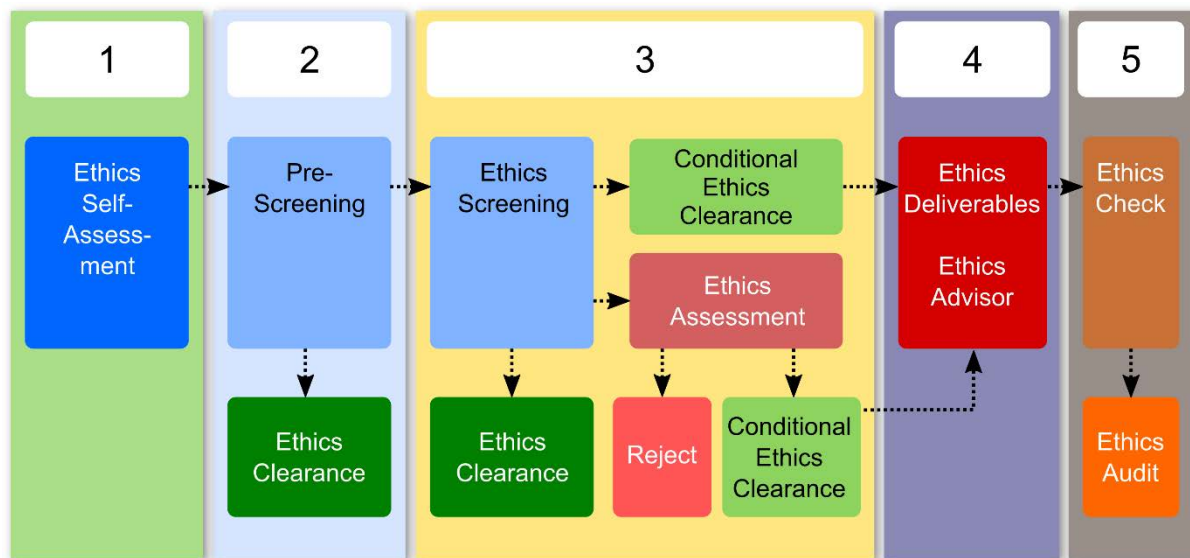
Ethics Checks and Audits in Horizon 2020

Funding obtained through Horizon 2020 is accompanied by a long-standing and thorough ethics review process. Article 29 of the *Regulation (EU) No 1291/2013* of the European Parliament and of the Council establishing Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020) reads¹⁰⁶: “Research and innovation activities supported by Horizon 2020 should respect fundamental ethical principles.” Diagram 5 summarizes the process of the Horizon 2020 ethics review.

¹⁰⁵ http://www.esrc.ac.uk/_images/framework-for-research-ethics-09-12_tcm8-4586.pdf

¹⁰⁶ <http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32013R1291&from=EN>

Diagram 5 – Horizon 2020 Ethics Review Process



Regulatory compliance means that those who are covered by a particular legal instrument, policy or rule, must adhere to it. In this regard, the entire ethics review process undertaken within Horizon 2020 contributes to regulatory compliance. For instance, the first step, ethics self-assessment, means that applicants have to consider which ethical principles they need to respect for their research and how to do it. This forces scientists to consider ethical issues during the application stage. These self-assessments are then checked by screening, and sometimes in an ethics assessment phase, by European Commission staff and/or external ethics experts. Obtaining research funding is then made dependent on adhering to “ethics deliverables”; items that need to be produced (e.g. approvals) to satisfy the funder that the research will respect fundamental ethical principles.

However, because ethics committee work is traditionally undertaken *before* any research begins, one cannot talk about a strict check for regulatory compliance until compliance is monitored during the implementation of research. Within the Horizon 2020 ethics review process, three possibilities exist for checking adherence to ethical principles during or after the implementation phase of a study.

