

Ethics and data protection in human biomarker studies

Written and edited by
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ECNIS is a Network of Excellence within the European Union Sixth Framework Programme, Priority 5: Food Quality and Safety. It brings together some of the best European research groups in a concerted effort to achieve improved understanding of the environmental causes of cancer, of the potential of diet to prevent cancer and of the ways by which heredity can affect individual susceptibility to carcinogens, with the ultimate aim of reducing the cancer burden in Europe.

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Executive summary

Human biomarker studies in environmental health are essential tools to study the relationship between health and environment. The development of relevant research potential and the setup of bio-monitoring surveys should ultimately lead to a better understanding and prevention of environmentally induced adverse health effects.

In this volume we review ethics and data protection in environmental health studies using human biomarkers. The question is raised whether study participants are adequately and equally protected throughout Europe and whether at the same time progress in environmental health related studies is safeguarded.

The collection of human samples and data is subject to regulations and rules of different kinds, from deontological codes to data protection laws, from the local to the international level. Within an EU context, the probably most important international references in this respect are the Data Protection Directive (95/46/EC), the Oviedo Convention, more in particular its Additional Protocol concerning biomedical research and Rec(2006)4 on research on biological material of human origin.

A critical analysis of research experiences in various EU countries shows that difficulties, ambiguities or even inconsistencies exist in the way ethical and juridical challenges are framed and being dealt with within and across countries. The diverse implementations of EU regulations or international guidelines in domestic law may in particular hinder transnational research and bring about inequalities in the level of protection.

Overall, in research on biological material of human origin emphasis is primarily on decisional autonomy and protection of the individual's rights whilst the collective need to protect health as a public asset is relatively less valued. This is particularly striking when personal data or samples collected for a specific research purpose could be of value in a new study. This secondary use often remains very complex or almost impossible, although there are strong and recognized arguments for facilitation of such further use in the context of environmental health research where public interest comes to the forefront and risks are minimal, on the condition that adequate collective protection and control against improper use of samples or data can be installed, and breach of confidentiality or any use of data which would be not in line with the subject's moral stakes can be excluded.

An increasing demand exists for adapted communication strategies at all stages of a study, not only at the individual level, but also at the collective level, and including the time of translation of results in preventive actions and policy making. The vital role of communication is obvious. Each communicative act may affect trust in the study at hand and in science in general. Expertise in the field of social sciences is therefore demanded.

Even though many improvements regarding the legal and ethical challenges in human studies have already been implemented in the EU in the last years, these issues are not well known among the actors involved and efforts should be devoted to better education and dissemination of information and enhanced transparency targeting researchers but also the general public, the media and the policymakers.

Research ethics committees play a pivotal role in assessing to what extent decision making processes fit with both individual and societal interest. Respect for human dignity and equality of moral status of all individuals, social justice, solidarity and democratic participation may thereby be appealing reflections of European values and useful complements to the four conventional bioethical principles (autonomy, beneficence, non-maleficence, and justice) that are widely applied for evaluating policies, programs or activities that may entail risk to human health.

To achieve more consistency in the research conditions nationally and internationally an ethics committee at the level of the 'European research area' could be envisaged, mainly focusing on transnational research. Moreover, the analysis and evaluation of different cases in different situations would build-up an extensive knowledge and experience that may serve as an inspiring starting point for a well informed societal debate. This way, gradually, more consistency in the handling of study proposals and increased transparency in decision making might be reached, lifting the daily practices and the protection of both individual and community interest to a higher level of meeting up with ethical concerns in transnational research.

Researchers have the duty to support the translation of research results in preventive actions at individual and at collective level whenever relevant. Participatory processes will facilitate the inclusion of arguments from the societal perspective and increase trust and mutual understanding between all parties involved, add to the legitimacy of the final outcome and the public support for the policy decision-making process, and implement democracy.

Introduction

In this volume we review ethics and data protection in environmental health studies using human biomarkers. The question is raised whether study participants are adequately and equally protected throughout the whole of Europe and whether at the same time scientific progress is safeguarded. In other words, whether the current ethical and legal framework protects what ultimately should be protected, or whether — and, if so, to what extent — it may need rethinking to achieve its goals.

Specific human biomarkers measuring exposure, effect and/or susceptibility related to environmental stressors have increasingly been used the last decades in the domain of environmental health. Their analysis should lead to a better understanding of the relation between environment and health and should ultimately contribute to preventive actions and increased awareness of environmental health issues at the personal as well as at the policy level (1,2).

A significant part of the total burden of disease in Europe can be attributed to environmental factors, ranging from chemicals and food to housing quality and noise. A WHO comprehensive and systematic worldwide study on how preventable environmental hazards contribute to a wide range of diseases and injuries reported that almost a quarter of all disease is caused by environmental exposure. Another major WHO study showed that in the European Region one third of the total burden of disease in children and adolescents (aged 0–19) are attributable to four environmental risk factors (outdoor and indoor air pollution, inadequate water and sanitation, lead exposure) and to injuries (3).

In 2003, the European Commission adopted a European Strategy on Environment and Health. It was followed by the European Environment and Health Action Plan 2004–2010, which proposes an integrated information system on environment and health as well as a coordinated approach to human biomonitoring (HBM) in European Union Member States to render more efficient the assessment of the environmental impact on human health (4,5). In the USA the Committee on Human Biomonitoring for Environmental Toxicants, established by the National Research Council of the National Academies in 2006, highlighted that human biomonitoring faces challenges in particular with regards to the improvements of study design, interpretation of biomonitoring data for public health, and the communication of study results to participants, policy-makers and the public. Biomarker research is needed to guarantee scientific sound results in current and future surveys that may support and evaluate environmental health policy (6).

The use of biomarkers in environment and health studies involves donation of tissues or fluids by volunteers and leads to sensitive ethical questions that will be described further. To ensure the protection of the rights and dignity of study participants a complex legal

and ethical framework applies, consisting of several international directives, conventions, and guidelines, whether or not translated in domestic laws.

In the first part of this volume attention is given to a working definition of public and environmental health and the current ethical and legal framework is outlined. Furthermore, a short introduction is included on guiding philosophical principles and the issue of conflicting societal goods is explored.

In the second part, important challenges in ethics and data protection in environmental health studies requiring human biomarkers are analyzed and discussed. Focus is on the application of the formal legal aspects, on decision making processes (mainly the informed consent procedure and the function, position and significance of research ethics committees) and on communication, going shortly into the most important aspects and highlighting some of the recent developments in this field.

An attempt was made to draw as much information as possible from concrete situations occurring in practice. To this end, we asked researchers in the field to share their personal experiences and difficulties regarding these issues. Other valuable contributions came from ethicists, lawyers and social scientists in the field of public health, and from studies assessing the perception of study participants. Illustrative example cases are presented, an analysis of specific problems is made and possible steps towards improvements are discussed.

The final part summarizes the considerations and adds suggestions for possible solutions.

In annex, relevant articles of the legal or guiding documents presented in the text are cited in full, ordered by topic.

We hope this volume will increase knowledge and reflection on ethical and legal aspects and add to the debate on ethical and legal issues with respect to human biomarker studies.

1. Context

1.1. Human biomarkers, human biomonitoring and environmental health

1.1.1. Human biomarkers

After exposure to an external agent, a continuum of biological events can occur that may result in health impairment. Biological markers are used as indicators of these events: from internal dose to biologically effective dose, early biological effect, altered structure or function, and finally clinical disease. A distinction can be made between biomarkers of exposure, of effect and of susceptibility. In humans, blood, urine, breast milk and other tissues or fluids are analyzed (see Box 1.1).

A conceptual model is proposed (Fig. 1.1) (7) of the complex interactions between exposure, acquired and inherited susceptibility and risk for disease. It can be used to clarify at which point in the continuum of biological events a particular marker is located. The exposure–effect relationship is highly complex, and susceptibility results from the interaction of a large number of inherited and acquired traits, many of which are still unknown. The genes that represent inherited factors could intervene at each step in the continuum.

Biomarkers have previously proven their added value in occupational health as part of a preventive approach, combined with workplace monitoring and hygienic measures (8).

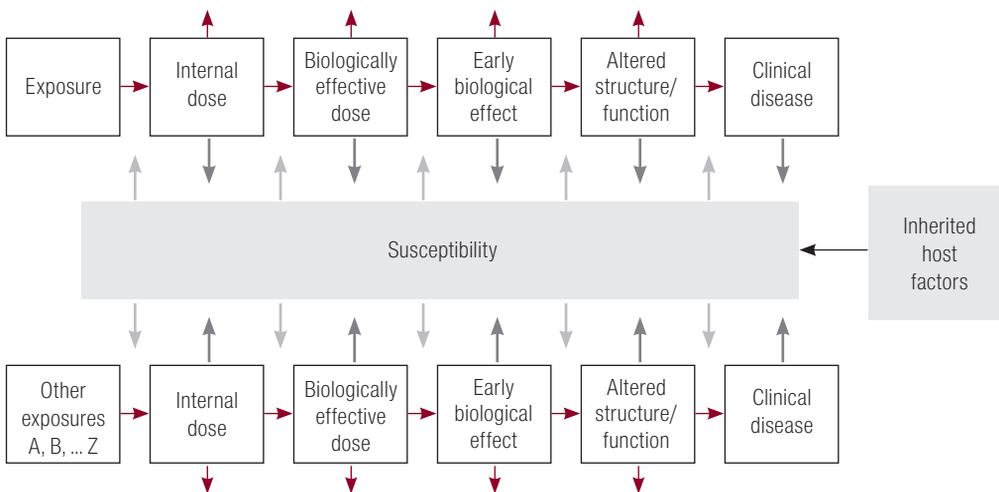


Fig. 1.1. Susceptibility model, presenting the complex interactions between exposure, acquired and inherited susceptibility and risk for disease (7).

- They are increasingly used nowadays in an environmental health context in (6):
- research studies, to improve our knowledge on the causal links between environmental factors and health, through hypothesis generation and testing (e.g. European research initiatives or projects (9));
 - survey studies, where periodical measurements furnish information on the prevalence of exposure to environmental agents and on the related public health impact, e.g. national programs such as the US National Health and Nutrition Examination Survey (10); the German Environmental Survey (GerES) (11); the Flemish program (12);
 - raising awareness campaigns, most often organized by NGOs. Examples are activities by various advocacy groups such as WWF and Health and Environment Alliance (13–15).

Box 1.1. Human biomarkers

A biomarker is defined as any substance, structure or process that can be measured in the body or its products and may influence or predict the incidence or outcome of disease (16). A distinction is made between biomarkers of exposure, effect and susceptibility.

- *Biomarker of exposure (17): An exogenous substance or first metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism.*
 - *Biomarker of effect: A measurable biochemical, physiological, behavioral or other alteration within an organism that, depending on the magnitude, can be recognized as associated with an established or possible health impairment or disease.*
 - *Biomarker of susceptibility: An indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific xenobiotic substance.*
-

1.1.2. Human biomonitoring

Human biomonitoring refers to monitoring practices in humans using biomarkers that focus on environmental exposures, diseases and/or disorders and (genetic) susceptibility, and their potential relationships (18). In principle, monitoring refers to a repeated or continued sampling and analysis; however, the term is also commonly used for ‘one time activities’. Biomarkers are commonly used in combination with other — more classical — methods such as environmental monitoring (e.g. of air, dust, water, food and soil), modeling, the collection of health and life style data through questionnaires, etc.

1.1.3. Environmental health and public health

Public health refers to scientific activities and the related preventive actions targeting a population. From the plethora of definitions that can be found, for the purposes of this book we refer to the following (Box 1.2):

Box 1.2. Public health

Public health may be described as “the science and art of preventing disease, prolonging life and improving health and well being through organized efforts of society” (19).

Childress et al. list the following features: “Public health is primarily concerned with the health of the entire population, rather than the health of individuals. Its features include an emphasis on the promotion of health and the prevention of disease and disability; the collection and use of epidemiological data, population surveillance, and other forms of empirical quantitative assessment; a recognition of the multidimensional nature of the determinants of health; and a focus on the complex interactions of many factors — biological, behavioral, social, and environmental — in developing effective interventions (20)”.

Rothstein explicitly recognizes that public health is a legal term of art referring to specifically authorized activities by public officials to protect, promote and improve population health (21).

In this volume we concentrate on environmental health focusing on humans. For the purpose of this publication environmental health is defined as follows (Box 1.3):

Box 1.3. Environmental health (22)

Environmental health addresses all the physical, chemical, and biological factors external to a person, and all the related factors impacting behaviors. It encompasses the assessment and control of those environmental factors that can potentially affect health. It is targeted towards preventing disease and creating health-supportive environments. This definition excludes behavior not related to environment, as well as behavior related to the social and cultural environment, and genetics.

Environmental health research, which is preventive by nature, is aimed at the characterization of the impact of chemical and physical environmental contaminants as health determinants. It is here that the project of the ECNIS Network of Excellence on environment, nutrition and cancer risk as modulated by diet and genetic disposition is situated.

1.2. Current ethical and legal framework

Studies using human biomarkers deal with sensitive personal health related data and should guarantee an optimal protection of the rights and dignity of every study participant. A complex legal and ethical framework is established by several international directives, conventions and guidelines. Below, the most important directives and guidelines at EU level are listed (Box 1.4) with a short — and thus by no means exhaustive — discussion of their main features. At national level they are implemented by national laws which may differ substantially between countries when it comes to application in detail or adjustment to other national legislation. However, it should be noted that a Directive shall be binding, as to the result to be achieved, upon each Member State to which it is addressed, whilst leaving to the national authorities the choice of form and methods. Jurisdiction shows that

national courts are “required” to interpret domestic law so as to ensure achievement of the objectives of the Directive, whether or not national provisions were enacted before or after the Directive¹. If a Member State has failed to implement a Directive by the deadline for doing so, or its implementing provisions are incompatible with provisions of the Directive that are unconditional and sufficiently precise to be given effect directly, then any national provision must give way to EC law².

Box 1.4. Important European and international regulation in human biomarker studies

1. *Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (hereafter “Data Protection Directive” — often called the privacy directive) (23).*
 2. *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Oviedo, 4.IV.1997 (hereafter “Oviedo Convention”) (24).*
 3. *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005 (hereafter “Additional Protocol”) (25).*
 4. *Recommendation (2006)4 of the Committee of Ministers to Member States on research on biological material of human origin (hereafter “Rec(2006)4”) (26).*
-

1.2.1. Data Protection Directive

The Data Protection Directive is implemented by domestic laws in all EU Member States. As is the case for all EC Directives, its field of application is the EU. The Data Protection Directive does not apply to data that is anonymous³.

Sanctions are imposed on any person, whether governed by private or public law, who fails to comply with the national measures taken under this Directive⁴ (art. 24).

Directive 95/46/EC

- Processing of personal data
- Including, but not restricted to, health data
- Not applicable to anonymous data

¹ *Marleasing SA v. La Comercial Internacional de Alimentacion SA (Case C-106/89) [1990] E.C.R. I-4135* was a decision of the European Court of Justice concerning the indirect effect of European Union law. It established that the courts of European Union member states have a duty to interpret national legislation in light of unimplemented European Union directives.

² E.g. *second Levy, Case C-158/91, [1993] E.C.R. I-4287.*

³ For a definition of anonymous data and anonymization, see 2.2.2. It should be noted that the definition of ‘anonymous’ that is used in the context of the Data Protection Directive is quite different from the one we use in everyday language.

⁴ E.g. in Belgium, any controller, his representative, appointee or agent who processes personal data in violation of the conditions imposed in fixed articles shall be punished with a fine of one hundred to one hundred thousand euro.

- Legitimate purpose
- Explicit consent or ‘substantial public interest’
- Transparency: right to information
- Personal results
- Notification to supervisory authority
- Proportionality

The processing of personal data (27)

The Data Protection Directive is extremely broad, covering the processing of several types of information about individuals. Processing refers to any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organization, storage..., blocking, erasure or destruction (art. 1.2(b)). It is not specifically oriented at health data, although at certain points it does make reference to public health (rec. 34 Data Protection Directive) and to medical data (rec. 42 Data Protection Directive). The Directive’s implications for the processing of personal data in health research must be inferred from what it has to say about the general processing of personal data, especially sensitive personal data, and about processing for research and statistics.

