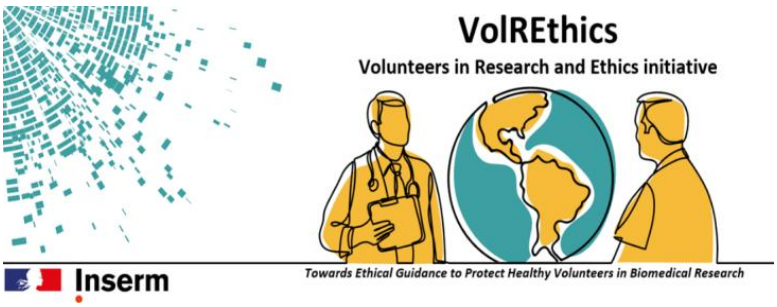

European Commission

https://www.inserm.fr/en/ethics/volrethics/
https://europa.eu/sinapse/directaccess/hvguidance

VolREthics Initiative - Volunteers in Research and Ethics

European Workshop, January 27, 2023

Focus on the risks of exploitation of healthy volunteers in biomedical research

Meeting report

Meeting agenda

→ The VolREthics Initiative –Framework and initial steps (10:00 – 10:15 am)
François Bompart *(Drugs for Neglected Disease initiative, Inserm Ethics Committee)*

→ Introduction by the co-chairs (10:15 – 10:30 am)
Lisa Diependaele (*Ethics Sector, DG Research & Innovation, European Commission*)
Filipa Ferraz-de-Oliveira (*Ethics Sector, European Research Council Executive Agency, European Commission*)

→ How to protect HVs from exploitation: European perspectives. 10:30 – 11:15)
Moderator: Dirk Lanzerath (*European Research Ethics Committees network- EUREC)*)
Set the scene:
- Antigone Dimas (*Biomedical Sciences Research Centre Alexander Fleming, Greece*)
- Renke Maas (*Friedrich-Alexander-Universität, Germany*)
- Ivan Vyshnivetskyy (*President of the Ukrainian Association for Clinical Research / Managing Director Ukraine at FutureMeds*)

→ Experiences of European Healthy Volunteers (11:15 – 11:45)
Moderator: François Hirsch (*Inserm Ethics Committee*)

→ Open discussion with the audience: identified risks of exploitation, field experiences, recommendations (11:45 – 12:15)
Moderator: Alexandra Rolaki (*Ethics Sector, European Research Council Executive Agency, European Commission*)
Sharing experiences:
- Roman Fishchuk (*Clinical trials department at Central City Clinical Hospital, Ukraine*)
- Thomas Hinault (*Neuropsychology and Imaging of Human Memory Unit, Inserm, France*)
- Aneta Sitarska Haber (*Polish Association for Good Clinical Practice (GCPpl)*)
- Shadreck Mwale (*West London Univ., UK*)

→Concluding Remarks (12:15 – 12:30)
Dirk Lanzerath (*European Research Ethics Committees network- EUREC)*)
François Eisinger (*Inserm Ethics Committee*)

Attendees: a total of 120 persons registered to attend the meeting, from European countries (Austria, Belgium, Croatia, Cyprus, France, Georgia, Germany, Ireland, Italy, Lithuania, Malta, Moldova, the Netherlands, Norway, Portugal, Serbia, Switzerland, Ukraine, the UK), as well as from Canada, Cameroon,

Ethiopia, Japan, India, Kenya, Liberia, Malaysia, Mali, Nigeria, South Africa and Tanzania, including 3 healthy volunteers from France.

Introductory presentations were made

Highlights included:

- Despite good quality safeguards for ethical conduct of clinical research in most European countries, challenges exist since
    - healthy volunteers are rarely considered by national laws and regulations as a specific subset of research participants,
    - new challenges keep emerging as new research practices involving human subjects appear.

- A specific focus was made on Germany which highlighted
    - The absence of a national healthy volunteers' registry, but the existence of commercial ones in which registration of healthy volunteers is required by some CROs.
    - There is no national "human research law". At the country level, research involving pharmaceutical and medicinal products is very regulated, unlike other areas of research. Regional regulations relevant for research with healthy volunteers apply to physician investigators, but not to other professionals.
    - IRBs often refuse projects involving team members as medical research subjects, but rules may be more flexible for non-medical research
    - Drug candidates presumed to be toxic are usually not tested in healthy volunteers, but some borderline situations may emerge where testing in healthy volunteers may provide valuable information and/or administration to patients may be problematic.
    - In some university curriculums in psychology and social sciences, students have the obligation to participate in research projects. To avoid peer pressure and compromise ability to provide true informed consent, it is recommended to give to students a wide choice of research projects.
    - Deliberate deceit of participants, primarily in human and social sciences research, may be required e.g. to hide the real questions under investigation. These pose difficult dilemma, which need to include post-study disclosure of "deceit". Ethics boards regularly require the disclosure procedure to be specified in the protocol, and to disclose at least the expected level of possible study related discomfort in the information for participants in advance.
    - Informed consent documents are often extremely lengthy due to increasing data protection and other legal requirements.

- A presenter from the United Kingdom focused on healthy volunteers engaged in commercial trials for first-in-man studies and made several points including:
    - Volunteers' associations do not exist because volunteering is usually a short-term, occasional activity, and there are too many very different ways for healthy people to participate in research projects
    - In his experience, payment was the key motivation for participants, who are often times unemployed, or with one or several underpaid jobs, with debts to repay, etc.
    - Risk of exploitation is strongly related with financial strain. He gave the example of an immigrant woman whose "boyfriend" obliged to take part in 3 studies in order to get money,
    - Volunteers sometimes said they felt they are abusing themselves to earn a living, not unlike prostitution.
    - Trust can only be established if there is a clear understanding of risks by the volunteers. This is a major challenge to address, especially when dealing with new types of medicines.