1. Independent, external ethics advisors can be assigned to projects, possibly with the requirement of submitting an ethics report to the European Commission on a regular basis. The decision whether a project requires an ethics advisor is usually made at the screening or assessment stage by experts assisting the European Commission with the ethics review.
2. Ethics checks are a paper-based mechanism undertaken by ethics experts supported by European Commission staff. The process is similar to an ethics review, but with “real-life” documents, for instance, informed consent sheets which have been used with research participants, animal experiment licences, which have been obtained etc. Ethics checks do not necessarily indicate that something is seriously wrong with the approach of the researchers. At an early stage, a project might have been selected for ethics checks because, for example, the research involves vulnerable populations or invasive medical procedures.

3. Ethics audits, by contrast, are usually undertaken when there is a suggestion of considerable violation of ethics principles. The Ethics Unit for Horizon 2020 formulates this as: “In case of substantial breach of ethical principles, research integrity or relevant legislation, the Commission can carry out an Ethics Audit”.¹⁰⁷ Ethics audits normally involve meetings with the researchers in Brussels or on site visits.

The Ethics Unit for Horizon 2020 points out the potential seriousness of not complying with ethics principles, noting:

The Checks and Audits can result in an amendment of the grant agreement. In severe cases, it can lead, upon the decision of the Commission services to a reduction of the grant, its termination or any other appropriate measures, in accordance with the provisions of the grant agreement.¹⁰⁸

The British Medical Journal’s Publication Requirements

David Resnik provides a detailed Research Ethics Timeline (1932 - Present) for American policies.¹⁰⁹ It shows why research journals became involved in research ethics in recent decades. According to Resnik, investigators found in 2002 that a physicist at Bell Labs published 17 papers with fabricated or falsified data in *Science*, *Nature*, and *Physical Review Letters*. In 2010, the *Lancet* retracted a fraudulent paper linking autism to the measles vaccine. In 2014, *Nature* retracted a fraudulent paper on deriving pluripotent human stem cells from somatic cells. The above are all instances of research misconduct. According to a Consensus Statement on Research Misconduct published in the UK:

“Research misconduct is defined as behaviour by a researcher, intentional or not, that falls short of good ethical and scientific standards. Research misconduct includes fabrication, falsification, suppression, or inappropriate manipulation of data; inappropriate image manipulation; plagiarism; misleading reporting; redundant publication; authorship malpractice such as guest or ghost authorship; failure to disclose funding sources or competing interests; misreporting of funder involvement; and unethical research (for example, failure to obtain adequate patient consent). Research misconduct is important as it wastes resources, damages the credibility of science, and can cause harm (for example, to patients and the public)”.¹¹⁰

What the above authors call “unethical research” is the main target of TRUST.¹¹¹ One mechanism to ensure regulatory compliance is to link publishing research results to good ethical conduct. In other words, if journals have ethics requirements, adherence to ethics principles might be increased, given that researchers generally want to publish their results.

¹⁰⁷ http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/ethics_en.htm

¹⁰⁸ http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/ethics_en.htm

¹⁰⁹ <http://www.niehs.nih.gov/research/resources/bioethics/timeline/>

¹¹⁰ http://publicationethics.org/files/A_consensus_statement_on_research_misconduct_in_the_UK.pdf

¹¹¹ For an article on research integrity in low and middle income countries, see <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001315>

A 1997 study submitted to the *British Medical Journal* (BMJ) started a significant debate about the role of journals in achieving ethics compliance. “Does HIV status influence the outcome of patients admitted to a surgical intensive care unit? A prospective double blind study”¹¹² was conducted in South Africa to ascertain whether HIV positive patients have a similar rate of mortality and duration of stay in intensive care units compared to HIV negative patients. In a country with considerable resource issues and a high burden of disease, answering this question might contribute to decisions about directing available resources. Researchers conducting the study decided that informed consent about checks on HIV status should not be obtained.¹¹³ After discussions amongst the editorial team, the BMJ decided to publish the study.