In principle, processing of personal health related data is prohibited. Exception to this general prohibition is allowed under specific conditions. The most applied condition for lawful processing of personal health data is if the data subject has given explicit consent to the processing of those data. In addition, other conditions⁵ are defined, most relevant to research being that Member States may, for reasons of substantial public interest, lay down other exemptions to the general prohibition either by national law or by decision of the supervisory authority (art. 8.4). According to rec. 34, scientific research and government statistics are stated to be “of important public interest”. Such exemptions are subject to suitable and specific safeguards so as to protect the fundamental rights and privacy of the individuals (art. 8.4 (rec. 34))⁶, which must be notified to the Commission (art. 8.6). As we will see later, in the Oviedo Convention, in contrast, the primacy principle implies that the individual interest comes first at all times⁷.

⁵ Other conditions are: If necessary to protect the vital interests of the data subject or another person where the data subject physically or legally cannot give consent (art. 8.2(c)); or if the data is manifestly made public by the data subject or processing is necessary to establish, exercise or defend a legal claim (art. 8.2(d)); or if necessary for the purposes of “preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, and where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy” (art. 8.3; rec. 33).

⁶ The fundamental rights and freedoms referred to are, most centrally, those recognized in the constitutions and laws of the Member States and the European Convention for the Protection of Fundamental Rights and Freedoms recs. 1 and 10. As indicated in art. 8 (which provides a right to protection of personal data), even though the Charter is not legally binding in its own right, it is anticipated that the ECJ will take it into account in its judgments. This is because the Charter is, essentially, a compendium of the rights that the ECJ (European Court of Justice) has in the past declared to have the status of fundamental principles of EC law.

⁷ For a discussion of the Oviedo Convention, see 1.2.2.

Legitimate purpose and proportionality

Personal data can only be processed for specified explicit and legitimate purposes (art. 6b)⁸. They have to be adequate, relevant and not excessive in relation to the purposes for which they are collected and/or further processed (art. 6c). Personal data may be kept in personal form for historical, statistical or scientific use for longer than is necessary for the purposes for which the data was collected or is being further processed if Member States provide adequate safeguards to rule out the use of the data in support of measures or decisions regarding any particular individual (art. 6.1(e), rec. 29).

The use of anonymous data is preferred, for which the Data Protection Directive does not apply. However, when such is not possible, a cascade system should be adopted: when it is not possible to work with anonymous data, encoded data⁹ should be used. Only when no other options are available one can resort to non-encoded personal data.

Secondary use of data

As a general rule, data should not be further processed in a way incompatible with the specific purposes for which the data was collected in the first place. As an exception to this, the “further processing of personal data for [...] scientific purposes is not generally to be considered incompatible with the purposes for which the data have previously been collected” provided that Member States furnish suitable safeguards which “must, in particular, rule out the use of the data in support of measures or decisions regarding any particular individual” (rec. 29) (art. 6b). This is the so-called secondary use of data.

Transparency at collective level

The researcher (“data controller”¹⁰) has the duty to inform. On the one hand, he has to inform the data subject; on the other he must notify the supervisory authority before he starts any data processing (art. 18)¹¹, although exemptions exist as indicated further. Except for public registers, Member States must take measures to publicize all processing operations. The supervisory authority is obliged to keep a register of processing operations

⁸ An exception to the demand of explicitness of purpose occurs in certain cases of secondary use of personal data. For more information, the reader is referred to 2.2.4.

⁹ For the definitions of anonymous, encoded and non-coded data, see 2.2.2.

¹⁰ Article 2: [...] (d) ‘controller’ shall mean the natural or legal person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data; [...]”.

¹¹ Member States may provide for the simplification of or exemption from notification only in the following cases and under the following conditions: (a) where, for categories of processing operations which are unlikely, taking account of the data to be processed, to affect adversely the rights and freedoms of data subjects, they specify the purposes of the processing, the data or categories of data undergoing processing, the category or categories of data subject, the recipients or categories of recipient to whom the data are to be disclosed and the length of time the data are to be stored, and/or (b) where the controller, in compliance with the national law which governs him, appoints a personal data protection official, responsible in particular: for ensuring in an independent manner the internal application of the national provisions taken pursuant to this Directive, for keeping the register of processing operations carried out by the controller, containing the items of information referred to in Article 21 (2), thereby ensuring that the rights and freedoms of the data subjects are unlikely to be adversely affected by the processing operations.

carried out by the controller (art. 18) containing information such as the name and address of the controller, and the purpose of the processing (art. 19). This register is meant to be available to the general public (art. 21).

Even in relation to processing operations not subject to notification, controllers or another body appointed by the Member States shall make available at least certain information¹² in an appropriate form to any person on request. Member States may provide that this provision does not apply to processing whose sole purpose is the keeping of a register which according to laws or regulations is intended to provide information to the public and which is open to consultation either by the public in general or by any person who can provide proof of a legitimate interest (art. 18.3).

Transparency at individual level

Data subjects have a right to information on the processing of their data (art. 10, 11). This entails the right to know the identity of the researcher and his affiliation, the purpose for which the data is collected and any further information such as the recipients of the data, whether replies to questions are obligatory or voluntary, the existence of the right of access to and the right to rectify the data concerning the data subject, in so far as such further information is necessary, having regard to the specific circumstances in which the data is collected, to guarantee fair processing in respect of the data subject (art. 10).

Where the data was not obtained from the data subject (see e.g. secondary use), the data subject must be granted similar rights to information (art. 11.1). However, exemptions exist if the data is processed for statistical purposes or for the purposes of historical or scientific research and if the provision of such information proves impossible or would involve a disproportionate effort or if recording or disclosure is expressly laid down by law and if Member States provide appropriate safeguards (art. 11.2). No further specification is given of the meaning of “disproportionate efforts”¹³.

In addition, data subjects have the right to access to and rectification of personal data (art. 12). This implies that every data subject has the right to obtain from the controller without constraint at reasonable intervals and without excessive delay or expense a.o. confirmation as to whether or not data relating to him are being processed and information at least as to the purposes of the processing, the categories of data concerned, and the recipients or categories of recipients to whom the data is disclosed. This implies also that the data subject has the right to obtain in an intelligible form the data undergoing processing and of any available information as to their source (art. 12). Again, subject to adequate legal safeguards, in particular that the data is not used for taking measures or decisions regarding any particular individual, Member States may, where there is clearly no risk of breaching the privacy of the data subject, restrict by a legislative measure the rights to access when data is processed solely for purposes of scientific research or are kept in personal form for a period which does not exceed the period necessary for the sole purpose of creating statistics (art. 13).

¹² Referred to in art. 19.1 (a) to (e).

¹³ More details on concepts such as ‘disproportionate efforts’ are given in section 2.2.4.

Transnational research

Regarding the transfer of data, by whatever means, from EU Member States to other (non-EU) countries the Data Protection Directive stipulates that “the Member States shall provide that the transfer to a [non-EU] country of personal data which are undergoing processing or are intended for processing after transfer may take place only if [...] the [recipient] country in question ensures an adequate level of protection”. Criteria applied to determine this adequacy of protection relate to the nature of the data, the purpose and duration of the proposed processing operation, the country of origin and the country of final destination and the rules of law in force in the country in question (art. 25).

Sanctions

Member States must, without prejudice to any administrative remedy, provide a judicial remedy for any breach of rights guaranteed by implementing national legislation (art. 22), provide for compensation from the data controller for damage resulting from unlawful processing operations, except where the controller can prove that he was not responsible for the event causing the damage (art. 23), Member States must adopt suitable measures to ensure full implementation of the provisions of the Directive, which must include sanctions for infringing implementing provisions (art. 24).

1.2.2. Oviedo Convention and the Additional Protocol concerning biomedical research

The Oviedo Convention is an international convention, so its action field extends to all countries that have ratified¹⁴ it, also outside the EU. The Oviedo Convention has currently been signed by 34 Member States of the Council of Europe¹⁵, of which 21 have so far also ratified the Convention¹⁶. The European Court of Human Rights¹⁷ uses the Oviedo Convention as an expression of European human rights standards, even in cases involving countries that have not signed or ratified the convention. It is therefore advisable to stay within the limits of the

¹⁴ Where the signature is subject to ratification, the signature does not establish the consent to be bound. However, it is a means of authentication and expresses the willingness of the signatory state to continue the treaty-making process. Ratification defines the international act whereby a state indicates its consent to be bound to a treaty if the parties intended to show their consent by such an act.

¹⁵ Whereas the EU has 27 Member States, the Council of Europe has a membership of 47 countries. It is an inter-governmental organization whose aims include the protection of human rights and the promotion of democracy and the rule of law. Its treaties are not directly binding in national law, unless ratified by the normal parliamentary procedures of the Member State concerned. It is especially known for the European Convention on Human Rights, which was signed in 1950 and, through the European Court of Human Rights.

¹⁶ Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Georgia, Greece, Hungary, Iceland, Lithuania, Moldova, Norway, Portugal, Romania, San Marino, Slovakia, Slovenia, Spain, Turkey (status on February 18th, 2010).

¹⁷ Article 29 of the Oviedo Convention states that the European Court of Human Rights may give, without direct reference to any specific proceedings pending in a court, advisory opinions on legal questions concerning the interpretation of the present Convention at the request of: (a) the Government of a Party, after having informed the other Parties; (b) the Committee set up by Article 32 (of the Oviedo Convention), with membership restricted to the Representatives of the Parties to this Convention, by a decision adopted by a two-thirds majority of votes cast.

Oviedo Convention and its Additional Protocol

- Participation in biomedical research
- Includes anonymous data
- Primacy of the individual
- Informed consent
- Transparency principle: right to information
- Personal results
- Submission to research ethics committee
- Proportionality principle

Oviedo Convention even for researchers in countries that have not signed. In structural terms, the Oviedo Convention is a framework convention, whose provisions are to be built on by means of additional protocols. To date, four additional protocols have been established: one prohibiting the cloning of human beings (1998), one on transplantation of organs and tissues of human origin (2002), one on biomedical research (2005) and one on genetic testing for health purposes (2008).

The Additional Protocol on biomedical research entered into force after 5 ratifications¹⁸ on 01/09/2007¹⁹. The number of countries that have signed the Additional Protocol, but not yet²⁰ ratified it, is 16. The Parties of the Additional Protocol guarantee compliance with the provisions of the Additional Protocol and must install juridical procedures in domestic law for infringement of the provisions and determine sanctions (art. 30–32).

The purpose of the Additional Protocol is to define and safeguard fundamental human rights in the field of biomedical research, in particular of those participating in research. Even though a broad description is given of what is to be understood under research activities, no exact definition of the term is taken up in the Additional Protocol²¹. All areas of biomedical research are covered that may involve intervention on individuals, use of biological materials of human origin or use of personal data collected for specific research projects. The Additional Protocol covers all aspects from start to finish, including selection and recruitment of data subjects.

Research on human beings can only be undertaken if there is no alternative of comparable effectiveness and if it shall not involve risks and burdens disproportionate to its potential benefits, including not only physical risks and burdens but also social or psychological risks. Furthermore, research must be scientifically justified and meet generally accepted criteria of scientific quality.

¹⁸ Article 37 of the Additional Protocol (Entry into force) states that “the Protocol shall enter into force [...] after the date on which five States, including at least four member States of the Council of Europe, have expressed their consent to be bound by the Protocol [...]”.

¹⁹ Countries that ratified the Additional Protocol: Bosnia, Bulgaria, Hungary, Slovakia and Slovenia.

²⁰ Dated March 2010.

²¹ Problems resulting from this unclear definition of the term research are illustrated and discussed in example cases 2.1. and 2.2. (2.2.1.).

Issues covered by both Data Protection Directive and Additional Protocol concerning Biomedical Research

A number of conditions in the Additional Protocol are concurrently covered in the Data Protection Directive. These issues are, however, not identical in the way they are handled. A list of such common issues is listed below, together with a short explanation on the differences in approach. Probably the most important points in the context of biomarker research in environment and health are the right to information and the duty to make public the results of the research, since often these requirements are not known of by researchers and not implemented. Wrongly so, however, for if biomarker studies are to be supporting policy making, notification and dissemination of results are of utmost importance.

- Research cannot occur without the informed, free, explicit, specific and documented consent of the data subject. Art. 14 of the Additional Protocol is more elaborated and specific with respect to the research field concerned in comparison with art. 8 of the Data Protection Directive where consent is one of the conditions for the processing of personal data related to health.
- According to the Additional Protocol, the data subject has a right to information on the purpose, the overall plan, the possible risks and benefits and the results of the research (information of individual research results, art. 26, 27 and 28 of the Additional Protocol). In comparison, the Data Protection Directive focuses on the right to information about *i.a.* identity of controller, recipients and categories of data as well as on the participant's right to access to this information, but is again less specific for application in human biomarker studies (art. 10, 11 and 12 of the Data Protection Directive).
- According to the Additional Protocol, researchers have the duty to inform at the collective level by submitting a summary or report of the research to the ethics committee (for a discussion of research ethics committees see 2.3.1.1.) and to make public the results of their research (art. 28 of the Additional Protocol). The Data Protection Directive specifies the obligatory notification of any research study to the national supervisory authority that is maintaining a register which is meant to be available to the general public (art. 18, 19 and 21 of the Data Protection Directive).
- According to the Additional Protocol, data subjects have to be informed on their right to refuse consent or to withdraw at any time without giving reasons and without being subject to any form of discrimination (art. 13 and 14 of the Additional Protocol). The Data Protection Directive articulates the participant's right to object at any time on — only — compelling legitimate grounds. Taking into account the broad application field of the Directive, it is clear that this right to object was not designed out of the perspective of the processing of data related to health (art. 14 of the Data Protection Directive).

It should be noted that in art. 26 of the Additional Protocol reference is made to the Data Protection Directive. This is quite a new given, since this was not yet the case for the Oviedo Convention. In the Oviedo Convention, dating from 1997, the following is stated regarding respect for private life: "Everyone has the right to respect for private life in rela-

tion to information about his or her health” (art. 10 Oviedo Convention). The Additional Protocol, in contrast, dating from 2005, states the following in art. 26: ”1) Research participants shall be entitled to know any information collected on their health in conformity with the provisions of Article 10 of the Convention. 2) Other personal information collected for a research project will be accessible to them in conformity with the law on the protection of individuals with regard to the processing of personal data”.

Analyzing the guidelines and requirements for review by Research ethics committees it appears that in most EU Member States, data protection is one of the elements taken into account in the review process. However, the extent to which this aspect is reviewed can vary a lot (28,29). Whereas in certain Member States data protection is mentioned only generally, in other States explicit reference is made to data protection legislation and specific questions relating to the treatment of personal data are incorporated in the review process (30)²².

Specific conditions in the Additional Protocol concerning biomedical research

A number of conditions are specific to the Additional Protocol and no analogue exists in the Data Protection Directive.

- The Additional Protocol requires that a research project is approved by a competent body after independent examination of its scientific merit and multidisciplinary review of its ethical acceptability (art. 7). This examination of a research project by an ethics committee is required in each State in which any research activity is to take place (art. 9). Chapter III of the Additional Protocol describes the functioning and composition of these ethics committees. According to the Additional Protocol, best practice is to submit a research project to an ethics committee in every research location within each State. A positive assessment is not necessarily required; the role of such bodies or committees in many states is merely advisory.
- Researchers have the duty to make public the results of their research and to submit a summary or report to the ethics committee, even if the research hypothesis is not confirmed. This is required in order to prevent the needless repetition of research using persons and the suppression of negative or positive results for commercial or other non-scientific reasons (art. 28)²³.

1.2.3. Recommendation (2006)4 of the Committee of Ministers to EU Member States on research on biological material of human origin

In contrast to the Oviedo convention, Rec(2006)4 belongs to the EU regulatory framework, and is therefore addressed to the 27 Member States. As a recommendation it has no legal binding force.

²² These findings are in accordance with results we found conducting a review of several ethical review guidelines and documents in different Member States (unpublished results).

²³ See Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research, art. 28, p. 23.

Rec(2006)4

- Research activities in the health field
 - (Residual) biological materials
 - Or biological materials from previous projects
 - Associated personal data
- Informed consent
- Ethical review
- Secondary use: reasonable efforts

Rec(2006)4 builds on the principles embodied in the Oviedo Convention and its Additional Protocol concerning biomedical research. Yet, there is a difference in focus between the Additional Protocol and Rec(2006)4. The Additional Protocol covers interventions to remove biological materials for *specific* research projects and other interventions on human beings for *specific* biomedical research projects, or data collected for and resulting from these research projects. In contrast, Rec(2006)4 excludes research involving such interventions for a *specific* research project. Rather, it focuses on the study of biological materials that have been *stored after originally being collected* in a diagnostic or therapeutic setting, during research projects with human subjects or during autopsy.

