



1st MEETING EXECUTIVE SUMMARY REPORT

BACKGROUND

To ensure that healthy volunteers (HV) rights, well-being and safety are safeguarded, the Belmont Report has identified 3 ethical principles which, in simple terms, can be summarized as follows:

- **Respect for persons**, through a genuinely informed and consent process, adapted to HV information needs and literacy level, that ensures they are fully cognisant of the risks and benefits of the biomedical research project, and of their rights during and after the study.
- **Beneficence** by minimizing the risks HV are exposed to but also minimizing their discomfort during and after the study period.
- **Justice** by ensuring that specific steps are taken to prevent exploitation of vulnerable people. A critical issue in respecting HV's autonomy is that of monetary compensation, which is the primary motivation of HV in most situations, which can translate into undue influence when HV are economically vulnerable.

METHODOLOGY

The workshop aimed at discussing ways to ensure that the above principles are effectively applied throughout the world, and throughout all types of research projects that involve HV, namely:

- Clinical studies with administration of pharmaceutical compounds
- Human infection studies, with a focus on COVID-19
- Non-clinical research (cohorts for biobanks and preventive HIV vaccine, behavioural and cognitive research)
- Non-drug related interventions (vaccines, living cells donations, medical devices)
- Research in particularly vulnerable populations.

Best practices were discussed and a '4Rs' framework was proposed (Respecting, Reducing, Refining and Replacing HV) as a possible way to optimize the use of HV in biomedical research.

KEY MEETING OUTCOMES

Attendees: 164 registered from 46 countries

- **Africa:** Jordan, Morocco, Uganda, Mozambique, Madagascar, Congo, DRC, South Africa, Mali, Gambia, Kenya, Gabon, Guinea, Liberia, Cameroon, Nigeria, Botswana, Senegal, Ivory Coast
- **Americas:** USA, Canada, Argentina, Colombia, Brazil
- **Asia:** Japan, Malaysia, The Philippines, India, PR China.

- **Europe:** Estonia, Moldavia, Serbia, Belgium, Sweden, UK, Switzerland, Italy, Greece, Germany, Czech Republic, Norway, Russia, Malta, Romania, France, Austria.

Institutions/NGOs: Inserm, EDCTP, Wellcome Trust, European Commission (DG Research & Innovation, European Research Council), Council of Europe, NIH (USA), UNESCO, WHO, CIOMS, DNDi, Epicentre-MSF, Action contre la Faim.

Pharmaceutical companies and CROs: Biotrial, Clinexel, Cipla, Sanofi, Pharmetheus.

Best practices examples from France, India, Malaysia, Morocco, People's Republic of China, UK, USA

- Laws and regulations that explicitly protect HV among participants in biomedical research (*many countries do not consider them apart from other study participants*)
- Informed consent processes and documents specifically tailored to HV's needs and potential vulnerabilities (*should address different literacy levels, be explicit about potential risks, consider questions to check understanding of key messages before consent is obtained, ensure information throughout the study, etc.*)
- National or international HV registries to avoid undue repeat participation in research projects (*require unique identification number, confidentiality to be ensured, may be designed to maximum amount of compensation authorised, authorized wash-out periods can be standardized or not, etc.*)
- Adapted Institutional Review Boards to ensure scientific validity of research and protection of HV
- Insurance coverage for adverse events occurring during and after the study (*especially in countries with no universal insurance coverage*),
- Regulations on permitted means of recruitment of HV, *including through social media and third parties ("recruiters")*,
- Formalized processes to determine fair amounts of compensation (*to ensure transparency and consistency at country level, provide guidance to IRBs*)
- Accreditation and inspection of investigational sites (*to ensure the qualification of investigators, the availability of life-saving interventions, the decency of housing conditions, etc.*)

Other issues discussed

- How to involve HV representatives in all the work and discussions that concern them? How to involve communities?
- How to avoid excluding particularly vulnerable people who might be representative of important population segments?
- Appropriateness of the term "healthy volunteer": what is it to be healthy? what is it to be a volunteer?
- How to define and how to avoid "exploitation"
- How to manage research projects involving particularly vulnerable HV populations
- How to minimize Adverse Events reporting biases
- How to ethically perform studies with HV for traditional remedies and how to account for use of traditional remedies during studies with HV
- How to avoid ethical dumping when strict local regulations may encourage exportation of studies in other countries.

Additional research needs were identified in multiple fields, in particular

- Data on the actual number and types of studies involving HV in the world
- HV motivations to participate in research in various countries and types of research

- Value of national registries in preventing over-volunteering (*as is done in the UK by monitoring attempts at repeat participation*)
- Reducing, Refining and Replacing healthy volunteers (*for instance: optimisation of study designs to involve less subjects, mutual recognition mechanisms between regulatory agencies to avoid repeating studies, increased use of mathematical modelling, and in vitro and in silico experiments*).

Note on the proposed “4Rs framework”

Most of the meeting discussions revolved around Respect, where rapid improvements can be expected based on existing best practices. The other 3 “Rs” represent an aspirational objective to be reached over time since they will require working on new scientifically sound approaches in close coordination with regulatory agencies (to be further discussed).

NEXT STEPS

An International Steering Committee (ISC) is being set up to organise working groups that will explore more in-depth the identified key issues and best practices to enable the development of international guidelines during a meeting to be organised end 2022/early 2023.

The ISC will also advise on other activities that could be pursued in terms of publications, advocacy work and training opportunities for researchers, regulators, funders, media and civil society.