Almost 20 years later, the BMJ has expanded its ethics policies considerably. A specific committee, the BMJ Ethics Committee, develops and reviews editorial policies on relevant ethics topics (e.g. consent, confidentiality, prior disclosure to research participants, competing interests), and advises editors on ethical issues in editorial work.¹¹⁴ The BMJ now “requires every research article submitted to include a statement that the study obtained ethics approval (or a statement that it was not required), including the name of the ethics committee(s) or institutional review board(s), the number/ID of the approval(s), and a statement that participants gave informed consent before taking part”.¹¹⁵

In addition, authors are invited to discuss ethical issues encountered during the study in the relevant manuscript, and peer reviewers are invited to consider these aspects as part of their review. BMJ editors are also encouraged to ask questions of authors, should they be concerned about aspects of the work, in terms of ethics.¹¹⁶

This approach is likely to contribute to ethics compliance, as it impinges directly on the interests of researchers to publish their work, which is also usually required from the funder.

The UK’s Economic and Social Research Council Compliance Framework

As noted earlier, ethics approval in itself is sometimes not sufficient to ensure that a study is *implemented* in an ethical manner. Some kind of follow-up is usually helpful to make sure researchers are implementing the study as outlined in the ethics documentation.

The UK’s Economic and Social Research Council (ESRC) has developed an ethics framework for researchers¹¹⁷ in receipt of ESRC funding, which includes a range of follow-up mechanisms. The ESRC requires of research organisations that they:

- establish procedures for monitoring research; this can include

¹¹² <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2126473/>

¹¹³ Details about the reasons given are discussed on page 1080 of the BMJ article.

¹¹⁴ <http://www.bmj.com/about-bmj/advisory-panels/ethics-committee>

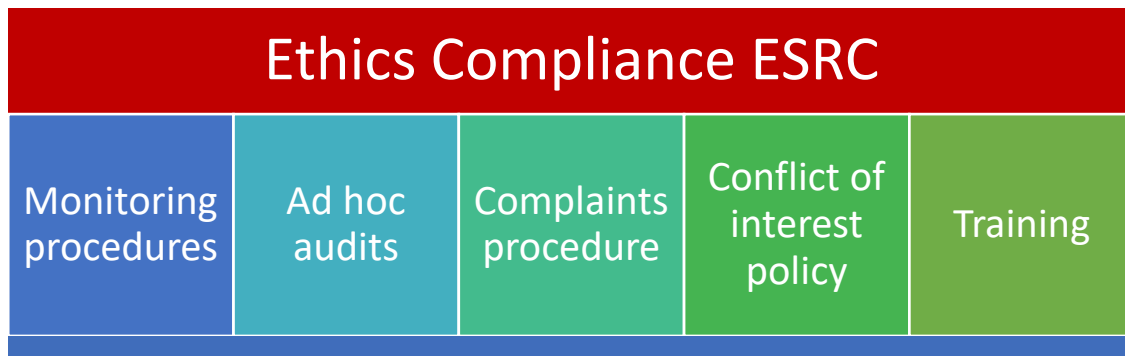
¹¹⁵ <http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/ethics-approval-research>

¹¹⁶ Ibid.

¹¹⁷ <http://www.esrc.ac.uk/files/funding/guidance-for-applicants/esrc-framework-for-research-ethics-2015/>

- occasional ad hoc audits of ESRC-funded research, and it must include
 - a complaints procedure, which ensures that complaints or expressions of concern are addressed in a timely manner, as well as
 - a conflict of interest policy, and
 - arrangements for ethics training of researchers, research students, supervisors and members of research ethics committees.¹¹⁸

Diagram 6 – ESRC Ethics Compliance Mechanisms



The Research Fairness Initiative (RFI)

This section introduces a compliance tool that is not yet operational, but has been suggested to ensure the fairness of North-South collaborations. The Research Fairness Initiative (RFI) is designed to optimize research partnerships in a global sense.¹¹⁹

