Beyond One Million Genomes

POLICY DOCUMENT

B1MG WP2 Recommendations for a 1+MG Minimal Standards for Inclusion of Special Subjects

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Leader: Signe Mezinska

Contributors and reviewers: Regina Becker, Mihaela Matei, Susanne Rebers, Adrian Thorogood

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1. Scope

Recommendations for the responsible inclusion of special groups of data subjects in 1+MG such as minors, persons not able to consent, minorities, vulnerable persons and groups, and deceased persons. The recommendations are directed towards researchers, research ethics committees (RECs), and 1+MG data centres and oversight bodies.

2. Objectives

- To identify existing approaches and best practices for inclusion of special groups.
- To develop 1+MG minimal requirements for inclusion of special subjects.

3. Background

The term 'special subjects' in the context of 1+MG project applies to a diverse set of potential research subjects: minors, persons with diminished capacity to consent, persons not able to consent, other vulnerable groups, deceased persons etc. These special subjects in at least some respects are incapable of deliberating or acting based on their own plans or are controlled by others. To respect a person representing special group means to protect him/her to ensure that the person is not subjected to abuse, exploitation, or discrimination.

Usually, definitions of vulnerability combine two aspects: (1) lack of ability, capacity, means and/or willingness to protect one's own interests, and (2) exposure to the possibility of being harmed, especially through exploitation. As outlined in the Declaration of Helsinki, vulnerable groups and individuals "*may have an increased likelihood of being wronged or of incurring additional harm*" (WMA, 2013), including physical, psychological, social and other types of harm, e.g., harm resulting from the withholding of access to standard of care. In case of involving vulnerable persons and groups in research "*specific protections should be provided for vulnerable subjects and vulnerable populations, based on the general principle of acting in their best interest*" (ESHG, 2003).

There is ongoing discussion in the field of research ethics regarding the usefulness of the concept of vulnerable groups. CIOMS Guidelines advise to "*avoid considering members of entire classes of individuals as vulnerable*" (CIOMS, 2016) and instead

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suggest looking at specific characteristics and situations that may render persons vulnerable, as this can "*aid in identifying the special protections needed*" (CIOMS, 2016). CIOMS Guidelines also remind us that different characteristics and situations generating vulnerability may co-exist, making some individuals more vulnerable than others. Evaluating vulnerability of research subjects or groups before involving them in research is a duty of researchers and respective research ethics committees (RECs). For initial identification of vulnerability, a useful tool is Kipnis's taxonomy of vulnerability in research (see Table 1).

Table 1. Taxonomy of vulnerability in research (Kipnis, 2001)

Cognitive	Does the person have the capacity to deliberate about and decide whether or not to participate in the study?
Juridic	Is the person liable to the authority of others who may have an independent interest in that participation?
Deferential	Is the person given to patterns of deferential behavior that may mask an underlying unwillingness to participate?
Medical	Has the person been selected, in part, because he or she has a serious health-related condition for which there are no satisfactory remedies?
Allocational	Is the person seriously lacking in important social goods that will be provided as a consequence of his or her participation in research?
Infrastructural	Does the political, organizational, economic, and social context of the research setting possess the integrity and resources needed to manage the study?

When planning involvement of vulnerable subjects in research, it is also important to consider differences regarding capacity of these persons: many of them are autonomous persons, some are not yet fully autonomous (minors), some have fluctuating autonomy, some are persons of diminished autonomy, and others are permanently non-autonomous.

Researchers implementing primary collection of data and biological samples from vulnerable subjects for inclusion in 1+MG initiative must impose protective conditions, including providing appropriate information and seeking consent or

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assent, in accordance with applicable international and national law and ethical principles.

4. Minimal standards

4.1. Primary collection and storage of data and samples

- Before recruiting subjects for primary collection of data and samples, researchers and RECs must first determine whether vulnerable individuals and/or groups are involved and to ensure the well-being and rights of vulnerable research subjects.
- The research planned in the framework of the 1+MG initiative has no potential to produce direct benefit to a person's health; at the same time, it is likely to entail only minimal risk and minimal burden (assuming appropriate safeguards are in place). Data from minors, persons not able to consent, patients in emergency clinical situations and persons deprived of liberty may be involved for secondary use in the 1+MG initiative if (1) research of comparable effectiveness cannot be carried out without the participation of these groups of persons; (2) the research has the aim of contributing to the ultimate attainment of results capable of conferring benefit to these groups of persons. (CoE, 2005a)
- Vulnerable persons and/or groups should not be unnecessarily excluded from research participation, and in turn the benefits of scientific progress. Resources should be provided to ensure their responsible inclusion in research.
- Many vulnerable persons (e.g., many persons with psychiatric diagnosis) have normal cognitive function, are able to evaluate risks and benefits of research, and are able to give informed consent. Regarding persons with limited capacity to give consent or where the capacity to give consent is in doubt, "*arrangements shall be in place to verify whether or not the person has such capacity*" (CoE, 2005a). RECs and researchers must ensure that procedures for assessment of capacity are in place in accordance with applicable international and national law and ethical principles.

