VolREthics Initiative - Volunteers in Research and Ethics

Second plenary meeting, Brussels April 24-25, 2023

Meeting report

Attendees: a total of 95 persons registered to attend the meeting, from Argentina, Belgium, Brazil, Canada, Republic of Congo, France, Germany, Greece, India, Italy, Ireland, Japan, Kenya, Malawi, Malaysia, Malta, Mozambique, Nepal, Poland, South Africa, Spain, Switzerland, Uganda, UK, USA, Vietnam, including 2 healthy volunteers from Uganda, one from the USA, one from Malaysia and one from India.

Healthy volunteers’ testimonies highlights

The US healthy volunteer, who had taken part in 15-20 studies, described an industry that uses large number of poor people, who are sometimes homeless or illegal aliens with no work permit. He described the overall experience as one of suffering from discomfort and pain with multiple venous punctures, and from side-effects some of which may last long after the trial is over. He made clear the financial motivation of volunteers, who need the money to feed themselves or their family, and described the hardships that poor people may experience to get to the study site in time, on public transportation, regardless of the weather conditions. People who are late or miss their appointments due to bad weather conditions for example, are financially punished. They may end-up on a blacklist if they withdraw from the study before its completion, barring participation in future studies at the institution and sometimes other institutions. He begged for more care, patience and understanding from study staff of the issues faced by volunteers in their lives and during their stay at the facility. He insisted on the need to keep access to the study facility to be able to run health tests, after the study is over, in case of suspected adverse events.

The volunteer from India, a young health professional had taken part in 2 vaccine clinical studies, one to benefit from a meningococcal vaccination to enable foreign travel, the other with a COVID-19 vaccine. Not being able to know if she received a placebo or active vaccine created problems for her with the family (did she risk exposing her elderly patients to the virus?) and for travel abroad since she could not get a vaccination certificate. She felt somehow trapped by participating in vaccine trial as she could not benefit from the new vaccine when it was made available to the public. Post-trial access to the active vaccine was not clearly defined when she enrolled into the study.

The two volunteers from Uganda and the one from Malaysia, all with a scientific background reported overall more positive experiences. But all indicated the misunderstanding of friends and family members, and sometimes the stigma related with study participation (you are going to die, etc.), leading them to conceal sometimes for long durations of time their activities as HVs.
Key learnings

Our overarching objective is to get, among research participants, healthy volunteers recognised as a “group that should receive specifically considered protection”.

“Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection” WMA Declaration of Helsinki (2013 §19.

For this, we need to

- Highlight what is “special” with healthy volunteers in terms of risks they are exposed to and what specific safeguards are needed,
- Develop plans to inform/educate stakeholders such as staff members, Ethics Committees and other project review bodies, about the specificities of HVs. A 3C approach may apply: Commitment, Care, Communication.
- Promote the 4R approach: Respect, Reduce, Refine, Replace HV in research as a very effective way to communicate on our objectives. First Respect that our current focus, then in a mid-to long-term perspective to support ways to reduce, refine and replace HVs.
- Highlight the very positive contribution of HV to science, not only negative aspects.

Moving forward, we need to

1 Define the scope of the future guidance document(s)

Our objective is to publish a guidance document (or several). We need to strike a balance between addressing the needs of many research fields vs. being effective in issuing a focused, implementable, guidance document.

Several options to consider:

- Include all “health related research”, as does CIOMS, including epidemiology, human and social sciences, socio-economic research, etc.
- Focus on interventional (as opposed to observational) health-related research
- Focus on interventional health-related research with the highest risks of exploitation and harm (repeat participation in studies for economic reasons)
- Focus on medical research involving human subjects, with primary focus on physicians as does the Declaration of Helsinki.

2. Work on the definition of a “healthy volunteer”

Various ideas were expressed:

- Defining who is “healthy” is impossible. The only reliable option is that of each study’s inclusion/exclusion criteria.
- Instead of vulnerability, we could use the level of risks of exploitation and/or harm to define various categories of volunteers.
- The term “volunteer” is outdated, and true volunteering can be questioned in situations of vulnerability. Nevertheless, healthy people most often proactively express their desire to participate in a study before even knowing any detail about it (they “volunteer” their participation), unlike patients who, usually, react to a proposal from a health professional.
- Not everyone who is not “a patient” is a “healthy volunteer”. Only people whose “healthy” status was determined by medical examination and tests should be called “healthy volunteers”. The others are “study participants”.