The Council on Health Research for Development (COHRED)¹²⁰ is driving the development of a global reporting system aimed at creating transparency, increasing the use of best practices, and developing new benchmarks to improve research capacity worldwide – especially in relation to the needs of LMICs. Over a period of two years, a wide global consultation process has resulted in a practical framework to operationalise ‘fairness’ in research collaborations. As experience begins to accumulate, it is becoming increasingly clear that creating an environment that is ‘more fair’ will also have other benefits, including efficiency and competitiveness. The RFI is therefore designed to benefit all stakeholder groups.

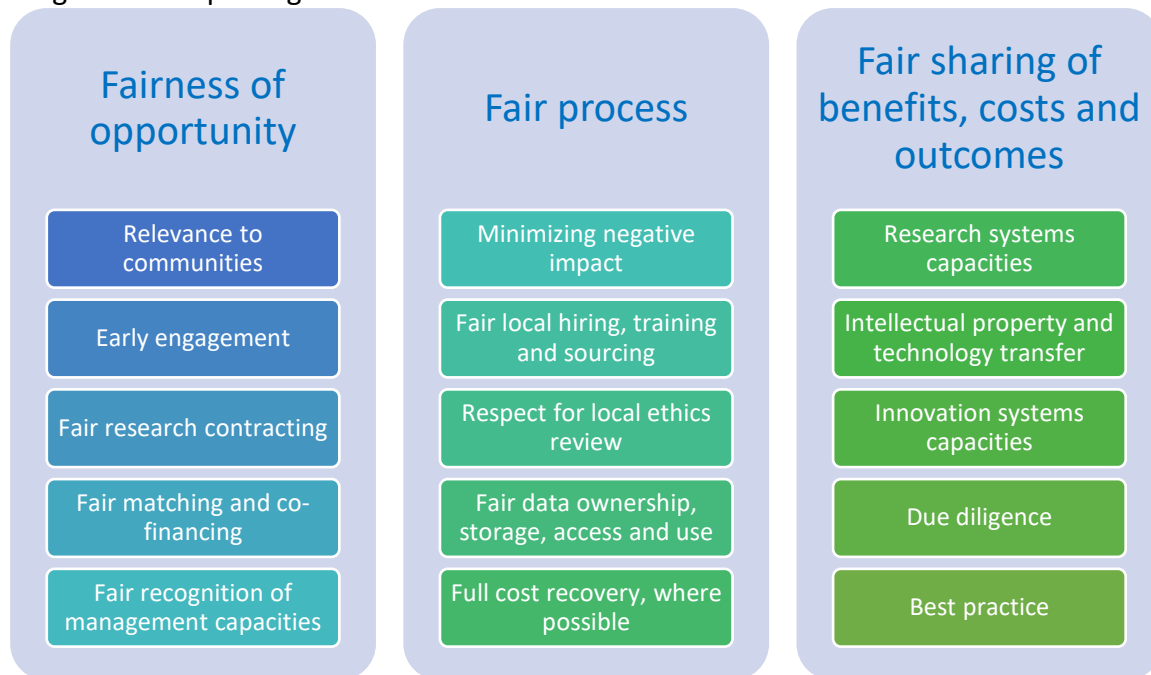
The RFI is conceptualized as a comprehensive compliance tool for responsible partnership behaviour, which makes use of a compliance mechanism that is popular in corporate responsibility, namely reporting on given criteria. By producing the RFI Report, stakeholders will be asked to explain the foundations on which they base partnerships – referring to existing publications, guidelines, policies or legislation. The following diagram shows the 15 areas that will be reported on.

¹¹⁸ Ibid. sections 1.6 and 1.7.