Biomedical research utilizing stored biological materials of human origin is a powerful tool to improve human health and healthcare systems. If these materials were not utilized and research had to be undertaken relying only on prospective collection of biological materials specifically for each project, it would mean in many cases comparable research results would not be available for much more years. Stored biological materials of human origin have often been used in ways that were not originally foreseen either by those who were the sources of the materials or by those who collected them. This raises questions concerning the right to respect for private life, which is guaranteed by art. 8 of the European Convention on Human Rights and by art. 10 of the Convention on Human Rights and Biomedicine. Rec(2006)4 attempts to formulate recommendations for such further use. Its purpose is to set out and safeguard the fundamental rights of individuals whose biological materials are used in biomedical research, while recognizing the importance of freedom of research. It applies to the full range of research activities in the health field that involve the removal of biological materials of human origin to be stored for research use; it also applies to the full range of research activities that involve the use of residual biological materials of human origin that were originally removed for clinical or forensic purposes or for a previous research project. The recommendation also applies to associated personal data.

Further use of biological materials in research projects

As a general rule, research on biological materials should only be undertaken if it is within the scope of the consent given by the person concerned (art. 21). Also, research should only be undertaken if the research project has been subject to an independent examination

of its scientific merit, including assessment of the importance of the aim of the research, and verification of its ethical acceptability (art. 24). However, in the case when further use of data or material is advisable or necessary, the following distinctions are made.

Identifiable biological materials

When consent for a further use has not originally been obtained (due to for example unforeseeable purposes, no consent asked for further research), reasonable efforts, both in terms of means and time, should be made to re-contact the person whose biological materials and personal data could be used, in order to ask for consent. Efforts should include public advertisements or the use of the internet, and should be designed to give the person concerned the possibility to opt out. The objection of the person concerned to being re-contacted should be respected²⁴. If re-contacting the person concerned is not possible despite reasonable efforts, the biological material should only be used in a research project subject to independent evaluation of the fulfillment of the following conditions (art. 22):

- the research addresses an important scientific interest (this is understood in the respect of the proportionality principle between the rights of the person concerned and the expected scientific benefits);
- the aims of the research could not reasonably be achieved using biological material for which consent can be obtained; and
- there is no evidence that the person concerned has expressly opposed such research use.

It should be noted that over time an evolution can be observed with regard to the explicitness with which is described what qualifies as a reasonable effort. In 1995, the Data Protection Directive also made reference to the disproportionality of efforts, but was much less specific and much more subject to interpretation: art. 11 solely states “[...] where [...] the provision of such information proves impossible or would involve a disproportionate effort or if recording or disclosure is expressly laid down by law [...]”.

Unlinked anonymized biological materials

Unlinked anonymized²⁵ biological material may be used for secondary use provided that such use does not violate any restrictions placed by the person concerned prior to this ano-

²⁴ When providing potential study participants information about the research project, the wish of the participant not to receive certain information or the wish not to be re-contacted in the future should be recorded and documented.

²⁵ This expression refers to non-identifiable biological materials. This implies that, alone or in combination with associated data, the material does not allow, with reasonable efforts, the identification of persons concerned. Unlinked anonymized biological materials and data would be materials and data that contain no information that could reasonably be used by anyone to identify individuals to whom they relate. All identifiers would have been removed from this type of biological materials of human origin and data. Unlinked anonymized data therefore do not fall under the scope of the Data Protection Directive. For the definition of unlinked anonymized material/data see also 2.2.2.

nymization. The procedure followed for the anonymization itself of the material should however be submitted to an appropriate evaluation procedure; this evaluation remaining valid for any further use of the material thus anonymized (art. 23).

Overview of legal framework

Table 1.1. presents a concise overview of the main features of the texts with respect to the legal context discussed above. Clearly the scopes of these documents are different and only partially overlapping. Different authorities are given the responsibility to handle the rules, for different purposes in each document. Therefore, by definition differences exist. In practice, however, practitioners use these various forms of reasoning in analyzing the situation at hand. While each form of reasoning is distinct, all the forms overlap in important ways and the researcher has to take them all into account. The table intends only to highlight some of the specificities to facilitate the researcher's understanding.

1.3. Philosophical principles

Moral reasoning involves deliberating about ethical questions and reaching a decision with the help of judgment and rational analysis. In such deliberations, particular decisions and actions may be justified by ethical theory or an integrated body of rules and principles. The approach that has figured most prominently in biomedical ethics is the principle-based approach to moral reasoning explicated by Beauchamp and Childress (31).

1.3.1. Principlism

This principle-based approach was originally developed to address ethical issues in clinical research. The four principles of beneficence, non-maleficence, justice, and respect for autonomy are well known as the Georgetown Paradigm. Respect for autonomy implies to acknowledge a person's right to make choices, to hold views and to take actions based on personal values and beliefs. Beneficence refers to provide benefits to persons and contribute to their welfare. Non-maleficence is the obligation not to inflict harm intentionally and justice entails to treat others equitably, to distribute benefits and burdens fairly. In addition Beauchamp and Childress also mention four rules to guide ethical practice. These are veracity, privacy, confidentiality and fidelity. The two that concern researchers most are veracity and confidentiality. Veracity refers to the need for researchers to tell the truth and to impart information in a comprehensive and objective way. There may be a methodological reason for limited disclosure but this must be carefully justified (31). Confidentiality²⁶ is also the subject of a considerable literature and legislation in the form of the Data Protection Directive (see also 1.2.1.).

²⁶ Confidentiality refers to the protection of obtained data against disclosure and use in a way which is not in accordance with the agreement with the individual concerned and/or societal deontological rules or regulations.

Table 1.1. Overview of legal framework

Topic	Data Protection Directive	Oviedo Convention	Additional Protocol to Oviedo Convention	Rec(2006)4
Year of issuing	1995	1997	2005	2006
Focus	Protection of personal data of any nature, comprising health (related) data	Protection of human rights and dignity with regard to biomedicine	Protection of human rights and dignity with regard to biomedicine, concerning biomedical research	Recommendation on research on biological materials of human origin
Application domain	EU	International	International	EU
Ratifications	N/A	21 countries*	5 countries**	N/A
Legal status	Legally binding in all EU Member States	Legally binding in countries that ratified the Convention	Legally binding in countries that ratified the Additional Protocol	Not legally binding
Key points	<ul style="list-style-type: none"> — Does not apply to anonymous data — Informed consent — Notification to supervisory authority — Right to know — Primacy of the individual can be overruled (substantial public interest) 	<ul style="list-style-type: none"> — Includes anonymous data — Informed consent — Submission to REC — Right to know — Primacy of individual 	<ul style="list-style-type: none"> — Builds on Oviedo Convention — + Implicit reference to Data Protection Directive — + Duty to make public the research results 	<ul style="list-style-type: none"> — Builds on Oviedo and its Additional Protocol — + Secondary use: reasonable efforts
Definition of: Reasonable efforts	No definition	No definition	No definition	Both in means and time. Efforts should include public advertisements or the use of the internet, and should be designed to give the person concerned the possibility to opt out
Research	No definition	No definition	No definition, but in explanatory note: “[...] the full range of research activities in the health field involving interventions on human beings. [...] all aspects of the research project from start to finish, including selection	No definition, but in defining the scope: “[...] full range of research activities in the health field involving the removal of biological materials of human origin to be stored for research use. [...] full range of research activities in the health

Table 1.1. Overview of legal framework — cont.

Topic	Data Protection Directive	Oviedo Convention	Additional Protocol to Oviedo Convention	Rec(2006)4
Anonymous data/material	No clear definition, but in preamble: anonymization refers to any process that makes identification of the person concerned no longer possible. However, at the same it is stated that “to determine whether a person is identifiable, account should be taken of all the means likely to be used either by the controller or by the any other person to identify the said person”	No definition	and recruitment of participants. [...] The scope does not extend to studies whose purpose is not to gain new scientific knowledge but to collect or process information for purely statistical purposes”	field involving the use of biological materials of human origin that were removed for a purpose other than that mentioned in previous paragraph, this includes material removed for a previous research project”
Withdrawal	The participant has the right to object at any time on compelling legitimate grounds. In the Directive, this right to object was clearly not designed out of the perspective of the processing of data related to health	The person concerned may freely withdraw consent at any time. No mention is made of the consequences of withdrawal	No definition, however implicit reference to Data Protection Directive regarding treatment of data and confidentiality: “Any information of a personal nature collected during biomedical research shall be considered confidential and treated according to the rules relating to the protection of private life”	Definition of identifiability of biological materials: “Identifiable biological materials are those biological materials which, alone or in combination with associated data, allow the identification of the persons concerned either directly or through the use of a code. [...] Non-identifiable biological materials [...] are those biological materials which, alone or in combination with associated data, do not allow, with reasonable efforts, the identification of the persons concerned
Substantial public interest	No definition	No definition	According to the Additional Protocol, data subjects have to be informed on their right to refuse consent or to withdraw at any time without giving reasons and without being subject to any form of discrimination	The person giving consent should retain the right to withdraw or alter the scope of that consent. The withdrawal or alteration of consent should not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care
	No definition	No definition	No definition	No definition

* Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Georgia, Greece, Hungary, Iceland, Lithuania, Moldova, Norway, Portugal, Romania, San Marino, Slovakia, Slovenia, Spain, Turkey (Status on February 18th, 2010).

** Bosnia, Bulgaria, Hungary, Slovakia and Slovenia (Status on February 18th, 2010). N/A — not applicable.

In a public health context, the specific principles of the Georgetown Paradigm are not necessarily considered the best ones to guide analysis of ethical issues (32). In general, the main shortcoming of principlism is that in situations where there is conflict between principles, it may be necessary to choose between them or to assign greater weight to one. Specifically for the Georgetown model, very often the principle of autonomy claims a prioritized position. This prioritization seems logical considering the fact that the Georgetown model was originally designed for an individualistic approach, fitting particularly well in the context of clinical medicine and research in a clinical context, where communication between the physician and the patient is often considered independent of its social context. However, in a public health context — which has a strong social component — decisions taken by individuals primarily based on self-interest may conflict with the societal interest in the long run, e.g. such as scientific knowledge and progress leading to better understanding of, and protection against, environmental risk factors.

One could argue that the justice principle in the Georgetown paradigm could be considered as representing the societal perspective and thus serves as a counterweight to the autonomy principle. However, there is no guidance as to how individual concerns should be weighed against societal interest. More generally, the Georgetown paradigm completely leaves open the balancing of the four principles. Such a lack of guidance is in line with the criticism that the meaning and the relationship between the four principles is found to be opaque (33). In the public health field, the specific decisions that emerge in particular cases may therefore remain unaddressed within the Georgetown model²⁷. The practical problems in public health ethics require that the principles be made more applicable through a process of specification and reform (34).

1.3.2. Public health ethics

The analysis of moral issues that arise in practice requires reflection on the question how to balance different and possibly conflicting concerns. Tradeoffs between individual interests in personal (e.g. autonomy, privacy, and liberty) and economic (e.g. contracts and intellectual property) freedoms on the one hand and collective interests in health safety and security on the other need to be guided by ethical values and be attentive to legal procedures and norms, as well as human rights (39). In the legal and ethical framework described above and currently applied in environmental health human biomarker studies, emphasis often lies on the need for individual decisional autonomy and protection of the individual's rights, whilst the collective need to protect the public's health by acquiring and applying scientific knowledge is relatively less valued. However, as public (environmental) health is primarily concerned with the health of the entire population, rather than the health of individuals, it is exactly the notion of public interest that comes to the forefront and may deserve more attention. Other ethical concerns in public health relate to the need to ensure a just distribution of public health resources (35).

²⁷ For example, if study participants want to learn their individual results, two principles from the classical paradigm, non-maleficence and autonomy, seem to give different answers. See further under 2.3.2.2.

Alternative approaches to moral reasoning, such as rights-based theories, duty-based theories, contractarianism, ethics of care, narrative ethics and communitarianism have, so far, not been widely applied in public health. Virtue ethics and the moral rule-based system of Gert and Clouser, however, have been discussed as potential alternatives to other leading approaches to moral reasoning in public health ethics (36).

In conceptualizing public health ethics and distinguishing it from other areas of bioethics, often mandatory or coercive public health measures, such as quarantining people with contagious diseases, are highlighted. However, in the field of environmental health research using human biomarkers, most studies depend upon the voluntary support and informed consent of members of the public.

Ethical principles in public health should give guidance on how all actors directly and indirectly involved should interact with each other. In essence, they should offer a reference frame for assessing the ethical acceptability of the decision making processes within a societal context: who decides upon what, for whom, why how, on which grounds and with which consequences for whom.

1.3.3. A set of reference values

For public health issues we suggest a reference value set that may aid in further specification and may constitute a sound basis for assessing in how far decision making processes fit with both the individual and societal interest. This value set was originally elaborated for the occupational health field (37), and also its use as a reference value set in other health related fields (38) was attempted. It may be an appealing reflection of European values and is presented below.

1. Respect for human dignity: the guiding principle in social relations is equality in moral status of individuals, which includes that people will not be discriminated against in any way for reasons which are not justifiable in a democratic society.
2. Social justice: striving for equality in distribution of burdens and benefits among all members of society, by structural measures of social protection.
3. Solidarity: the expression of willingness to contribute to and develop a societal dynamics aiming at developing social justice, and aiming at avoiding social exclusion of any individual or group of persons.
4. Democratic participation: the pluralistic process of societal decision-making in parliament or bodies of governance empowered and controlled by parliament, issuing in adopting or putting in practice regulations or frameworks for regulations by elected or democratically appointed representatives, who are bound in their choices by democratic constitutional principles, which include tolerance and striving for the right balance between the rights and duties of every individual, between individual freedom and social coercion, such that respect for human dignity, social justice and solidarity are not compromised but promoted.

Respect for human dignity and equality of moral status of individuals implies that a public health care provider or researcher must actively and respectfully involve and inform the individual at his or her own level of understanding, and must build up trust and confidence whilst avoiding any form of manipulation, authoritarian behavior or moral pressure. Based on the thus established trustful relationship, he or she may solicit an informed consent. He or she must respect the participant's privacy and confidentiality.

Social justice can constitute an unambiguous explicatory extension of the justice principle used in the Georgetown paradigm, leaving aside any arbitrary or opportunistic interpretation. It puts to the forefront striving for a socially more equal distribution of burdens and benefits in a structured way, and impedes any public health practice or research initiative which increases or reconfirms inequalities. Environmental health problems are known to be unequally distributed amongst different social groups. In this perspective, state intervention and thus social coercion can be considered opportune for reaching a more equal distribution of burden and benefits, for instance if research studies are part of a strategy to reduce pollution and the associated stigmatization in certain areas.

Solidarity implies both the willingness of individuals — *in casu* all members of society — to contribute to the wellbeing of others, as well as the structural measures of anchoring social justice. This is especially relevant for environmental health problems because of the (frequently) unequal distribution of burdens and benefits it enhances.

The principle of democratic participation is one of the basic pillars of western social liberal societies. Decision making processes at the collective level require input from a public space. At individual level, democratic participation and education can be a stimulus for autonomous functioning: social participation is important in the life of most citizens because the possibility to participate in social life encloses the germ for the process of self-realization. Democratic participation must be organized and stimulated at different levels. Citizen groups, NGO's, health committees, municipality councils, social dialogue bodies, parliaments, and even ethics committees can be considered as actors in a democratic participation process, with parliaments as the ultimate expression. Seeking for the right balance between individual autonomy and solidarity in human biomarker research and practices must be subject to weighting and decision making in fully transparent democratic participation processes.

We hypothesize that critical analyses of practices in environmental health studies and concepts such as informed consent, privacy and confidentiality is necessary, bearing in mind that they are means to create an environment in which respect for human dignity and equality of moral status of individuals; social justice; solidarity and democratic participation are fully respected. The intention is not to embed a new set of values and principles into a legalistic framework. It is merely to say that such a critical analysis for a specific research field may give guidance in recommendations and evaluations on the current legal and ethical framework. Proposals need to be supported with solid arguments from within the field, but they also need to be shared

strongly by the community in which these practices take place. This requires a strong philosophical foundation, whilst safeguarding a pragmatic and casuistic approach. A better understanding of the ethical issues at stake and commitment to these issues by different stakeholders involved in human biomarker research is an essential part of the solution.