Specific considerations should be given to
- Military healthy volunteers or students, who may be exposed to risk of subordination, peer pressure, but also of incidental findings that could jeopardize their job or university credits. Some similarities with other jobs e.g. airline pilots and astronauts.
- Elderly volunteers whose “healthy” status may require specific definitions, require monitoring over time, and adaptations required by “normal” aging.
- Pregnant women, who may expose themselves and their unborn child to risks.
- Women of child-bearing potential.
- Children.

3. Support the creation of HV advocacy groups
To gather more insights into the realities of HV and to enable the participation of HV in all steps of research that involve them: recruitment processes, then design, review and monitoring of appropriate conduct of research studies.

4. Address financial compensation as a key differentiating factor for HV in research
Financial compensation is what makes HV different from other research participants, in particular patients.
- Many discussions around the appropriate terms to use: indemnity, compensation, reimbursement, other? In Poland, HV sign an employment contract that gives them a salary, this case seems rather unique.
- Relative unanimity to say that the level of risk should not be taken into account to determine the level of compensation since only the most minimal risk levels could be acceptable for healthy people. Compensation should be based on time spent and level of inconvenience imposed by the study. Lost income is much more difficult to take into account.
- What is a fair compensation when several countries, with different living standards are involved?
- The issue of making “completion bonuses” compatible with the right of withdrawal at any time or upon termination of the study by the sponsor, without suffering consequences is a major one but was not extensively reported upon. It was only proposed that the financial consequences of withdrawal or possible termination of the study be clearly stated in the informed consent document.

5. Work on implementation of healthy volunteer registries
There was virtual unanimity to support the creation of registries to protect HV from the risks of over-volunteering, managed by government agencies or non-profit public entities.
Proposals were made to
- Make registries multinational, if not global.
- Use biometrics to ensure identification of HV, particularly in countries where ID documents are not widely available or can be counterfeited.
- Take into account issues of data privacy and confidentiality.
- Access rights to the registry is related to the issue of accreditation of study personnel.
- Wash-out periods could be made flexible based on the investigator’s assessment (reviewed by an ERC) rather than standard (3 months in some countries).
- Consider building registries to gather data on the number of studies, number of HV involved, number of over-volunteering cases prevented, etc.
- France is currently the only country that tracks payments to HV through a registry, with a maximum of 6000 Euros per 12 months. Registry created in 1988, over 7500 trials and 50 000 HVs registered.
There were suggestions to expand the role of registries as platforms to interface with / recruit healthy volunteers. Some people expressed their preference for limiting the objective of registries to the protection of HV, by preventing over-volunteering.

**Other meeting highlights (non-limitative, please refer to meeting slides and recordings)**

**Introductory presentations highlights**
Unlike patients, healthy volunteers are not involved in the design and running of clinical trials. In pharmaceutical clinical trials, healthy volunteers are involved throughout the drug/vaccine’s life-cycle from Phase I to post-marketing studies. Patients with liver and renal impairments are involved in clinical studies which are close to those involving healthy volunteers. There are no international guidelines for defining normal biological tests values nor physiological constants such as heart rate. Decentralised trials allow patients to stay at home, rather than travel to/ be housed in health facilities. EU guidelines were issued end 2022. Specific issues may be raised by the extensive, and virtually exclusive, use of remote communication, as opposed to personal interactions.

**Ethics Research Committees**
No country reported having special ERC composition recommendations or training materials specifically designed to address issues related with the review of projects involving HV. The group felt that this was a key problem and that some understanding of HV specificities must be found at the ERC level, for instance through the “lay person(s)” member of the ERC.
- Belgium Association of Research Ethics Committees (BAREC) recommends the presence of a HV when research implicating HVs are evaluated.

**Informed consent process**
Many discussions around the need to simplify and adapt the informed consent process and documents to the specificities of HV. HV should be involved in this work, but are not currently. Be mindful of the risk of oversimplifying the information which may bias the way risks are explained. In addition to the investigator’s contact information, HV who want to report a problem should be given, the contact information of another (neutral) person of body (for instance ERC).