¹¹⁹ Research Fairness Initiative, available at <http://rfi.cohred.org>

¹²⁰ www.cohred.org

Diagram 7 – Reporting Areas in RFI



Each of the 15 topics has specific measurable indicators. For instance, the indicators of relevance to communities are:

- Research priorities in communities where research is being conducted
- Actions if there are no research priorities
- Justification to research low priority topics

The RFI is planned as a user-driven reporting system, as well as a learning platform that allows global sharing of best practice and the development of new and relevant benchmarks.

The Community Advisory Board

Community Advisory Boards (CAB) are a way of ensuring that study design and implementation can be influenced by research communities. For instance, the HIV Vaccines Trials Network (funded by Fred Hutch) has a CAB consisting of volunteers “to provide community input into study design and local procedures”.¹²¹ The CAB website notes that:

“CAB members include community activists and/or professionals associated with HIV/AIDS prevention and services delivery. Some of our CAB members are trial participants. Many have considerable scientific sophistication or relevant professional training, while others have no medical or scientific background but have a strong interest in HIV prevention”.¹²²

Diagram 8 – Key Features of CAB

¹²¹ <http://www.hvtn.org/en/community/community-advisory-board.html>

¹²² Ibid.

CAB as a compliance tool

- Ensures the implementation of the research protocol & social value of the research
- Negotiates the availability of the products of research to the local communities to:
 - Ensure benefit sharing
 - Ensure local capacity building

Community participation, or collaborative partnerships, refers to several elements that should be part of the research process to avoid, or at least minimize, the possibility of exploitation:

“One can speak of exploitation when we treat [others’] vulnerabilities as opportunities to advance our own interests or projects. It is degrading to have your weaknesses taken advantage of, and dishonourable to use the weaknesses of others for your ends”.¹²³

“A exploits B when B receives an unfair level of benefits or unfair burden of risks as a result of interacting with A”.¹²⁴

Research in LMICs has a greater potential for exploitation of local participants than research in high income countries. It is acknowledged in ethics guidelines as well as the ethics literature that community participation is a key to diminishing the risks of exploitation. The involvement of a CAD is a good way to develop and ensure mutual trust between Northern and Southern actors, and between local populations and international researchers, but also to inform the research team of the issues they may encounter on the ground related to, for example, health, anthropological, sociological, economic, and political issues.

When a sponsor wants to conduct a research project in an LMIC, they should automatically design the project protocol in collaboration with a CAB in order to anticipate risks of exploitation of disadvantaged or vulnerable populations, and potential harms and misunderstandings. The consultation of this same CAB should also be an automatic requirement for full validation of the research project when a research project is submitted to a Research Ethics Committee. Moreover, this CAB may also contribute to monitoring the conduct of the project, from beginning to end, and after the research is completed, for the purposes of ensuring compliance with the approved protocol.

Partnership/collaboration with a CAB would normally involve:

¹²³ Definition of exploitation (TRUST project grant agreement); from *European Textbook in Research*, 2010:127.

¹²⁴ Emanuel et al, 2004.

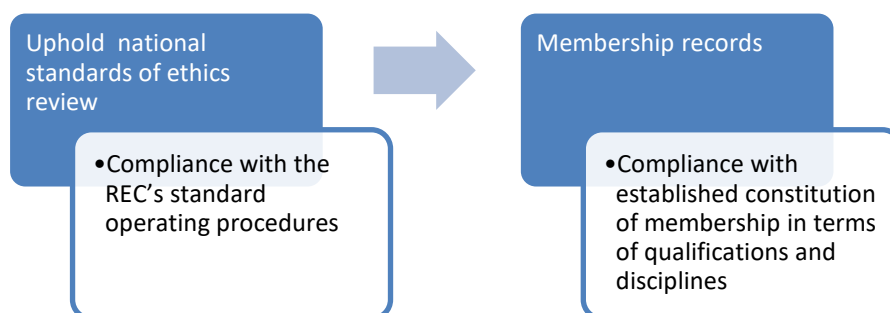
- Discussion of the social value of the research project, ensuring that the research is responsive to the research needs of the community which will be involved. This means that the importance of a problem and the setting of priorities for research will be determined or assessed in partnership with local communities.¹²⁵
- Ensuring that successful interventions are reasonably made available to the community, in the case of medical research. This requires the sponsor of the research to initiate a negotiation with stakeholders in the host country, amongst these are not only national governments, but also representatives of the communities from which participants are drawn, and non-governmental organizations such as health advocacy groups, in order to determine the practical implications of making the products of research available to the local community.¹²⁶
- Developing local capacities in collaboration with the involved community.¹²⁷
- Ensuring that the participants and communities receive benefits.¹²⁸