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2. Ethics and data protection in human biomarker studies

2.1. Human biomarkers in different contexts

Human biomarkers have a long tradition in health care. They are used in curative and preventive medicine in several domains. Also in environmental health they may be applied in different contexts that may involve different risks and benefits and ask for a different analysis of moral issues and a different balance of possibly conflicting ethical values.

In this section we will situate the use of biomarkers in different contexts. It will be illustrated how, depending on the context, the relevance of a biomarker, the ethical aspects and the communication needs may vary.

2.1.1. Biomarkers in clinical medicine

In clinical medicine a biomarker has been defined as “a characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”. Biomarkers are mainly used because they are cheaper and easier to measure and because they can be measured earlier and more quickly than “true” endpoints. Biomarkers are used at any point in the chain of events that leads from the pathogenesis of a disease to its clinical manifestations, at the molecular, cellular, or organ levels (1). Examples are the measurement of ocular pressure instead of loss of vision in patients with glaucoma and the analysis of the number of lymph nodes to stage cancer.

In clinical medicine biomarkers are essentially used in a doctor patient relationship and a connection exists with a treatment to the direct benefit of the patient. Physicians are due to promote the best interests of individual patients and respect their autonomy.

The ideal biomarker in clinical medicine is one through which the disease manifests itself or through which an intervention alters the disease. Often the Bradford Hill guidelines are used to assess the relevance of a biomarker for its aim (2) (Table 2.1).

Table 2.1. Bradford Hill’s guidelines that increase the likelihood that an association is causative (2)

Guidelines	Characteristics of useful biomarkers
Strength	A strong association between marker and outcome, or between the effects of a treatment on each
Consistency	The association persists in different individuals, in different places, in different circumstances, and at different times

Table 2.1. Bradford Hill's guidelines that increase the likelihood that an association is causative (2) — cont.

Guidelines	Characteristics of useful biomarkers
Specificity	The marker is associated with a specific disease
Temporality	The time-courses of changes in the marker and outcome occur in parallel
Biological gradient (dose-responsiveness)	Increasing exposure to an intervention produces increasing effects on the marker and the disease
Plausibility	Credible mechanisms connect the marker, the pathogenesis of the disease, and the mode of action of the intervention
Coherence	The association is consistent with the natural history of the disease and the marker
Experimental evidence	An intervention gives results consistent with the association
Analogy	There is a similar result to which we can adduce a relationship

2.1.2. Biomarkers in public health

Making abstraction of research activities, most public health experience relevant to biomarker studies is situated in population screening and in occupational health screening and monitoring. The increased use in environmental health is more recent.

Population screening

In population screening biomarkers are used to identify people at high risk for a specific disease before the symptoms of the disease actually appear. Tests are administered to individuals in a defined population who have no apparent symptoms of the disease being screened. A primary goal of population screening is to predict with high accuracy which individuals in the tested group are at significant risk of developing or transmitting the disease. Once these high risk individuals are identified, additional (diagnostic) tests are performed to increase certainty and rule out false positives. These diagnostic tests are typically more expensive and/or more invasive and are therefore not used as part of the initial screening process.

In population screening the tests are performed in a medical environment and serve the direct individual interest. Interpretation of the results is in principle quite straightforward and is communicated to the subject (called “patient” here) by a health professional. Testing is offered for a specific, targeted population and is most often undergone voluntarily. It may however also be mandatory (e.g. screening for tuberculosis), to protect the population at large.

For population screening to be beneficial, a disease should meet several conditions as illustrated in Table 2.2. showing the list of criteria for screening adopted by the WHO and the National Health and Medical Research Council (NHMRC) when planning screening programs (3).

Examples of routine population screening currently used in the health care field include Pap smears for women to predict their risk for cervical cancer, mammograms for women to predict their risk for breast cancer and the prostatic antigen screening (PSA) test for men to predict their risk for prostate cancer.

Table 2.2. WHO and NHMRC criteria for screening (4)

Criteria
The condition sought should be an important health problem for the individual and community
There should be an accepted treatment or useful intervention for patients with the disease
The natural history of the disease should be adequately understood
There should be a latent or early symptomatic stage
There should be a suitable and acceptable screening test or examination
Facilities for diagnosis and treatment should be available
There should be an agreed policy on whom to treat as patients
Treatment started at an early stage should be of more benefit than treatment started later
The cost should be economically balanced in relation to possible expenditure on medical care as a whole
Case finding should be a continuing process and not a once and for all project

Occupational health screening and monitoring

For more than a century, occupational physicians and industrial hygienists have used human biomarkers to monitor worker populations for exposure to a variety of hazardous substances, as part of a preventive approach, combined with workplace monitoring and hygienic measures. Biomarkers were and still are used extensively for metals such as lead, cadmium, mercury, nickel, chromium and arsenic, and for organic chemicals such as aniline, benzene, carbon disulfide, styrene, chlorobenzene and chlorinated aliphatic hydrocarbon solvents. Such (repeated) biological monitoring is seen as a component of medical surveillance that is the periodic examination of putatively exposed workers.

Recently, discussions on the acceptability of using genetic markers at pre-employment selection for the detection of inherited characteristics, which can point to greater susceptibility to certain disorders in relation to certain occupational risks (genetic screening) indicated that the use of these markers is not considered part of a rational policy aiming at the protection of workers' health. Consequently, the use of those tests is generally not advocated and even prohibited in certain countries. In contrast, genetic biomonitoring that finds changes in the hereditary material, which are the result of exposure to harmful substances, is considered relevant (5).

In occupational health human biomarkers are used in the specific context of occupational settings and relationships. This is, at least in Europe, a context of collective control and hierarchical decision-making. Results are of personal relevance and/or of relevance at the local level (e.g. a department of a plant). Communication is done by health professionals with a clear, legal definition of their role in protecting the health, work and privacy of workers. Testing may be mandatory for certain professional functions. Communication at the individual level is done through a health professional (occupational health physician or nurse). Communication of aggregated data at the collective level to employers and workers representations may support or evaluate preventive measures.

Biomarkers in environmental health

As mentioned before, in environmental health, human biomarkers are mainly used in research studies — to improve our knowledge on causal links between environmental factors and health — in survey studies — where periodical measurements provide information on the prevalence of exposure to environmental agents and the related public health impact — and in raising awareness campaigns. Recently, important advances in analytical chemistry have led to the detection of an ever-increasing number of chemicals with reduced limits of detection in human samples

Particular to the use of human biomarkers in environmental health surveys is the requirement that activities should support, lead and assess policy and preventive actions in the field and should raise awareness. Participation is always on a voluntary basis and requires the fulfillment of informed consent procedures. Results are often not relevant at the personal level or are not in the direct interest of the individual. Results are therefore in many cases not communicated at individual level.

With respect to biomonitoring, Morello et al. (6) recently termed the three frameworks in which the results of studies are reported to study participants as follows: ‘clinical ethics’, ‘community-based participatory research’ and ‘citizen-science data judo’. Researchers using a clinical ethics model assume that the decision about sharing research results with study participants should rest with the researchers. Community-based participatory research is based on the assumption that information should be shared equally between researchers and study participants; sharing results is seen to empower the study participants to make use of the data. Citizen-science data judo is used by advocacy groups to encourage study participants to pursue policy change as well as reduce individual exposure to chemicals; study design and communication of results are shaped by the intended policy goals of the researchers. The study stresses the important role of good communication and highlights the need for guidance on how best to communicate results from human biomonitoring studies. In their opinion study participants themselves need to be involved in the creation of these guidelines. We will go deeper into the subject in section 2.3. on decision making processes and communication in human biomarker studies.

Characteristics of valid biomarkers in environmental health according to WHO are listed in Table 2.3. (7).

Table 2.3. Characteristics of valid biomarkers in environmental health (7)

Biomarker	Characteristic of valid biomarker
Exposure	Biomarker should be: <ul style="list-style-type: none"> — consistently linked with exposure at relevant levels of exposure with confounding and background exposures assessed — establish a constant link with an adverse health effect or with the concentration of the chemical in the target organ
Effect	Biomarker should be consistently linked with an increased risk with confounding and effect modifying factors assessed
Susceptibility	Biomarker should be able to distinguish subgroups at risk given a specific exposure

Much research work is to be done in this respect for most exposure and effect biomarkers in environmental health since the relationship with health effects is currently unclear. This limits the interpretation of data in terms of health risk and the development of reference values and health-based values and therefore holds back the straightforward interpretation of data and their translation into policy actions (8). External quality assessment schemes are to be developed to ensure comparability of results²⁸.

2.1.3. Differences in aims, risks and benefits

Overall, the aim and context of the use of biomarkers in public health are different from those in clinical medicine. Clear differences exist in terms of benefits, risks and consequences at both the individual and collective level and in communication.

Whilst in clinical medicine physicians focus on the best interests of individual patients, public health professionals focus on the best interests of the population as a whole rather than on the interests of the individual patient or subject.

In most cases, actions in a public health setting will not be mandatory. However, under certain circumstances, the liberty and autonomy of the individual patient may be overridden for the good of the public. For example, in response to a serious, probable threat to the public, it may be appropriate for public health officials to impose mandatory testing, treatment, vaccination, quarantine, or isolation. Recent treatises and articles have set forth criteria that must be satisfied to justify compulsory public health interventions (Table 2.4) (9).

Table 2.4. Criteria to be satisfied to justify compulsory public health interventions (9)

Criteria for intervention	Description
Necessity and effectiveness	Public health threat must be serious and likely; there must be a sound scientific basis for the intervention
Least restrictive alternative	The intervention should be the least restrictive alternative that will effectively respond to threat
Procedural due process	Persons deprived of their freedom should be offered the right to appeal
Fair distribution	Benefits and burdens of intervention should be fairly distributed in society, consistent with the epidemiologic features of the threat
Transparency	Public health officials should make decisions in an open and accountable manner

With respect to the specific domain of biomarkers studies in health and environment, the direct risks are generally considered minimal or non-existent if processing is done under correct conditions. In principle, study participants may receive direct benefits from

²⁸ Between 1985 and 2008, for instance, the German External Quality assessment scheme for biological monitoring in occupational and environmental medicine developed 137 Standard Operating Procedures (SOPs) for hazardous substances in biological materials.

participation in some studies, such as when a previously unrecognized, and possibly curable disease or preventable risk factor is detected during examinations.

As will be discussed further in this volume²⁹, risks and potential harm can be minimized by carefully paying attention to study procedures and to communication, paying particular attention to the consequences knowledge on data on exposure or effect may have on the study participant and the need for help that may exist for the correct assessment of the meaning and the possible use of the data.

2.1.4. An example

The major impact context has on relevance, ethical aspects and communication can be illustrated with a real life example on Prostate-specific antigen (PSA). This is a well known clinical marker for prostate cancer. It is used as a *diagnostic test* (diagnosis in a person suspected of disease), to *follow the progress of the disease* or effect of a treatment and as a *screening test* (looks for signs of disease in persons — in a targeted at risk population — without symptoms). PSA may according to some sources also be *linked with exposure* to pollutants.

The use of PSA for cancer screening purposes is however controversial. Risk and benefit analysis has demonstrated that in large scale testing a considerable amount of false positives are detected. In addition, diagnostic procedures after a positive PSA test may cause important side effects. Furthermore, the test may detect small tumors that would never become life threatening. So, from a clinical point of view, it is not yet known whether the test actually saves lives, nor is it clear whether the screening benefits outweigh the risks of the follow up diagnostics and cancer treatments. Also the test is not generally accepted nor validated with respect to its relevance regarding environmental exposure. Despite all this, the PSA marker was included in a large environmental health program, which combined research with survey purposes.

Depending on the context in which the PSA tumor marker is used, risks, benefits and consequences are clearly different. Decision making on the applicability of a test has to take these aspects into account and may therefore need input from skilled experts from within the specific application domain. Moving from a clinical or diagnostic to an environmental context, decision making implies weighing all aspects presented in Table 2.5.

²⁹ See 2.3.

Table 2.5. Use of PSA in different contexts

Context	Use	Benefits	Risk of knowledge	Decision Making	Communication	Acceptability
Clinical	Diagnosis in person suspected of disease	Confirmation of diagnosis in person with clinical complaints Result should support decisions for treatment		Doctor-patient relationship	By treating physician Interpretation of the test result is quite straightforward in combination with other data	Accepted practice
Public health, population screening	Screening, look for signs of disease in persons without symptoms	Result might support decisions for early treatment	False positives Diagnostic procedures can cause important side effects	Public health professionals	By public health professional or treating physician Not straightforward Interpretation of cancer risk	Controversial
Environmental health research	Validation as a marker to assess impact of environmental pollution	No relevance at individual level with respect to environmental pollution Information on cancer risk	False positives Further diagnostic procedures can cause important side effects	Researchers and institutions organizing the research study	By recruiter (= treating physician or researcher) Not straightforward indication of cancer risk Study participant has legal right to know his results. Often only abnormal results are communicated	Assessment of acceptability by ethics committee (REC) REC does not always include experts in this field

Table 2.5. Use of PSA in different contexts — cont.

Context	Use	Benefits	Risk of knowledge	Decision Making	Communication	Acceptability
Environmental health surveys	Survey impact of pollution in a population	Link of marker with exposure and/or effects not yet accepted No relevance at individual level with respect to environmental pollution Information on cancer risk	False positives Further diagnostic procedures can cause important side effects	Institutions organizing the survey	By recruiter with often no relation with treating physician or researcher Not straightforward indication of cancer risk Study participant has legal right to know his results. Often only abnormal results No (test is not validated) are communicated	Questionable Assessed by REC

PSA in a clinical context

In a clinical context, the PSA biomarker is used in a medical environment as a tumor marker and directly serves the individual interest. Testing is carried out because complaints exist or certain symptoms have come to light. Interpretation of the results is done in combination with a clinical examination (and eventually other tests) and results are communicated to the patient by a health professional. In a clinical context everything falls within the doctor patient relationship and decisions regarding communication strategies are to be made within this relationship, respecting patient rights.

PSA in population screening

In population screening the PSA biomarker is used in a public health context as a tumor marker and directly serves the individual interest. Interpretation of the result should be straightforward but unfortunately is not. Communication to the subject is done by a health professional. Testing is offered for a specific population of males with a certain age, but is voluntary. Decisions on the acceptability of the use of the PSA marker in a screening program are to be made by the public health policy makers and professionals.

PSA in environmental health

In environmental health, the PSA biomarker is used as a marker for environmental contamination. The result is not relevant at the personal level nor is it in the direct interest of the individual. However, as it has a certain (yet not straightforward) meaning as an indicator of cancer risk, in practice results are communicated to the study participant in case of the finding of abnormal results (unless he has specified not to want his results, whether they are abnormal or not). Decisions on the use of the test are made by the researchers and institutions organizing the study, whether it is for a research objective or for a survey. Even though the test is on a voluntary basis, it may be difficult for the individual to correctly assess the risks and benefits of such a test. An overall assessment of the acceptability of this type of testing practices by an ethics committee is therefore recommended. Expertise from within the public health domain is thereby essential.

2.2. Formal legal aspects

The number of regional and national regulations to cope with in environmental health studies using human biomarkers is steadily increasing. Tissue research is currently regulated through an amalgam of different and occasionally unclear laws and policies.

The general conditions in the current EU regulative framework were already presented in chapter 1.2. In the current section, focus is put on a number of aspects in the EU regulatory framework that may need clarification or even rethinking. Each aspect is illustrated by an example case and suggestions for improvement are given with the streamlining of regulations in the EU in mind, taking into account different national, cultural and political sensitivities. The examples cases refer to real life situations.

Although this may seem a legalistic and formal approach, the analyses may allow the reader to gradually become more familiar with the application and implementation of various formal aspects.

2.2.1. Definition of “research”

Recently, the visibility and policy impact of human biomarker studies have increased a lot. While previously mainly restricted to academic research and occupational health studies, human biomarkers now become more widely available, more practical and less expensive and are increasingly used by environmental advocacy organizations and non-profit research institutes (6). Indeed, showing personal blood levels of specific substances is a powerful tool for awareness raising on exposure issues. So, studies using human biomarkers now come in various shapes, raising the question whether they all fall under the category of research and have to fulfill all corresponding legal requirements.

Example case 2.1. The WWF surveys

The past years WWF has organised several biomonitoring surveys testing people across the whole of Europe (10). The goal of these surveys was not to test a scientific hypothesis, but rather to raise awareness among the general public about the extent of chemical pollution in Europe and to show the necessity of a strict European regulation for chemicals. Thereto, a few (identifiable) samples were taken in many EU Member States.