**Well-being of HV**
The 3C concept was coined: Study staff should Care, Commit and Communicate with HV. In addition to the investigator’s contact information, HV who want to report a problem should be given the contact information of another (neutral) person of body (for instance the ERC).

**Post-study information**
Proposal was made to give HV several options to choose what post-study information, if any, they want to receive, with the possibility to change their mind. The practicalities of providing individual data need to be weighed against the rights of HV to get access to it (e.g. unexpected genetic findings that may impact HV relatives).

**Insurance:**
It is extremely difficult to provide insurance for clinical trials in the absence of a real market. Guidance documents could help create a market.
Incidental findings:
Management of incidental findings needs to be anticipated and clearly expressed in all study documents.
Complex issues exist in countries with no national health care / health insurance system.

Medical devices
Have usually a physical action and can be used for disease treatment, diagnosis or prevention. These may expose to the risk of irreversible harm more often than medicines. In some condition, (e.g. test of implantable device) the right to withdraw becomes impossible.
Artificial Intelligence devices pose specific problems and should be kept in sight because they are bound to proliferate and expose to specific risks e.g. of manipulation of individuals.

CONCLUSION

Opportunities to seize
- The draft report of the CIOMS Working Group on Good Governance Practice for Research Institution (GGPRI) is available for public consultation on the CIOMS website https://cioms.ch/working_groups/principles-of-good-governance-for-research-institutions/ . Comments to be provided by June 7, 2023
- Revision of the Declaration of Helsinki (timeline 12-18 months)

Creation of working groups:
At the end of the meeting, a proposal was made to create 3 thematic working groups to continue working on some of the key issues discussed during the meeting:

Group 1: Overall protection of healthy volunteers
- Work on problem statement
- How to promote the creation of HV advocacy groups
- How to raise awareness on specificities of HV, including positive contribution of HVs for the societal welfare
- Oversight: define the role of ethics committees, regulators, etc. to protect HV and how to help them to do so. Review of protocols in line with 4Rs and other ethics frameworks?

Group 2: Protection from exploitation / promotion of the interest and welfare of the participants
- Financial compensation
- Recruitment practices
- Informed consent, including appropriate re-consent and opportunity to withdraw. Best practice re: contact number/hotline for reporting bad conduct [appropriate actors to manage this: REC, regulator, civil society, etc.]
- Monitoring/ensuring well-being during the study
- Sharing information/benefits with volunteers

Group 3: Protection from risk of harm and ensuring validity of studies
- Healthy volunteers registries: Site-based, national or multinational
- Accreditation and inspection of investigators and sites (consider relation with ability to access and use registries)
- Representativeness of healthy volunteers for the target populations
- Plans for incidental findings and ancillary care
- Insurance/liability/redressal approaches.

### Appendix

**Summarised meeting agenda**

**SESSION 1 – Healthy volunteers’ involvement in research projects**

**SESSION 2 – VoIReEthics progress to date (with HVs testimonies and regional seminars reports)**

**BREAKOUT SESSIONS to discuss good practices**

**BS 1:** Protection from exploitation; Focus on: - Informed consent processes and documents tailored to volunteers’ needs and vulnerabilities - Processes to determine fair amounts of compensation - Management of study completion bonuses vs. right to withdraw

**BS 2:** Protection from exploitation; Focus on: - Permitted means of recruitment of healthy volunteers - Standards to ensure well-being during the study - Information of healthy volunteers on study findings

**BS 3:** Protection from harm and ensuring validity of studies; Focus on: - Adapted Institutional Review Boards and study review processes - Accreditation and inspection of investigators and investigational sites - Representativity of healthy volunteers for target populations

**BS 4:** Protection from harm and ensuring validity of studies; Focus on: - Healthy volunteers’ registries - Management of incidental findings - Insurance coverage for adverse events occurring during and after the study

**SESSION 4 – Keynote Lecture**

**SESSION 5 – Reporting of breakout sessions**

**SESSION 6 - Roundtable discussions:**

Roundtable 1: Relevance of proposals made for non-pharmaceutical biomedical research areas

Roundtable 2: Study sponsors and CROs

Roundtable 3: Regulatory agencies

**SESSION 7 – Next steps: How to progress in the elaboration of international guidelines for the protection of healthy volunteers globally?**

**SESSION 8 – Open discussion, including topics for further work**

**Concluding remarks**