However, it is also important to note that CAB agreement to a study does not in any way replace the need to obtain individual consent from the prospective participants.

Accreditation of Research Ethics Committees

A national accreditation process for research ethics committees has been suggested in current literature as a tool for ensuring compliance with high ethical standards irrespective of where the research is conducted.¹²⁹ This compliance tool is currently used in all LMICs that are represented in the TRUST project, namely Kenya, India, and South Africa. The common criteria that are used for the accreditation of RECs in these countries are shown in diagram 9.

Diagram 9– Common criteria for the accreditation of RECs



In Kenya, the National Commission for Science, Technology and Innovation registers and accredits all RECs in the country.¹³⁰ Equivalent authorities are the Central Drugs Standard

¹²⁵ Mwinga & Moodley (2015); Pratt et al., (2015).

¹²⁶ Pratt et al., (2015), pp.20-21.

¹²⁷ Reddy et al., (2010), p.5.

¹²⁸ The National Health Research Ethics Council (2012), para 3(1) (c).

¹²⁹ Omosa-Manyonyi et al, (2015); Walanj (2014); Coleman & Bouësseau (2008).

¹³⁰ <http://www.nacosti.go.ke/services/accreditation>

Control Organization (India)¹³¹ and the National Health Research Ethics Council (South Africa).¹³² The period of registration and accreditation in all countries is three years, after which the REC must apply for reaccreditation.

Although the criteria focus mainly on structure and process, accreditation qualifies as a compliance tool because of its ability to ensure effective ethics review, which is the first means of ensuring compliance with high ethical standards. Notably, the criteria are widely used in regional and independent initiatives that promote voluntary recognition of RECs to ensure quality ethics review. Two examples of such initiatives are first, the Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP), which is a regional forum under the umbrella of the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER).¹³³ Secondly, the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP), is an independent non-profit accrediting body that “uses a voluntary, peer-driven, educational model to ensure that [human research protection programs] meet rigorous standards for quality and protection.”¹³⁴ One of AAHRPP’s envisaged values of accreditation is to reduce the risk of non-compliance with ethical standards that are contained in policies and procedures.¹³⁵ The accreditation process may take up to 12–18 months, and includes document reviews, site visit and individual interviews of those involved in the research program. Compliance with all applicable regulatory requirements is a necessary condition for the accreditation.¹³⁶

In summary, the compliance tools we identified for this report can best be mapped according to their main effectiveness on the time-line of a research study. As noted earlier, the traditional means of ensuring compliance with ethics guidelines and requirements - the ethics review - has the disadvantage of happening very early on in the process, usually without follow-up. It is therefore interesting to see where the other identified compliance tools fall on a time-line.

Ethics Checks and Audits (as undertaken in Horizon 2020), take place during the project or after the research concludes. The same applies to the BMJ’s Publication Requirements, with a tendency towards the conclusion of the research. The elements of the UK’s Economic and Social Research Council (ESRC) Compliance Framework as well as the Research Fairness Initiative apply across the time-line. The CAB can get involved in research throughout the timeline, but is usually most heavily involved before the research takes place, in a way similar to ethics committees. The accreditation of RECs to ensure their functioning takes place well before any relevant individual research project is assessed.