The WWF communicated results at press conferences and through published reports and showed that people are contaminated with a cocktail of persistent, bio-accumulative and toxic man-made chemicals.

Question

Is this raising awareness project to be considered “research” and do laws and regulations concerned thus apply? More specifically, do surveys like the WWF one need approval from an ethics committee?

A. According to the Additional Protocol of the Oviedo Convention

- According to the Additional Protocol every research project has to be submitted for independent examination of its scientific merit and ethical acceptability. Approval of an ethics committee is required before the start of a research project (art. 9 of Additional Protocol).
- However, nor the Oviedo Convention, nor the Additional Protocol gives a clear definition of “research”. This lack of definition thus makes it unclear whether in this example case the requirements of the Oviedo Convention and the Additional Protocol need to be complied with.
- Exploring the guidelines further, we can, however, try to deduce what is covered by the term “research”. In articulating its scope, the explanatory report of the Additional Protocol states that art. 2.1 covers the full range of research activities in the health field involving interventions on human beings. This includes all aspects

of the research project from start to finish, including selection and recruitment of participants. The Additional Protocol covers research into molecular, cellular and other mechanisms in health, disorders and disease; and diagnostic, therapeutic, preventive and epidemiological studies involving interventions. It also mentions that this list is not meant to be exhaustive but that the scope does not extend to studies whose purpose is not to gain new scientific knowledge but to collect or process information for purely statistical purposes such as for audits or monitoring of the healthcare system (explanatory note concerning art. 2.1).

- The term “intervention” covers physical interventions as well as any other intervention in so far it involves a risk to the psychological health of the person concerned (art. 2.3). It must be understood in the broad sense: it includes all medical acts and interactions relating to the health and well being of persons in the framework of health care systems or any other setting for scientific research purposes. Questionnaires and interviews taking place in the context of a biomedical research protocol constitute interventions when they involve a risk to the psychological health of the person concerned; they can be troubling to a person if they address the sensitive sphere of private life of the individual. An ethics committee could evaluate the potential risks and assess possible problems.
- The broad description of the term “research” implies that different Member States may furnish different interpretations to it when implementing³⁰ these principles into national law. Looking at the definition of “research” in the applicable law in some Member States confirms not only the diversity in interpretation, but also the imprecision of the definition itself. Consequently, this leaves us with an unsatisfying answer.
 - For example, in Section 2 of the Swedish Act (2003:460) concerning Ethics Review of Research involving Humans, research refers to “scientific, experimental or theoretical work to obtain new knowledge as well as developmental work carried out on a scientific basis”³¹.
 - The Dutch Medical Research involving Human Subjects Act (2006) is strongly focused on a clinical context defining research as “clinical trials in which persons are subjected to treatment or are required to behave in a certain manner” (Section 1.1.b)³².

³⁰ Not all EU Member States have ratified the Oviedo Convention and its Additional Protocol (see 1.2.2.). Some national laws resulted from improvements of regulations started in the 1960s and are also inspired by the Helsinki Declaration or by the Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

³¹ “[...] with the exception of that which is carried out as part of a program of study at an institute of higher education at a basic or advanced level” (Section 2).

³² Although in the Act itself no further specification is given of the definition of research, an international publication regarding the Act published by the Dutch Ministry of Health, Welfare and Sport states the following: “research in the sense of the Act is medical research that is intended to lead to generally valid statements based on systematic observations and reasoning. Amongst other things, this may relate to the effects of new methods of treatment but also to obtaining information about the normal physiological situation or pathological processes”.

Concluding, despite the broad description or interpretation of research, it remains unclear whether the example case classifies as research or not according to the Additional Protocol. One could argue that there is no systematic process of collecting and analyzing information to increase our understanding of a certain phenomenon, but that it entails only the demonstration of the existence of a possible problem. In this opinion, the intervention would not be situated in a framework of scientific research purposes. While the Additional Protocol does not provide a straightforward answer whether an approval is required or not when collecting and analyzing samples in one Member State, the situation may become even more unclear when coping with the collection of (only a few) samples in several Member States, as is the case in the WWF campaign.

B. According to the EU Data Protection Directive

— In the context of the Data Protection Directive, the problem of the definition of research is not relevant. The Data Protection Directive concerns the processing of identified or identifiable data, irrespective of their purpose (research or not). Since the campaign does involve the processing of identifiable health related data which are processed by automatic means or by non-automated means within a filing system, all regular conditions for the legitimate processing of this special category of data have to be met, including the need for informed consent and a notification to the national supervisory authority prior to the start of the project.

Conclusion

- The broad description of the term “research” in the Additional Protocol hinders a clear determination whether a raising awareness campaign is research or not and thus whether approval from an ethics committee is required. At national level, Member States also adopt different, wide-ranging and sometimes vague definitions. For a raising awareness campaign collecting a few samples in different Member States, this ambiguity makes it even more problematic to know whether approval is needed in each Member State³³.
- A common interpretation or clarification at the EU level on the applicability of the concept of research in such cases would be helpful. This could be realized by a permanent working group of experts who continuously analyze and — where necessary — adapt and explain notions and concepts important to the field. A similar concept is used for the Data Protection Directive as will be explained further (cfr. Article 29 Working Party). In addition, in case of doubt, the possibility could be created for the researcher who wants ad hoc advice to consult an ethics committee.

³³ For the problem of multiplication of approvals see also transnational context (2.2.3.).

Example case 2.2. Samples taken for optimization of experimental settings

Biological samples obtained from volunteers — sometimes from children or newborns — are to be considered as precious and should accordingly be optimally used. To avoid the apparently unnecessary use of these samples for the optimization of experimental and methodological procedures, samples from friends or colleagues in the laboratory are often used instead. These samples can be obtained freely and quickly, so the actual precious research samples can be preserved.

Question

Is for this kind of (technical) optimization, using samples from friends or colleagues, an informed consent and/or approval from an ethics committee necessary and/or does this fall under the scope of the Data Protection Directive, implying the obligatory notification to the national supervisory authority?

A. According to the Additional Protocol of the Oviedo Convention

- As described in the previous example case, the Additional Protocol is applicable for research projects. It could be argued whether the technical optimization of a methodology falls under this description of research, since it depends whether improving methodology is considered as increasing knowledge. If considered research, a free informed consent should be obtained and the optimization procedure should be included in the proposal submitted to the ethics committee. If not, no informed consent, nor approval from an ethics committee is required.
- If an informed consent is required, an underlying but essential issue should be taken into account: to what extent is such an informed consent “free” if the person who donates a sample is an employee of the researcher or a fellow colleague? The Additional Protocol refers to the ethics committee for providing response; the ethics committee should assess the project in such a way to satisfy themselves that no undue influence is exerted on persons to encourage participation in research, specifically for vulnerable persons or persons in a weak or dependent position (art. 12).

B. Concerning the Data Protection Directive

- As already pointed out above (example case 1), to determine whether the Data Protection Directive applies, it is irrelevant whether the project is considered research or not.
- However, to decide on the applicability of the Data Protection Directive in this case we need to consider whether the information in question is “data” (either processed by automatic means or by non-automated means within a filing system) and whether the “data” is “personal data” in that it relates to an identifiable individual.
 - We may expect that the information obtained will be processed by automatic means or at least within a filing system. A filing system is: “any structured set of personal data which are accessible according to specific criteria, whether

centralized, decentralized or dispersed on a functional or geographical basis” (art. 2c).

- We may also expect that the data will be identifiable in the present example case. One could argue that data obtained for experimental optimization can be rendered non-identifiable, implying that it would not fall within the scope of the Data Protection Directive. However, if only a few samples are taken, samples may be identifiable through indirect identification.

The Data Protection Directive is thus to be applied.

- Concerns about undue influence analogous to the ones expressed in the Additional Protocol can also be found in the context of certain domestic implementations of the Data Protection Directive: art. 27 of the Belgian Royal Decree (2001)³⁴ prohibits for instance the processing of sensitive health related data on the sole basis of the data subject’s written consent when the controller³⁵ is the data subject’s current or potential employer or if the data subject is in a dependent position with respect to the controller, preventing him from freely giving his consent. This prohibition is lifted when the processing aims at procuring a concrete benefit for the data subject. In contrast, the Personal Data Protection act in the Netherlands does not mention such an analogous condition.

Conclusion

- Classification as research and processing by automatic means or by non-automated means within a filing system of identifiable data define whether respectively the Additional Protocol and the Data Protection Directive are applicable.
- Obtainment of samples from friends or colleagues for technical optimization purposes reveals another, more essential problem. The context of power inequality needs to be carefully considered if the aim is to protect the rights of individuals, especially the weaker. According to the subsidiarity principle, (precious) samples should be used strictly in line with the research purposes and should not be used for the optimization of experimental and methodological procedures if this can be done in another way. Samples from children for instance should not be used for optimization purposes unless only children’s or newborns’ samples fit the validation purposes. Facilitation of the use of samples from colleagues and friends for optimization purposes only might therefore be advisable, on the condition that sufficient guarantees against undue influences to encourage or impose participation are provided.

³⁴ In Belgium, data protection legislation is contained in the Law of December 8, 1992 on Privacy Protection in relation to the Processing of Personal Data as modified by the law of December 11, 1998 implementing Directive 95/46/EC. Furthermore, there is the Decree of 13 February 2001 implementing the Law of 8 December 1992.

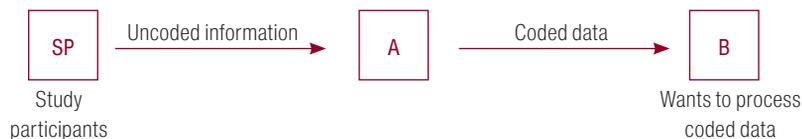
³⁵ Data Protection Directive, art. 2: “‘Controller’ shall mean the natural or legal person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data; where the purposes and means of processing are determined by national or Community laws or regulations, the controller or the specific criteria for his nomination may be designated by national or Community law; ‘Processor’ shall mean a natural or legal person, public authority, agency or any other body which processes personal data on behalf of the controller”.

2.2.2. Concept of “anonymization”

Personal health related data is sensitive data and require treatment with discretion. In principle, the Data Protection Directive prohibits the processing of sensitive data, but exceptions exist (art. 8 of the Data Protection Directive). As a general principle, the Directive advocates the use of non identifiable data as the rule, unless that is deemed impossible. In the latter case, processing is permitted solely under strict conditions.

To circumvent (too) harsh conditions or juridical difficulties, researchers often resort to the anonymization of data or samples. For certain research purposes, it is however not always the preferred way of working, since the anonymization of data or samples may seriously limit the possibilities for acquiring new knowledge through the use of those data and samples³⁶. When data and samples are obtained from volunteers, it seems, from an ethical standpoint, apparent that they should be optimally/maximally used for scientific progress. In addition, it is sometimes unclear how to act correctly due to inconsistent definitions of anonymization in the law. An example case is presented here to illustrate important issues that arise in the anonymization and the processing of data.

Example case 2.3. Samples taken for optimization of experimental settings



Researcher Abe (A) obtains information (name, address, age, concentration of lead in blood) from study participants and intends to file it by automatic means as identifiable data and to pass on the information without identifier (only leaving a code and the concentration of lead in blood) to Barney (B) for purpose Q. Abe, however, keeps the key linking the code with the identifiable data of the study participants.

Question

Is an approval from an ethics committee necessary for the processing by Barney? Which principles of the Data Protection Directive apply and who is responsible for guaranteeing that these principles are conformed to for the processing of the data by Barney? Is it Abe, who has the identifier/key? Or is it Barney, who does the actual processing? Or could it be argued that the processing by Barney is outside the scope of the Data Protection Directive because Barney cannot identify the study participants?

A. According to the Additional Protocol of the Oviedo Convention

- With respect to the application of the principles of the Additional Protocol, there is no distinction between identified, identifiable and completely anonymous data. The

³⁶ Examples of recent British research studies for which identifiable data were deemed essential highlight six research applications: to understand the natural history and development of disease; to identify causes of disease; to evaluate health care interventions; to assess equity of care; to describe trends in health care utilization; and to ensure the methodological rigor of research (11).

general rule is that every research has to be submitted for approval to independent examination (art. 9). This is not only so in the case presented where Abe transmits coded data, but also if Abe would have transmitted anonymous data (whether collected anonymously or rendered anonymous). In the case of transmission of anonymous data, the ethics committee should be informed if this foreseen anonymization would prevent the feedback of relevant information to the study participants (art. 11).

- If the data were not originally collected by Abe with the aim of processing it as coded data by Barney, the new study by Barney should be submitted to an ethics committee. If the data was originally collected by Abe with the aim of passing it on to Barney, the processing by Barney was included in the original approval by an ethics committee and no further steps are necessary.

B. According to the Data Protection Directive

- The Data Protection Directive is applicable for information relating to an identified or identifiable natural person (see Box 2.1) but not to anonymous data. Coded data is not considered anonymous data but are identifiable data. Thus, although Barney is not able to directly identify the person to whom the data belongs, the data is still in a form that under the Data Protection Directive classifies as personal (and thus protected) data. It is at this point that confusion may arise. Experience shows that researchers sometimes regard such data as in the example case as having been rendered anonymous (12). The source of the problem is that while researchers may fully appreciate the definition of “anonymization” within their own professional practice and ethical culture, they do not fully appreciate the significance and scope of the description of “anonymization” given by the Directive (13). As a consequence, often unintentionally, the use of the label “anonymization” operates as a metaphor or an ideological tool to relieve researchers, at least in their own minds, from the need to comply with the data protection law’s demands. If the purpose of Barney’s processing of coded data was incorporated within the scope originally defined in the study proposal by Abe, Abe (i) obtained consent for the processing purpose of Barney; (ii) provided the participant with the necessary information, including the recipient (Barney) of the data and (iii) notified the supervisory authority. It is also Abe whom the study participants should turn to to obtain information on the processing of their personal data. If the purpose of Barney’s processing of coded data was not incorporated within the scope originally defined in the study proposal by Abe, we are dealing with a secondary³⁷ processing and Abe should in principle re-contact the study participants and ask for a new informed consent for this new purpose and notify the supervisory authority. However, exceptions may apply if this re-contacting is considered to involve disproportionate efforts

³⁷ For a discussion of processing conditions for secondary use, see 2.2.4.

(art. 11) (see also Example case 2.5 on secondary use). Again, it is Abe to whom the study participant should turn to obtain information on the processing of the data. Suppose that Abe would have stripped the data irreversibly from their identifiers before transferring them to Barney, then Barney would process anonymous data, which fall no longer within the scope of the Data Protection Directive. It should however be noted that the Data Protection Directive already did apply to the data before its anonymization. Because processing refers to anything done to personal data, thus including rendering it anonymous (art. 2b³⁸) and because art. 10 of the Directive requires study participants to be informed of the intended purposes of processing, this suggests, at the very least, that study participants must be informed about any intended anonymization and the consequences thereof. This means that until anonymization is actually carried out, the data will be considered personal data (14). This has been criticized because it is considered an impossible standard to live up to in practice (15).

Box 2.1. Definition of “personal data” (art. 2 of the Data Protection Directive)

“Personal data” shall mean any information relating to an identified or identifiable natural person (‘data subject’); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.

Conclusion

- The Additional Protocol does not make a distinction between research projects using identifiable or anonymous data with respect to the need for submission of the research project to an ethics committee. In either case, submission for approval is required.
- The Data Protection Directive applies to identified or identifiable data. Only if data is rendered completely anonymous, implying that it is impossible to identify the person concerned, the data does not fall under the scope of the Data Protection Directive. According to rec. 26 “to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person”. Hence, by introducing the word “reasonably”, the level of impossibility of identification is limited to a certain degree; using exceptional procedures, that person could still be identified. Rec. 26 moreover refers to codes of conduct — to be formulated at national level — as useful instruments for providing guidance as to the ways in which data may be rendered anonymous and

³⁸ Art. 2b: “processing of personal data’ (‘processing’) shall mean any operation or set of operations (which is performed upon personal data, whether or not by automatic means, such as collection, recording, organization, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction”.

retained in a form in which identification of the study participant is no longer possible (16,17).