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- If vulnerable persons have the capacity to consent and are able to consent, informed consent must be obtained from the individuals themselves for storage and research use of their data and biological samples.
- In case of non-autonomous persons, in addition to the consent of a legal representatives, the assent of the person must generally be sought, meaning that the person "*is meaningfully engaged in the research discussion in accordance with his or her capacities*" (CIOMS, 2016). Assent is a process, not "*merely the absence of dissent*" (CIOMS, 2016). The person must receive information, be engaged in the conversation at the level of his/her capacity to understand, and be given an opportunity to agree to or to decline participation.
- Researchers and RECs must plan in detail the content, form, and most effective way of communication of information to vulnerable subjects, bearing in mind the specific type of vulnerability. It is highly advisable to involve persons with respective types of vulnerability, or appropriate representatives, in this planning process. (Diez-Domingo, 2021; Rotimi & Marshall, 2010)
- Researchers and RECs must ensure that no undue influence is exerted on vulnerable persons to participate in research or donate samples and data to a biobank. (CoE, 2005a) It should be taken into account that undue influence may take different forms, e.g., pressure, misuse of power, undue inducement or presence of therapeutic misconception. If necessary, RECs and researchers should consider incorporation of voluntariness assessment into the consent process by using appropriate voluntariness assessment instruments. (Mamotte & Wassenaar, 2015)
- Vulnerable persons or their legal representatives, as any other research subject, generally have the right to withdraw their consent or assent to research participation at any time and to ask for their identifiable data and samples to be withdrawn from the research project or a biobank (i.e., anonymised, no longer used in future research, or destroyed).
- Refusal to give consent or assent or the withdrawal of consent or assent to participate in research or donate data and biological samples to a biobank

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shall not lead to any form of discrimination of vulnerable persons or groups, as any other research subject.

4.1.1. Minors

- Researchers must specifically plan the informed consent/assent process for collection of data and biological samples from children or adolescents to adjust to their developing capacity and maturity. It is advisable to prepare age-appropriate information and supplement it with visual information, as well as to involve children and adolescents in this planning process, e.g., by testing the perception and understandability of informative materials. (Nuffield Council on Bioethics, 2015)
- The conditions (e.g., risk/benefit ratio, level of risk, safeguards, requirements for consent/assent procedures) that govern the participation of the minor in research are subject to applicable national law and vary from jurisdiction to jurisdiction. The legal age of consent to research and details of assent procedure are established by the national law. (Lepola et al., 2016)
- Researchers should seek REC advice about all aspects of informed consent/assent process and ensure that specific protections are in place to safeguard the best interests, rights, and welfare of minors.
- Usually, informed consent for collection of data and biological samples from children or adolescents must be obtained from at least one parent or guardian; however, some national legislations may establish that the permission of both parents is required. (Lepola et al., 2016)
- Researchers must actively involve children and adolescents in the informed consent/assent process, taking into consideration their age and maturity. The assent should be documented, and in case it is not possible to seek assent from the minor the reasons should be explained.
- The opinion of the child or adolescent must be taken into consideration as an increasingly determining factor in proportion to his/her age and degree of maturity. "*The potential subject's dissent should be respected*." (WMA, 2013) In the case of infants or very young children, it is necessary to evaluate their attitude, taking account of their age and considering both verbal and

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non-verbal resistance. Researchers and parents/guardians should discuss beforehand whether and when resistance will be considered a reason to stop research participation.