- Another focus was provided on Ukraine which highlighted:
    - An increase in the number of Phase I trials from 1 in 2015 to 21 in 2020,
    - There is no specific provision for healthy volunteers in the national laws on medicinal products and clinical trials, nor in the national adaptations of CIOMS and ICH guidelines.
    - The potential risks of exploitation of healthy volunteers are the same as in other parts of the world, although financial payments are usually not very high. There is no standardised methodology for defining appropriate financial compensation.
    - The invasion war has had drastic consequences on research in Ukraine overall, and many population segments are at risk of becoming more vulnerable on many aspects, including risk of falling into poverty.
    - The presenter stated that research sponsors should contribute to building research capacity, as recommended by CIOMS guidelines and the TRUST code of conduct among other, this is even more important given the consequences of the war,
    - He concluded by making a vibrant plea for all relevant stakeholders to support research in Ukraine.
- Information was provided on initiatives taken in Poland:
  The GCP Association and MHR (Medical Research Agency) in Poland are working on guidelines related informative campaign in Clinical trials but this is not specific only for healthy volunteers. They recommend that properly prepared materials about clinical trials should be very informative and transparent, meet the requirements of legal regulations. Recruitment campaigns cannot have the characteristics of aggressive commercial advertisements to induce or coerce participants. The special part is focused on healthy volunteers to avoid manipulation based on financial motivation (« bribe » elements observed in some advertisements) but showing their role as participants in clinical trials including risks. They are intended to target pharmaceutical industry sponsors, IRBs, investigators and volunteers. The point was made that it is still crucial to build awareness and knowledge on the role, responsibilities and rights of HV. Having special groups/organizations (Patient Advocacy Groups) would be very beneficial to share good standards and bring awareness on patient's /HV rights. The presenter suggested considering setting up a formal HV Register (like in some countries) to avoid situation when HV participate in more than one study using clinical trials as source of earning.

During the meeting, 3 healthy volunteers shared their insights on their involvement in biomedical research studies.

The 3 volunteers, two women and one man, were middle-aged and highly educated but not heath professionals (a PhD in physics, a PhD in astrophysics and a lawyer).

One had become engaged in a COVID vaccine study, and convinced her 83 years-old mother to participate in the same trial. One had participated in multiple biomedical research projects in Tunisia and in France, and one was part of a healthy volunteers' cohort created by Institut Pasteur.

All had overall very positive experiences to share, their primary motivation was an altruistic desire to help science (particularly at a time of a pandemic). They all highlighted the way they felt always respected by investigators and study staff.

Nevertheless, they mentioned improvement opportunities in several areas

- Simplify informed consent documents. They are too long, complicated, they look too much like legal disclaimers and useful information is not always easy to find.
- Address the complexities created by successive protocol amendments which can be extremely confusing for volunteers,
- Clarify ahead of time what results will be shared with volunteers: what information? Individual or collective? when? etc.
- Study sponsors should better inform ~~v~~olunteers regarding release of press statements on study results, and key publications: volunteers should be proactively informed, and made feel they are

"special" in the eyes of the sponsors. Importantly, both negative and positive results should be shared.

Insights were provided in the following areas

- Elderly volunteers: a series of specific issues apply such as
  - Large heterogeneity of population subsets: how to define "normal"?
  - Representativity of volunteers when highly educated and highly motivated persons tend to represent most study participants.
  - Motivations: altruistic motivations prevail largely (benefit science, future generations, etc.) but also some personal benefits such as ability to benefit from early signals of medical problems, Alzheimer Disease, etc.
  - Management of incidental findings
  - Informed consent for people with cognitive impairments.
- Study results publications: the new EU Clinical Trials Regulation 536/2014 requires that as from February 1, 2023, Phase I results be published on a public repository, publication can be delayed up to 30 months to protect commercially confidential information.
- Students as volunteers: when participation in a research gives university credits, one needs to be very aware of the need to respect people's ability to truly provide consent (see introductory presentation on Germany: this may be alleviated by giving students a wide choice of studies).
- Investigators as volunteers: may deserve specific discussion. Some of the same considerations apply as for students, with the added complexity of peer pressure.
- Incidental findings: the issue of incidental findings made during research remains an area deserving consideration since these can have consequences not only for the health of study participants, but also for their families, insurance contracts, etc.
- Insurance coverage: consideration needs to be given to ease of submitting insurance claims for problems emerging especially after the study, which can get very complex when long periods of time have elapsed.

Concluding remarks included the need to consider the respective responsibilities and needs of all relevant stakeholders (sponsors, CROs, investigators, IRBs, regulatory bodies, lawmakers, etc.). The point was also made that adding new administrative steps intended to protect volunteers should not end up creating systems that end up being excessively complex and lengthy.

And a proposal was made to reflect upon 3 key words:

- Diversity: we must deal with very diverse stakeholders, research purposes, legal and regulatory frameworks and types of vulnerabilities. This makes it difficult to elaborate a common rule.
- Trust: the issue of trust among many different stakeholders is of paramount importance. Several speakers referred to the need to keep building trust, which is always at risk of being broken,
- Improvement: a first step towards improvement of the situation is the sharing of information and experiences, then should come improvements in laws and regulations.

The insights shared during this and the previous 4 regional meetings, will greatly contribute to the preparation of the VolREthics April 24-25 plenary meeting in Brussels.