- Nevertheless, the fact remains that the seemingly large variety of understandings of the term “anonymization” still creates a lot of confusion. Despite the fact that definitions and interpretations of “anonymization” and related terms are elaborated on and under continuous scrutiny and subject to change (see also intermezzo below on Article 29 Working Party), this debate is not known by many researchers, and researchers cannot be expected to become experts in these matters. More attention should therefore be paid to a basic education of researchers in these issues, and more possibilities to seek advice with people who are familiar with the field should be created.
- With respect to definitions of personal and anonymized data, those presented in Rec(2006)4 on research on biological materials of human origin, can serve as a good reference point — biological materials may be identifiable or non-identifiable:
 - i. *Identifiable biological materials* are those biological materials which, alone or in combination with associated data, allow the identification of the persons concerned either directly or through the use of a code. In the latter case, the user of the biological materials may either:
 - a) have access to the code: the materials are referred to as “coded materials”; or
 - b) not have access to the code, which is under the control of a third party: the material is referred to as “linked anonymized material”.
 - ii. *Non-identifiable biological materials*, referred to as “unlinked anonymized materials”, are those biological materials which, alone or in combination with associated data, do not allow, with reasonable efforts, the identification of the persons concerned.

**An evolving concept of personal data:
The Article 29 Data Protection Working Party³⁹**

The Article 29 Data Protection Working Party was set up in the frame of the Data Protection Directive, to a.o. promote the uniform application of the general principles of the Directive in all Member States through the co-operation between data protection supervisory authorities⁴⁰.

³⁹ The Article 29 Data Protection Working Party has been established by Article 29 of Directive 95/46/EC. It is the independent EU Advisory Body on Data Protection and Privacy. Its tasks are laid down in art. 30 of Directive 95/46/EC and in art. 15 of Directive 2002/58/EC. The Article 29 Working Party has advisory status and acts independently. It is composed of a representative of the supervisory authority or authorities designated by each Member State and of a representative of the authority or authorities established for the Community institutions and bodies, and of a representative of the Commission (18).

⁴⁰ Other tasks of the supervisory authorities are: to provide expert opinion from member state level to the Commission on questions of data protection; to advise the Commission on any Community measures affecting the rights and freedoms of natural persons with regard to the processing of personal data and privacy; to make recommendations to the public at large, and in particular to Community institutions on matters relating to the protection of persons with regard to the processing of personal data and privacy in the European Community.

In June 2007, the Working Party adopted Opinion 4/2007 on the concept of personal data “as information about current practice in EU Member States suggested that there is some uncertainty and some diversity in practice among Member States as to important aspects of this concept which may affect the proper functioning of the existing data protection framework in different contexts [...]”. Important in the context of our analysis is that Opinion 4/2007 stressed the need for a substantial degree of flexibility⁴¹, so as to strike the appropriate balance between protection of the study participants’ rights on the one side and the legitimate interests of data controllers, third parties and the public interest which may be present on the other. Flexibility in the application of the rules to the data is said to be already embedded in the text in order to provide an appropriate legal response to the circumstances at stake.

The Opinion clarifies terms such as “identified”, “identifiable”, “identifiers”, “directly identified or identifiable persons”, “indirectly” identified or identifiable persons and “anonymous” data with examples. Often the interpretation will depend on the circumstances, and a case-by-case analysis should be carried out. National Data Protection Authorities play an essential role in this respect: their role involves providing interpretation of legal provisions and concrete guidance to controllers and study participants. They should endorse a definition that is wide enough so that it can anticipate evolutions and catch all “shadow zones” within its scope, while making legitimate use of the flexibility contained in the Directive.

According to the Article 29 Working Party, identifiability relates to the phenomenon of “unique combinations”, whether small or large in size. In cases where *prima facie* the extent of the identifiers available does not allow anyone to single out a particular person, that person might still be “identifiable” because that information combined with other pieces of information (whether the latter is retained by the data controller or not) will allow the individual to be distinguished from others. The criterion of “all the means likely reasonably to be used either by the controller or by any other person” should in particular take into account all the factors at stake, such as the cost of identification, the intended purpose, the advantage expected by the controller, the risk of technical failures. This test is a dynamic one and should consider the state of the art in technology at the time of the processing and the possibilities for development during the period for which the data will be processed.

⁴¹ Exemptions under art. 3 take into account the technical way of processing (in manual non-structured form) and the intention of use (for purely personal or household activities by a natural person). Even where processing of personal data within the scope of the Directive is involved, not all the rules contained therein may be applicable in the particular case. Some examples of such provisions are contained in art. 6 (retention period depending on data being necessary), 7.f (balance of interest to justify processing), last paragraph of 10 (c) and 11.1 (c) (information to the study participant where necessary to guarantee fair processing), or 18 (exemptions from notification requirements), just to mention a few cases.

An evolving concept of personal data: an example at national level

In the UK, the Durant judgment⁴² in 2003 resulted in the courts holding a narrower interpretation of “personal data” and “relevant filing system” than most practitioners and experts had followed previously, so that data became personal only in certain circumstances. After the Durant decision the UK Information Commissioner’s Office⁴⁵ issued guidelines (<http://www.informationcommissioner.gov.uk>) titled “the ‘Durant Case’ and its impact on the interpretation of the Data Protection Act, 1998”.

Following Opinion 4/2007 (01248/07/EN-wp136) (20) of the EU Article 29 Working Party on the definition of “personal data” and a letter of formal notice issued by the European Commission, the Information Commissioner issued a revised Technical Guidance (21) in 2007 which significantly extended the narrow definition of “personal data” again.

Many kinds of information can count as personal data, even in situations in which people may not consider it to be so. Moreover, a decision on personal data must be revised on occasion, and it must not be assumed that any decision is final. “Means of identifying individuals that are feasible and cost-effective, and are therefore likely to be used, will change over time. If one decides that the data one holds does not allow the identification of individuals, one should review that decision regularly in light of new technology or security developments or changes to the public availability of certain records” (22). Particular emphasis is put on the fact that the same data may be processed for different purposes and that it may be personal data in one set of circumstances with one data controller but not when passed on to another controller. Moreover, some information can count as personal data in one person’s hands, but not in another’s⁴⁴. Also, parts of documents can count as personal data without the whole document counting as such (22).

2.2.3. Transnational research

With globalization and the promotion of collaboration in an EU context, more and more transnational research projects are being set up. However, the transnational nature of these projects is accompanied with new, specific problems. Below, two examples cases are presented to illustrate some of those issues.

⁴² Michael John Durant v Financial Services Authority [2003] EWCA Civ 1746, Court of Appeal (Civil Division) decision of Lord Justices Auld, Mummery and Buxton dated 8th December 2003 (19). Michael Durant was an unsuccessful litigant, pursuing disclosure of additional information held by the Financial Services Authority (FSA) in relation to a complaint he had made against Barclays Bank. Dissatisfied that the FSA had dismissed his complaint against the Bank, Durant made several requests to the FSA under Section 7 of the Act (the relevant Subject Access Request section of the UK Act) for Disclosure of personal data held about him in the FSA’s manual and computerized records. The FSA provided Durant with copies of documents held in computerized records but refused his request for manual record copies on the grounds that the information did not constitute ‘personal data’. The Court of Appeal ruled that just because a document contained his name it was not necessarily defined as personal data. This changed the perception of how wide a definition of personal data could be.

⁴⁵ The UK Information Commissioner’s Office is the supervisory authority in the UK.

⁴⁴ The guidance gives the example of two near-identical photographs of a street party, one taken by a policeman, the other by a journalist.

Example case 2.4. Validation of N²-ethylidenedeoxyguanosine as a biomarker of alcohol intake

European project was carried out to investigate whether N²-ethylidene-dG can be used as a biomarker for alcohol consumption and to determine the stability of this DNA adduct in humans in situ. Study participants were asked to abstain from alcohol during a certain time and then drink a controlled amount of alcohol, after which blood samples were collected. The experiment took place in Poland and samples were afterwards transferred to Sweden and the UK for analysis.

Question

When personal data and/or biological samples are collected and/or analyzed in several different countries, are notification to the national supervisory authority and ethical approval required in one, several or all participating countries?

A. According to the Oviedo Convention and its Additional Protocol

- Conforming art. 9 of the Additional Protocol, an independent examination by an ethics committee is necessary in each Member State in which any research activity is to take place. Since the Oviedo Convention and its Additional Protocol have been ratified by only a limited number of EU Member States (see 2.2.2.) these guidelines have no enforcing legal status in most Member States. However, their power is highly esteemed and many European ethics committees take into account the provisions of the Oviedo Convention and its Protocol in the review process.
- Submission for approval of a research proposal to an ethics committee is regulated by national laws, most of which originated in the 1960s and were basically inspired by the Helsinki Declaration. Most of these national laws have a strongly clinical and thus individualistic orientation, and when applying them to the domain of environmental health research, vagueness and uncertainties may arise (they focus for example on insurance aspects, which is much less of an issue in environmental health research).
- Summarized, conforming the Additional Protocol and according to the national laws relevant for this case, ethical approval is required in Poland, UK and Sweden.
 - Unlike other countries, Poland does not have a coordinating national centre for Bioethics Committees in human research. There are 54 independent Bioethics Committees. The topics of applications submitted for ethical evaluation to the Bioethics Committees vary according to the research area of the institutions applying. The functioning of Bioethics Committees in Poland is regulated by several laws. The detailed regulations concerning the functioning of Bioethics Committees in Poland are on the basis of Ordinance of the Ministry of Health and Welfare. All regulations comply with the most important guidelines such as the Helsinki Declaration, The Rules of Good Clinical Practice, EU Directives and legal

regulations binding in Poland, mainly the Act of the medical doctor profession and the dentist profession, as well as the Act of Pharmaceutical Law (23,24)⁴⁵.

- Research in the UK⁴⁶ requires ethical review when it involves material consisting of or including human cells⁴⁷. Ethical review of research taking place outside the UK is outside the scope of the National Research Ethics Service (NRES). Where a study will be taking place both in the UK and overseas, the REC will only review the arrangements for conduct of the research in the UK.

According to the Human Tissue Act 2004 (25) the import or export of tissue is not in itself a licensable activity. However, once tissue is imported, its storage or use for a scheduled purpose (including research) is subject to licensing by the Human Tissue Authority unless it is for a specific Committee. It is preferable for imported tissue to be stored in a licensed establishment where possible, and if so there is no requirement for National Health Service (NHS) REC approval to undertake research. However, if the premises where the tissue will be held are not covered by a Human Tissue Act license, each research project using the tissue will require NHS REC approval to comply with the Act (26).

If an application to a REC is required, the researcher should provide assurances to the REC that the tissue has been obtained ethically and in accordance with the requirements of the donor country, including specific consent for research conducted in the UK. Provided appropriate assurances are given, no further review will be undertaken of the consent arrangements in the donor country.

- In Sweden, according to the Act (2003:460) concerning the Ethical Review of Research Involving Humans (27), research that involves dealing with sensitive personal data may only be conducted if it has been approved subsequent to ethical vetting. Statute (2003:615) (28) concerning the ethical vetting of research involving humans states in section 2 that “when several responsible research bodies participate in the same project, only one of the responsible research bodies is to apply for ethical vetting. The application is to be submitted by the responsible research body that is mainly responsible for the research project in question”. Section 3 of Statute (2003:615) further specifies that “if the responsible research body is resident in a country other than Sweden, [...], the application is to be vetted by the board within whose catchment area the research will primarily take place”.

⁴⁵ The Act of the medical doctor profession and the dentist profession of 5th of December 1996 — unified text. Journal of Laws No 226, item 1943 with later amendments; 2005; the Act of Pharmaceutical Law of 6th of October 2001 — unified text. Journal of Laws No 53, item 533 with later amendments; 2004; the Regulation of the Ministry of Health and Welfare of 11th of May 1999 concerning the detailed rules of appointment, financing and the mode of operation of bioethical committees.

⁴⁶ For the UK, several laws apply. Moreover, policy responsibilities for the research ethics systems in each part of the UK (England, Northern Ireland, Scotland and Wales) vary. Ethical review of research by a REC is required where specified by the UK Health Department’s policy for research ethics review set out in the Department of Health’s Governance Arrangements for NHS Research Ethics Committees and/or by specific legislation for the UK as a whole or for particular countries of the UK.

⁴⁷ Human Tissue Act 2004, Part 2 Regulation of activities involving human tissue.

B. According to the Data Protection Directive

- Art. 4 of the Data Protection Directive states that each Member State shall apply its national provisions if the controller is established in that Member State and if the data processing is carried out in the context of the activities of that establishment. For all three Member States considered here (Poland, Sweden and the UK), the provisions imply a.o. notification to the supervisory authority⁴⁸ by the controller. So, if the researcher or research institute in Poland is considered the (only) controller, notification is to be done in Poland. Analogously, if the research institute in Sweden (UK) is considered the controller, notification to the Swedish (UK) supervisory authority is necessary.
- Say, for example, that in the above case the research institute in Sweden is considered the only controller. This would imply that only notification to the Swedish supervisory authority is necessary. However, the data were originally collected in Poland from Polish participants, and it is the Polish participants who have the right to be informed in their own language and via their customary political and cultural institutions. Would it therefore not make more sense if the notification was done in Poland?
- But who really is the controller?
 - According to art. 2 of the Data Protection Directive, the controller is the natural or legal person, public authority, agency or any other body which alone or jointly with others determines the purposes *and* means of the processing of personal data.
 - In the present example case, it is likely that the purposes and means of the project are decided upon together with all partners, meaning that for a joint EU project, there could be more than one controller (implying that notification is necessary in all of the Member States where the controllers are established).

⁴⁸ For Poland, the Act on the Protection of Personal Data (1997 — amended 2004) applies. The controller is “obliged to notify the data filing system to registration” by the supervisory authority, which in Poland is called the “Inspector General for Personal Data Protection” (art. 40 and 8, respectively). After registration of the file, the controller may start the processing of the data in the data filing system (art. 46.2). For the UK, the Data Protection Act 1998 applies. Regarding the application of the Data Protection Act, section 5 states that the Act applies to a data controller in respect of any data only if the data controller is established in the UK and the data are processed in the context of that establishment; or if the data controller is not established in the UK nor in any other EEA State but uses equipment in the UK for processing the data. Section 17 expresses the prohibition on processing without registration. Personal data must not be processed unless an entry in respect of the data controller is included in the register maintained by the Commissioner (section 17(1)). For Sweden, the Personal Data Act (1998:204) applies. Similar to the UK Data Protection Act, section 4 of the Swedish Personal Data Act states that it applies to those controllers of personal data who are established in Sweden. It is also applicable when the controller is established in a third country but for the processing of the personal data uses equipment that is situated in Sweden. Processing of personal data that is completely or partially automated is subject to a notification duty. The controller of personal data shall provide a written notification to the supervisory authority before the processing is conducted (section 36).

Conclusion

- Regarding the Additional Protocol, an independent examination by an ethics committee is necessary in each Member State in which any research activity is to take place. However, the conditions for examination may vary between countries and regions. Different ethics committees may adopt different standards (due to legal and cultural differences), which is not only confusing, but can also create the undesirable situation in which the ethical review process in one country is by-passed by obtaining data or samples in another country with less strict standards. In 2.3.1 (decision making at the start of research), further discussion on the functioning of ethics committees can be found, as well a proposal for steps for solutions to facilitate transnational research.
- Regarding data protection, notification is necessary in the Member State where the controller is established. A crucial question in transnational research projects is who will be considered as controller. Attention should be paid to the need for transparent processing which implies that the study participants should be able to be informed in their own language and via their customary political and cultural institutions.

2.2.4. Secondary use of data and/or samples

Example case 2.5. Study on DNA repair phenotypes

A research effort aimed at the development of new and the validation of new and existing DNA repair phenotypes. To this end, blood samples that had previously been collected from citizens to identify genotypes could be re-used for phenotyping. However, during the original informed consent procedure only genotyping was mentioned. For the researchers it was unclear whether a new consent was needed for the additional analysis.

Question

What needs to be done in order to continue with the additional phenotyping analysis? Is a new approval from an ethics committee required? Is it necessary to go back to the individual study participants to obtain a new consent and is likewise another notification to the national supervisory authority needed?

A. According to the Additional Protocol of the Oviedo Convention

- The Additional Protocol specifies conditions for a research project designed for a specific purpose and does not foresee specific guidelines for the re-use of data and/or material. However, the Additional Protocol does treat new developments *during* a research project. Art. 24 foresees that scientific developments or events arising *in the course of the research* may justify the re-examination of the research project by an ethics committee. The purpose of the re-examination includes the establishment whether study participants need to be informed of the developments or events. The consent form may need to be modified or it may even be appropriate to seek renewed consent.