- Researchers should involve the child or adolescent in the actual decision-making process and to provide information which is adjusted to the different levels of child's or adolescent's maturity and to the individual needs of the minor (e.g., psychological maturity, intellectual capabilities, cultural background, family situation). (Nuffield Council on Bioethics, 2015)
- If during the implementation of research a minor reaches the legal age of majority, at a minimum an opt-out policy should be introduced, but preferably his/her written informed consent should be sought for continued storage and research use of their data and biological samples. (Giesbertz et al., 2016)

4.1.2. Adult persons not able to consent

- Researchers and RECs must specifically plan the informed consent/assent process for collection of data and biological samples from adult persons not able to consent, as well as the process for withdrawal of consent.
- For collection of data and biological samples from an adult person not able to consent, the informed consent of his/her legal representative must be obtained according to the procedures established by national law.
- The adult person not able to consent must give assent, unless he/she is "not in a state to receive the information" (CoE, 2005b). For this, researchers must involve the person in the actual decision-making process and to provide information which is adjusted to the actual level of person's cognitive capacities and to the individual needs of the person.
- It is not acceptable to force a person who is not able to consent to donate data and biological samples against his/her will. The research subject has the right to object and to withdraw assent at any time.
- The relevant REC should advise researchers about all aspects of informed consent/assent process and ensure that specific protections, such as adjusted information, are in place to safeguard the best interest, rights, and welfare of persons not able to consent.

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- If there is reason to believe that the person not able to consent will attain or regain the capacity to consent, reasonable efforts should be made to seek the consent of this person for continued storage and research use of their data and biological samples after he/she attains or regains the capacity to consent.
- The instructions and wishes made by capable adults concerning a willingness or refusal to share and re-use of their samples and data, as well as their values and beliefs, must be considered by researchers and legal representatives in circumstances where they experience a diminishment of capacity. The initial consent should, however, clearly address that samples and data may continue to be used following a loss of capacity or death. (Thorogood et al., 2015)

4.1.3. Collecting and/or using data from deceased persons

- The data and samples of deceased persons should generally be treated with respect and care, like data and samples of living ones, with appropriate modifications for the fact that deceased persons cannot actively participate in the governance of their data and samples. "*Concerning postmortem uses of samples, a policy of unrestricted access cannot be justified on the grounds that the risk or harm for the subject are no more an issue."* (ESHG, 2003)
- For collecting and/or using data and biological samples from deceased persons, the researchers and RECs must follow to rules and procedures established by national law (e.g., requirements for consent from next of kin; consent waiver; data subject rights persisting (or not) after death).The person's consent to share data, restrictions to use of their samples and data, as well as persons' wishes regarding data sharing should be generally respected after their death. *"If individuals restrict use of their sample when they are still alive, those restrictions apply after their death*." (ESHG, 2003)

4.2. Inclusion in a 1+MG data repository, access, and secondary use of data in 1+MG initiative

- Before including data of persons, who had been considered vulnerable during the initial collection of data and biological samples, for secondary use in the 1+MG initiative, researchers and/or respective RECs must re-examine the

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content of the informed consent given during the initial collection of data and samples to ensure that the scope of the consent covers activities planned in 1+MG initiative and the way of communicating the information clearly delivers a message that the data may be used in an initiative, like 1+MG.

- National 1+MG nodes, researchers and RECs should recognize that vulnerability impacts not only the informed consent process, but also different aspects of the ongoing participation in 1+MG initiative, such as withdrawing consent, relationships with researchers, participation in public/patient involvement activities, dealing with incidental findings etc. These aspects should be discussed in detail among the stakeholders before including data for secondary use in 1+MG initiative.
- National 1+MG nodes, researchers and RECs should recognize that including the data for secondary use in 1+MG initiative may enable new types of vulnerability applying to already vulnerable groups, vulnerable persons, or groups that were not considered vulnerable at the time of primary collection of data and samples. Ongoing reflection on such possible new types of vulnerability emerging from, e.g., application of new analytical techniques, artificial intelligence or prediction tools should be pursued.
- If an ethnic or cultural group (including ethnic and cultural groups from third countries) is to be the subject of including their data for secondary use in 1+MG initiative, additional consent may be required "*at a group level through its cultural appropriate authorities*" (ESHG, 2003). The respective REC has to decide whether additional group level consent is needed, taking into account cultural differences, potential of discrimination and stigmatisation, and respecting rights of minorities within the group. (Kowal, 2015; Rotimi & Marshall, 2010) The rights and interests of the group should be protected, especially "*in terms of benefit sharing*". (WMA, 2016)
- In line with the "1+MG Incidental Findings Policy" including specific points-to-consider for research involving minors, return of clinically actionable findings in minors might be even more pressing than in less vulnerable groups. In general, if 1+MG incidental findings reveal conditions in minors that are clinically actionable during childhood through early life intervention,

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they should be communicated as considered to be in the best interests of the child. The communication must involve professional support to explain the research findings and to deal with the psychological and emotional impacts of information.

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