¹³¹ <http://www.cdsc.nic.in/forms/list.aspx?lid=2074&lid=23>

¹³² <http://www.nhrec.org.za/>

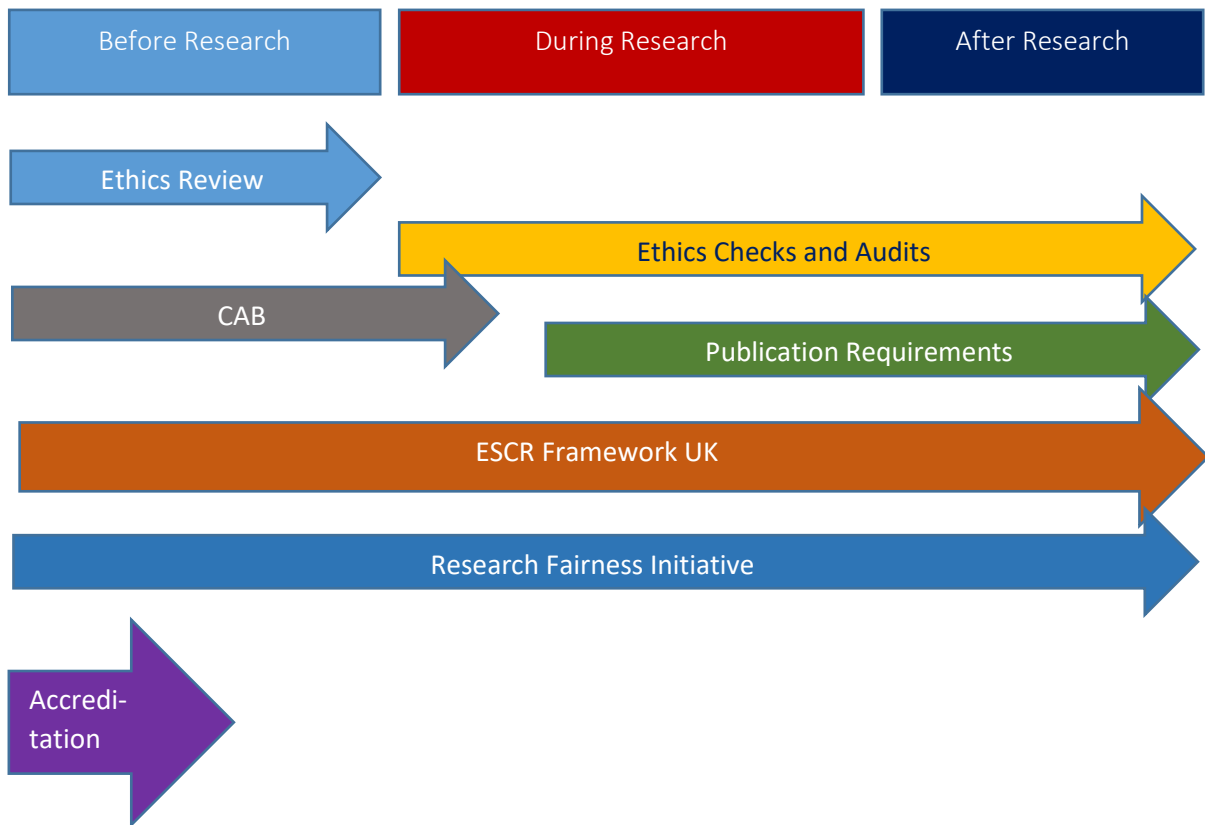
¹³³ <http://www.fercap-sidcer.org/whatsfercap.php>

¹³⁴ <http://www.aahrpp.org/learn/about-aahrpp/our-mission>

¹³⁵ <http://www.aahrpp.org/learn/considering-accreditation/value-of-accreditation>

¹³⁶ Coleman CH, Bouësseau M-C. (2008).

Diagram 10 – Compliance Tools Time-Line



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