- For the re-use of data and material from previous research projects, we refer to Rec(2006)4 on research on biological materials of human origin, which builds gradually on the principles of the Oviedo Convention and its Additional Protocol. The essential provisions of Rec(2006)4 are explained in 1.2.3.
 - Basically, Rec(2006)4 states that for further use of identifiable biological materials and data, research should only be undertaken if it is covered by the informed consent.
 - If the original consent does not include the purpose for the re-use of data, all reasonable efforts should be made, both in terms of means and time, to re-contact the participant to request new consent.
 - If re-contacting the participant is not possible despite reasonable efforts, these biological materials and data should only be used if the proportionality principle and the wishes of the participant — if expressed and documented — are respected and if no possibility exists of using material for which consent has been obtained.
- Essential questions with respect to the example case are therefore whether the additional analysis is to be considered a new development or not and whether the original consent does include the purpose for the re-use of data or not. In other words whether the phenotyping purpose can be considered compatible with the originally formulated purpose. If the additional phenotyping is considered a new development or event arising *in the course of the research* this justifies the re-examination of the research project by an ethics committee and this will define if study participants need to be informed of the new analysis, if the consent form may need to be modified and if it is appropriate to seek renewed consent. If the original consent does not include the purpose for the re-use of data, all reasonable efforts should be made to re-contact the participant to request new consent. If such is not possible, the recommendations formulated above (Rec(2006)4) should be considered.

B. According to the Data Protection Directive

- The essential question for the Data Protection Directive is whether this additional analysis is a new processing or whether the phenotyping purpose can be considered compatible with the originally formulated specified, explicit and legitimate purpose (i.e. genotyping).
- Art. 6.1(b) of the Data Protection Directive states that “*personal data must be collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes*”.
- At first instance, it is the controller⁴⁹ who decides whether the phenotyping purpose can be considered compatible or not with the originally formulated specified, explicit and legitimate purpose (i.e. genotyping).
- When the new processing is deemed compatible with the original purpose and the information and informed consent given to the study participants implicitly presumed the new analyses, no further steps need to be undertaken.

⁴⁹ For the definition and the identification of controller, see 2.2.3.

- If the new purpose is not compatible with the original one, art. 6.1(b) of the Data Protection Directive states that “*Further processing of data for historical, statistical or scientific purposes shall not be considered as incompatible provided that Member States provide appropriate safeguards*”. These safeguards must in particular rule out the use of data in support of measures or decisions regarding any particular individual (rec. 29). In principle, the data subject must be granted the normal rights to information. Exemption from this need to provide information is possible, if providing it would be impossible or would involve disproportionate effort (art. 11.2). The number of study participants, the age of the data, and any compensatory measures adopted may be taken into consideration when allowing the exemption. The national laws define in more detail the conditions for these exemptions⁵⁰.
- It is also up to the controller to decide on the “compatibility” and on the “disproportionate effort”.
- One could argue that the problem of secondary use may be evaded by adopting a longer-term vision before collecting data or samples and not formulating too narrow a research proposal in the informed consent form, thereby expanding the range of compatibility purposes. This may, however, create the problem of lack of specificity of informed consent.
- Steps for facilitation could be found on the level of collective decision-making about the re-use of data and materials, for which no new consent exists, with a vision of balancing the rights of the individual with the need for scientific progress. Legislation should offer guidance such that research is practiced following deontological rules, taking into account cultural, social and political arguments. Suggestions for elaboration of these steps for improvement are presented further in the concluding remarks (3.2.).

Conclusion

- According to the Additional Protocol, a new research proposal or new developments *during* a research project may justify the re-examination of the research project by an ethics committee. The purpose of the re-examination includes the establishment whether study participants need to be informed of the developments or events. According to Rec(2006)4 on research on biological materials of human origin, further use of identifiable biological materials and data, research should only be undertaken if it is covered by the informed consent. If the original consent does not include the purpose for the re-use of data, all reasonable efforts should be made, both in terms of means and time, to re-contact the participant to request new consent.

⁵⁰ In the Belgian Privacy Law for example, the compatibility is assessed taking into account relevant factors such as the ‘reasonable’ expectations of the data subject, or if further processing is provided for under a legal or regulatory provision. Other elements that may influence the assessment of the processing operation’s compatibility are the nature of the data, the (legitimate) interest of the controller, the potential risks for privacy, and the extent to which the data subject was informed in advance of the use of his data and/or has given his permission.

— Processing conditions of the Data Protection Directive require that personal data must be collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes. It is up to the controller to decide on the compatibility of purposes when personal data is further used for scientific research. The further processing of data for historical, statistical or scientific purposes facilitation is foreseen in the sense that an in principle incompatible processing may be considered as compatible provided that Member States provide appropriate safeguards. At the same time exemptions are allowed with respect to the rights to information of the study participant, if providing such information would be impossible or would involve disproportionate effort (art. 11.2).

Example case 2.6. Knowledge database on molecular epidemiology and cancer (MEC)

A knowledge database on Molecular Epidemiology and Cancer (MEC) was set up in Italy. The aim of this MEC database is to foster collaboration and facilitate future studies on the data in question, among other pooled analyses. The database was developed based on data (no samples!) received from several research partners (currently 15) and is intended to be available and/or expanded in the future. From a scientific point of view, the following conditions and possibilities were desirable, but proved problematic from an ethical and legal perspective:

- *The database was planned to contain personal data.*
- *It implied the unforeseen secondary use of data for new research.*
- *It implied the unforeseen transfer of data to other research groups.*
- *It implied research in several unforeseen countries.*

The design was considered too complex to handle given the current legal constraints for i.a. re-using data in a transnational setting. Finally, the MEC database has been constructed based on unlinked anonymized (i.e. completely anonymized data where identification is no longer possible) information.

Question

In the current example case, data were completely anonymized. If it would be preferred to keep the link for identification, what would be the legal requirements to comply with? (Note: We consider in this example case the problem of secondary use of data in a transnational context. The aim is not to deal with the setup and use of a biobank.)

In contrast with Example case 2.6. we are dealing here with a clear case of secondary use of data, since the construction and distribution of the database and the use of the data for pooled analysis were not foreseen in the objectives of the initial studies for which the data were collected, and were not foreseen in the informed consent.

A. According to the Additional Protocol of the Oviedo Convention

- As mentioned above, the Additional Protocol does not foresee specific guidelines for the re-use of data and/or material. However, Rec(2006)4 on research on biological materials of human origin defines conditions for situations where the original consent does not include the purpose for the re-use of data. Appropriate steps might be

- necessary in each country or each research institute contributing to the database. The details of the procedures may differ according to national legislation.
- Whether personal data has been anonymized or not, this has no impact on the applicability of the requirements of the Additional Protocol (see also Example case 2.3. on anonymization).
 - Ethical approval is required for the setup of the database itself.

B. According to the Data Protection Directive

- For completely anonymous data the Data Protection Directive is not applicable.
- If identifiable data would have been included, the same conditions apply as the ones described in the example case above. This means that several steps are to be taken, but that overall the procedure may be less demanding than the procedure for a completely new purpose as we are dealing with a secondary use for scientific purposes. However, the need for additional steps has to be assessed in each country or each research institute contributing to the database. Notification of the setup of the database itself is also required.

Conclusion

- This example case treats secondary use in a transnational context. It entails a combination of many aspects that have been identified as “problematic” in the previous cases. This includes *i.a.* the uncertainty whether the process of anonymization itself is considered as a processing that falls under the Data Protection Directive and thus the need to inform study participants about the anonymization process and further use. Also, the diverse interpretations on the need for approval from an ethics committee in different Member States come into play, including the differences this implies in cultural and political traditions with respect to the protection of the rights of the study participants. Certainly in the case of transfer of *unlinked anonymous* data, the value of this multiplication of efforts may be questioned.
- The issue of reusing data can be a very complex one to tackle — also in terms of effort, time and costs — under the current regulations, especially if identifiable data is to be used. Nevertheless, a strong call exists for more re-use of data (29). Not to re-use available data implies also that new samples will be needed and that volunteers will be bothered again. When volunteers donate data and samples with a wish to contribute to the interest of all, the material should be maximally used.
- The use of anonymous data might make the procedure lighter because the processing no longer falls under the scope of the Data Protection Directive. However, from a scientific point of view, and certainly in the field of environmental health and epidemiology, anonymization of data may lead to substantial loss of meaning of the results and of scientific opportunities, since *i.a.* possibilities for retrospective or prospective linking of the data are eliminated.
- Overall, it is shown that databases provide a powerful and essential resource for health research and that identification of individuals may be needed for several reasons: linkage within a database; linkage between databases; ensuring comparisons are

meaningful; ensuring completeness of recruitment; investigation of social factors; analysis of trends over time; and assessing the applicability of primary research findings (11). At the same time, when unexpected results would prove to be of relevance for the data subject, identification is paramount for getting information back to the study participant.

- If renewed consent is needed, the risk is real that not for all data renewed consent will be obtained, often for practical reasons rather than because of a real wish of the study participant to refuse participation. This may lead to a strong bias and to results that have lost much of their significance.
- Although it cannot be denied that study participants have the right to full information on the purpose, risks and benefits of the proposed study, too stringent a regulation may restrict access to precious data and impede possibilities for increasing knowledge with a strong public interest. Participants' material is often not available to other scientists for verification of results or for building further upon the findings, consequently delaying or hindering scientific progress. The scientific community recently pointed out this lack of synchrony between the act of research and the ethics relating to a field of study and called for action (30).
- Given the benefits for the general public of research activities, methods need to be found to ensure the optimal conditions for research while meeting legitimate concerns about individual privacy and confidentiality. Discussions on facilitation of secondary use in the environmental health domain should take into account the ethical obligations to maximize the potential benefits of studies to society, and the minimal risks compared with those that may be associated with clinical trials and other experimental studies.

2.3. Decision making processes and communication in human biomarker studies

Decisions have to be taken at several instances throughout a human biomarker study: from designing the proposal and submitting it for ethical scrutiny to anticipating ethical dilemmas that might arise whilst research is being planned, conducted and reported. Choices need to be made on study objectives, study population, chemicals to measure, treatment of study participants and their personal information and results, interpretation of study results, communication of results to individual participants, to policy-makers and agencies, and to the media and the general public. Interdisciplinary collaboration between environment and health scientists, ethicists, lawyers, social scientists will bring the entire process to a successful end as well as adequate communication to stakeholders as policy makers, patient or other social groups, industry and lay people.

As illustrated by the next example, the decision making processes require adequate communication and the communication process may considerably influence decision making.

Example case 2.7. Study on environmental triggers of type 1 diabetes

The purpose of a large prospective study is to identify environmental factors causing type 1 diabetes. To this end, the enrollment of 100 000 newborns is envisaged. At birth they are tested for a specific genetic factor assumed to indicate a higher risk for developing diabetes later in life. Buccal samples from the baby's mouth or cord blood are genotyped to identify the 2.1% of unrelated newborns who carry the high-risk genotype for type 1 diabetes. Parents are informed of the results. Children with the high-risk genotype are followed up for 15 years through the analysis of blood tests, questionnaires and stool samples at regular intervals.

The blood samples are tested for the earliest signs of diabetes development. This approach allows psychological preparation and the formation of preventive attitudes early on and to avoid ketoacidosis at disease onset.

The study started recruitment in 2001 in accordance with all national regulations and obtained the necessary approvals. In spring 2007, following a complaint from the physician of a parental couple with a high risk child the study came in the middle of a controversy at national level. A national newspaper stated that the study is performing genotyping against the Biotechnology Law. By the end of the year, approvals for the study were withdrawn and it was decided to stop all new recruitment for genotyping.

This example case shows that it is most fragile to communicate to people about their and their relatives' health. Ultimately, it seemed that the parents were not well enough informed at the time of recruitment on the impact receiving and assimilating information about a child being at high risk for type 1 diabetes and starting the follow up procedure could have. This undermined their trust and willingness to be involved and led to the events that had such a devastating influence on the whole project.

In the following section we analyze the decision making processes in succession from the start till after a research project, at collective as well as at individual level. A major question to be dealt with is: who decides upon what, for whom, why, how and on which grounds? We will mainly concentrate on the following matters:

- the role and functioning of ethics committees;
- the tension and balance between the individual and societal interest;
- the possible consequences of the requirement of informed consent;
- the impact of the professionalism involved, of the experience and the formal role of the researcher on the nature of the practice and the perception by the study participants;
- the influence of scientific uncertainties⁵¹ on the decision making process.

At the same time an attempt is made to go into some aspects of communication. procedures and their possible pitfalls throughout the whole duration of a research project.

⁵¹ E.g. when dealing with biomarkers which are not fully validated, or when the results have no informative value at an individual level.

2.3.1. Decision making and communication at the start of research

2.3.1.1. At collective level

Decision making: Research ethics committees

Research ethics committees (RECs) are charged with the task to ensure that research proposals are conducted with adequate protection of safety and wellbeing for human study participants. Their impact cannot be overestimated and without their approval, public health and medical science cannot proceed. The tasks and functioning of RECs are established by the Oviedo Convention and its Additional Protocol. These guidelines do provide a formal basis for the ethical review of research projects (see also 1.2.2). However, RECs cover a broad realm and also look beyond the formal aspects of these guiding documents and/or national laws. RECs embody and have the authority and the moral imperative to act for the good of study participants and their communities. They are well placed to play a major role in striving for the right balance between the protection of the study participants and the progress of research with an impact on community wellbeing and can set the conditions that allow such an equal, simultaneous and maximally possible progression for both these components.

Obviously ethics committees will weigh ethical principles against their reference regulations, which in most cases will be national regulations. In addition, equally talented groups can come to different conclusions when faced with identical problems, whether in a REC or a public policy discussion. Even stronger, the same group can deliver different answers to the same question on different occasions. This is not surprising if one recognizes that difficult decisions do not typically address “right versus wrong”. Difficult decisions invariably result when the choices involve “right versus right” (31).

In what follows, issues are highlighted that may affect the mission of RECs. They relate to the composition of the RECs, their procedures and their legal standing, in a national as well as in an international context. Suggestions for steps for improvement are proposed.

Composition of Research ethics committees

Numerous ethics committees exist, at institutional, regional, national and supranational level, and they are known by various names (institutional review board, ethical review panel etc.). Because of the key position of ethics committees, much importance is attached to their judgment. However, there is little guidance on how these committees should be organized or constituted and more and more criticism is being expressed about (i) the relatively haphazard organization of RECs; (ii) the lack of diversity in voices that are represented and (iii) the professional competence of RECs members.

A study about the demographic and professional characteristics of members of RECs in the Netherlands concluded that the membership of local committees still over-represents whites, medical researchers and those affiliated with the sponsoring institution. It was moreover discovered that 77% of committees do not have any member who is a professional ethicist and that laypeople are woefully under-represented (32). Another study examining whether those doing ethics consults in US hospital ethics committees are “competent”

to assume their role showed that formal bioethics education or experience was lacking for many ethics committee chairs, most ethics committee members, and approximately two-thirds of the individuals designated to perform ethics consults (33). Specifically for public health research, an additional problem regarding the membership of RECs is the fact that RECs are often composed of people who are experts in clinical situations, while in fact people experienced in the public health domain may be more apt to evaluate related projects. The degree of variation in composition suggests that there is limited uniformity in the purpose of RECs and their decision-making across Europe (34).

"When I submitted the application for an ethical permission for research in the context of a large international public health project where samples were collected abroad, but for which we would do part of the analysis, the national research ethics committee in its first response

- 1. asked for an insurance document which is common for clinical research.*
 - 2. asked to devise information leaflets for the study participants and informed consent forms. However, these were already included in our original application. We speculate that a foreign language issue was at play here, with English usually not being a problem, but material written in other languages causing difficulties.*
 - 3. asked for information on the inclusion and exclusion criteria of participant recruitment.*
- We replied that our institute did not do recruitment. Even though in the end they accepted our arguments, this took quite a while, causing us to lose precious time".*
-

Procedures and legal standing of Research ethics committees

Besides the issues related to the composition of RECs, several other problematic aspects can be discerned. Specific concerns expressed by researchers include excessive protocol dwell time, lack of accountability and of appeal mechanisms, ineffective communication with investigators and wide variations in decision making between different committees (35). Ultimately, for some researchers, RECs seem for most of all to impose incredible burdens on research, also creating bureaucratic nightmares or hindering progress of research.

Despite the international guidelines and legal instruments that define RECs and their role, the legal standing or other force of all these instruments varies from country to country, ranging from advisory to legally binding (approval required) (36). According to the Oviedo Convention and its Additional Protocol, each research project has to be submitted for independent examination by an ethics committee. These guidelines are however not ratified, nor implemented by all European Member States and lead to variation of requirements in national laws, many of which originated before the publication of the Oviedo Convention and are mainly inspired by the Helsinki Declaration involving less focus on recent new developments and trends in biomedical research.

A study comparing the requirements of RECs in 11 European countries for a non-invasive interventional study illustrated the many variations. A trial of a leaflet intended to improve older patients' involvement in general practitioner consultations was deemed not to require ethical review in Austria, France, Germany and Switzerland. In the UK, Belgium and Slovenia, however, the proposal had to be reviewed by full committees, some of which required multiple copies of the application and an estimated five days of preparatory

work (37). It has been mentioned that the burdens imposed by ethics review might be justified if it could be shown that, on balance, it does more good than harm to patients' interests. However, certainly in a clinical context, delays may have important consequences for participants (38). But also in environmental health research, the process of ethical review should not unnecessarily delay the research.

"Multiple ethical permits for collaborating institutions cause extra work and time delay when the institute collecting the samples has already obtained an ethical permit".

"It has been hard for us to find out if we need extra ethical permission for the analysis of samples that were collected (with permission) in other countries. The situation seems to be different for different countries".

"The 'rules' appeared to require us all to demonstrate that ethical approval had been obtained, not only in the institution of origin of the human material, but also from all the recipient organizations, despite the fact that there was no data protection issue and, as far as I can see, not any ethical issue either. I feel that in these circumstances the ethics system is too inflexible and bureaucratic. Where the use of human material is for research validation purposes only, with no exchange of patient data, it should be possible to bypass the cumbersome ethical review processes, or to comply with them much more simply".

It can be questioned to what extent a procedurally and juridically inextricable tangle affects the protection of study participants and scientific progress; not only do the current procedures risk the waste of valuable time and resources, the situation can also lead to a "shopping" phenomenon, where a project proposal is repeatedly being submitted to several distinct committees until approval is obtained.

Steps to solutions

Gradual improvement of the ethical review process may be achieved through actions undertaken at the levels discussed above: the composition of RECs, the procedures they adopt and their legal standing. In addition, at transnational level, approvals for transnational research projects deserve to be facilitated in favor of research progress (cfr. 2.2.2, Example case 2.4).

Related to the composition, RECs should be properly equipped to make a sound judgment on a study proposal and several disciplines may be required in view of judging the quality and scientific value of a study proposal and the risks for the study participants. Overall, RECs should at least include or consult scientific experts in their specific field of research (e.g. public health experts). Notably, there is increasing interest on the part of ethics committee members in the scientific validity of proposed research (39). The rationale is simple: if the design of proposed research does not offer the prospect of yielding objective and scientifically valid conclusions, there is no justification for either the expenditure of resource or subjecting participants to even *de minimis* risk. Research protocols that are fundamentally flawed cannot be justified in the light of the principles of beneficence and veracity. A recent review on

proposed research using pesticides makes the point well in terms of accepting research results for rule-making. “Any study that is not scientifically valid — for example, does not include a sufficient number of participants to provide statistically valid answers to the questions under investigation — must not be considered in standard setting” (40). Bioethical principles go further and support the argument that such decision should be made before the research is initiated. Poorly designed studies involving human subjects should not be undertaken

Informed medical judgments are also needed in order to make a reasonable assessment of the risk/benefit ratio for the study participants. These are matters on which medical experts, rather than layman, are properly qualified to judge. For studies including children, the expertise of pediatricians should be included (41). Some other disciplines can also be very helpful. For instance, in Poland, a lawyer and a priest are included in the committees in addition to doctors, pharmacists and ethicists. Furthermore, laypeople should be involved as well. It has been suggested that if nothing else, lay members can help create clearer consent forms and encourage researchers to a better job of explaining the risks and benefits of participation to potential participants (32). A committee could therefore consist of a fixed core group of members while other people with a specific expertise can be invited on a project by project basis.

Concerning the REC procedures and legal standing, at national level the issuing of guidelines with a view on uniform or at least consistent procedures and decision making processes could be executed by a central ethics committee. Besides, national and local committees could fruitfully collaborate by exchanging expertise and guiding decisions. Not only a highly qualitative advice should be given on the conditions to fulfill for ethical acceptability of the proposal, but also should a follow-up of the research project be organized that goes beyond the delivery of research results. Reflection on the impact of the results on (parts of) society and on the translation of results into policy is also needed, and could, besides social and political scientists, already be incorporated within the RECS. With a view on the right balance between the protection of the individual’s right and the progress of scientific research, RECs should achieve a moral authority that clearly outstands any legal standing. By taking into account the broader view of the RECs functions — including the strong emphasis on the needs and concerns of the general public as well as the individual study participants the research community will only be rewarded on the long term. With a view of a transparent decision making process, RECs should clarify their advices as far as possible. In case of disagreements, and in order to ground REC decisions and build up experience and expertise, both RECs and researchers should document their arguments.

For transnational research, the problem arises that national ethics committees weigh ethical principles against their reference regulations, which in most cases are national regulations. However, since regulations may differ from country to country, contradicting requirements may originate, creating a confusing situation for the applicants. One possibility to overcome this problem is the establishment of a Research Project Ethics Committee, at the level of the “European research space”. It could consist of a permanent staff and an

ethics committee with ethical subcommittees consisting of experts in the field for specific research domains. The permanent staff should survey consistency in the advising or decision making processes of the subcommittees and should report periodically to international institutions such as the European parliament and the Council of Europe. This Research Project Ethics Committee could also have the authority to provide ethical approval for multi-partner EU research projects in collaboration with the REC at local level. It should ground its decisions and researchers should have the possibility to appeal.

This centralized approach is opposite to what is issued in the Oviedo Convention and its Additional Protocol, requiring submission of a research protocol to an ethics committee in each state in which any research activity is to take place. However, in the particular case of transnational research projects, a central approach while still articulating a role for domestic RECs may bring about more consistency and uniformity, more efficiency, less paperwork, less multiplication and a more equal protection of study participants throughout the EU. At the same time, to close the gap between the international and the local context, local ethics committees can review local needs and guarantee follow-up and monitoring. Indeed, the importance of local ethics committees may not be underestimated, since possible differences in the praxis and sensitivities originating from differences in historical, religious and political background and legal regulations need to be taken into account. A process towards more uniformity will therefore not be an easy one (42), and might also not be the goal to strive for. In contrast, consistency is a necessity, so that ultimately the same protective level is achieved in every Member State.

The idea of a European Research Project Ethics Committee may be enforced by the success of similar small scale setups, such as the functioning of the Ethical Review Panel of ECNIS.

Example case 2.8. ECNIS ethical review panel (ERP)

Ethical review is intended to ensure that possible risks for participants are recognised and managed by ECNIS researchers and that all ECNIS research is conducted following the highest ethical standards, in accordance with European socio-ethical values To pursue this aim, the ECNIS Ethical Review Panel (ERP) functions as an advisory platform that develops and maintains procedures for ethical review for joint international research projects and at the same time promotes discussion of social, legal and ethical issues. The ethical review process takes place in an atmosphere of transparency, openness to dialogue and confidentiality.

The ERP is challenged to support researchers when novel ethical questions in the field of interface of environmental cancer, nutrition and genetics arise.

Relationship between Research ethics committee and Data Protection Authority

Besides the obligation to get the approval of an ethics committee, the national Data Protection Authority (DPA) has to be notified before the start of each research project⁵². Despite the many parallel requirements (see 1.2.2) between RECs and the DPA, there exist in general no regular contacts between these two institutions.

⁵² Article 18 of the EU Data Protection Directive 95/46/EC.

The REC and DPA may refer to not identical constraints, ultimately issuing in possibly contradicting advice on certain matters thus confusing researchers. For example, disagreement can exist about the right to know. In the practice, RECs may find it unethical to disseminate results to individuals in certain situations and so advice against it. This can be the case for instance when there is no clear interpretation of the results, when there is no consensus or when there is a chance that the participants will ask questions regarding their health that cannot be answered. However, the EU Data Protection Directive 95/46/EC and the DPA focus on the right to know.

On the other hand collaboration may allow benefiting from each others knowledge. In contrast to the REC, for instance, the national DPA does not review the scientific aspects of a research proposal. However, scientific correctness is a prior condition to the collection of samples. It has to be noted however, that in some cases RECs might neither master all knowledge about the latest evolutions in science and technology as discussed above.

In the case of secondary use, the DPA guarantees transparency in the use of the data, while the ethics committee can judge the usefulness and relevancy of the proposed secondary use of data and/or samples. Also, in balancing individual with common interest, it has to be noted that the Oviedo Convention and its Additional Protocol focus primarily on the wellbeing of the individual, while the Data Protection Directive differentiates between the individual and substantial public interest⁵³. The balancing between different interests should also be taken into account by ethics committees.

In general, it can be stated that the lack of interaction between the REC and the DPA leads to a potential loss of expertise and knowledge for both institutions and of precious time and resources for researchers. The arguments mentioned above strongly plea for a reciprocal relationship between both institutions, ultimately facilitating review by benefiting from each other's competences. This would be an important step to consistently and positively reconcile privacy and scientific needs.

Communication

Good communication of a general description of the research project at the collective level is of overriding importance for a person to consider participation at all. Good accessibility of that information and additional clarification if needed is crucial at this point. If it is too difficult for a potential study participant to get proper information, he will easily give up. This does not only result in the loss of one potential participant for the current research project, but possibly also jeopardizes any future participation of this person. The form in which information comes can take various shapes. Information can be spread generally — undirected — through e.g. flyers, posters or websites and the organization of information sessions. In addition to this, an info line can be set up to answer questions that still exist or arise afterwards. When a particular population or community is targeted, a more directed approach can be adopted.

⁵³ See also 1.2.1.

The Example case 2.7. on diabetes mentioned above shows that it is most fragile to communicate to people about their and their relatives' health. Other experiences also show that the communication aspects of research are still very much overlooked or underestimated when it does not relate to communication towards science. One major cause of this is lack of time. In a study comparing three organizations undertaking environmental health research it was found that researchers who actually did work closely with community partners found that it took a great deal of time, often time they could ill afford. Since building community partnerships is time consuming (e.g. because it requires bridging social divisions) and science funding depends on successful grant applications, the use of time for this kind of communication is not perceived as "production". The term "grant plantation" was used to describe the drive for knowledge production disconnected from investment in social relationships (43). In academia, the publish-or-perish demands can put a serious time constraint on researchers, and unfortunately in cases where time is lacking, communication outside the scientific world may be the first to be dropped.

Lack of time is not the only reason why communication not directed at the scientific world is being given so little attention. In practice, that communication aspect of research is often interpreted narrowly as the communication during the individual informed consent procedure. Yet, communication in (environmental health) research entails so much more; it is not just limited to the informed consent procedure, but stretches out over the recruitment, research and follow-up phases and plays at the individual as well as the collective level.

To deal with these issues, first of all the importance of good communication should be appreciated. It should be recognized that it really is worthwhile to invest in good communication, not only for reasons of respect for the study participants and the tax payers that ultimately provide the necessary funding. Researchers obviously need study participants for their projects or they will not have research at all. This need has to be seen at a longer term as well and therefore requires long-term investment. Indeed, using poor ad hoc solutions for current research projects does not only risk losing volunteers for that specific project. It is very likely that the person who withdraws because of ill communication will be very hesitant regarding participation in any research again. Moreover, by word of mouth the message will easily spread to other people, eventually losing other potential participants as well.

Since time is money and good communication can be time consuming, and more importantly, because communication needs specific skills and expertise, it is advisable that the communication aspects of a research project are dealt with by a person with expertise in the field. Similar to the budget calculations for sample analysis, investment in hiring a good recruiter may result in the obtainment of samples associated with qualitative data on a prolonged basis. A long term vision should therefore be adopted in staffing policy.

For human biomarker studies, appropriate communication strategies should be set up for each research project. They should take into account the parties involved (such as individual study participants, the community, policy makers, the media, researchers and field workers),

the type of biomarker used and the specificities of each research. Moreover, they should address the question what is to be communicated to whom in which manner (how to transfer a message with a scientific and technical content to an audience with no background in science?) and at which moment in time. For example, policy makers need very specific short messages in due time, so that they can prepare for an appropriate response. To avoid unforeseen problems at any moment during the research it is important to establish these communication strategies well in advance of the start of the project. This will also generate an increased feeling of trust in the correct reporting of results according to a procedure that was established *in tempore non suspecto*, minimizing undue influences on communication.

Attention should be paid to also provide satisfactory information about a particular kind of research to the clinical professionals, who are often not skilled in the field of public health research, but to whom their “patients” may turn to in order to seek advice on participation or on results.

On a wider scale or transboundary level, appropriate communication strategies need to take into account that certain situations can be of transnational importance and thus require a consistent approach. Depending on the nature and the seriousness of the results of a research project, an additional counseling service or info line can be set up.

Finally ethics committees can point to the importance of efforts for thorough and honest communication with all stakeholders while they should also be able to act against current productivity pressures of the research system. Indeed, trust and confidentiality in research are key conditions for voluntary participation. If potential research participants are involved in an honest and transparent approach, if they feel respected and free in their personal decision and if they are confident that they are adequately protected against any possible misuse of personal data, it is highly likely that they will, being convinced to contribute to the improvement of collective health, unequivocally be motivated to participate. Even more, such participants may be considered as the best incentive for also engaging their colleagues, friends and relatives in research proposals, which may only be beneficial for biomarker research in general and thus possibly contribute to the wellbeing of the whole community.

2.3.1.2. At individual level

Recruitment — value of informed consent

Informed consent is an autonomous authorization by an individual regarding participation in a study. It is a process between the recruiter and a study participant that must contain an information component and a consent component.

Thinking about informed consent within biomedical research mainly accelerated with the publication of the Nuremberg Code in 1947 (44). It emerged from the World War II trials and abandoned the classical paternalistic approach of scientific research and medical interventions in humans. Instead, it adopted an individual oriented perspective — with emphasis on autonomy and self-determination — by asserting that the

voluntary consent of the study participant is necessary under all circumstances of biomedical research. This way, assurance should be provided that study participants are neither deceived nor coerced.

Both the Oviedo Convention and the Data Protection Directive have a strong focus on informed consent (art. 5 and art. 7, respectively). In juridical terms, the principle of autonomy is based on the assumption that by disclosing adequate information to the study participant, he or she can make a free decision. Study participants are nowadays encouraged to actively participate through a two-way dialogue during informed consent (29,44). To meet the principle of autonomy the standard for informed consent is set to “explicitness” and “specificity”. Consent should be FREE, written, signed, documented and contain information on a.o. the aims of the research, the sources of funding and the benefits and potential risks.

The requirement of informed consent raises certain problems and questions at the level of the individual study participant as well as at the level of scientific progress. Though the importance of informed consent is undisputed, its prerequisites of explicitness and specificity are difficult to comply with. Explicit consent, for example, always relies on a background understanding that remains implicit. The longest and most complex information gives no guarantee for a complete understanding of the research objectives and procedures and its impact on the study participant. It always remains unsure whether a study participant has profoundly understood the information he or she received. Shorter and more readable forms could even improve the participant’s understanding. Moreover, in the context of international research projects, more and more challenges are presented by linguistic barriers and (even within one country) by cross-cultural applications.

One should be aware of the different interpretations of the concept of autonomy in different cultures. For example, in research on gene-environment (exposure by way of food intake) interactions, there is a growing interest to integrate different ethnic groups, since they represent different dietary habits and possibly different exposures. In Western society, informed consent is originally based on the principle of autonomy. But not all cultures favor the model of decision-making in a very individualistic mode. How are we going to approach ethnic minorities with our usual tools for recruitment? Some questionnaires contain questions that are extremely sensitive to certain minorities, and sometimes the cultural background is such that the woman is not allowed to participate in a medical examination or even in filling a questionnaire. The meaning of informed consent is certainly not the same for all the ethnic minorities. If we are unaware of variable expectations we may advertently transgress the cultural integrity and personal dignity of some of the minority study participants despite well-meaning efforts to obtain informed consent in the usual manner, ultimately contravening in the process the very principle of respect for persons that the doctrine of informed consent was meant to protect. A way of promoting recruitment in non-western cultural minorities is to ask support from a representative of this specific minority group, as is illustrated in the following case example.

Example case 2.9. Obtaining fathers' blood and sperm samples for comparison with mothers' and babies' blood samples in the context of a paternal impact study

This was not a straightforward process. Since Moslem men were to be involved, permission had to be sought from religious leaders. This involved consultations with the Imam and the Mufti. A person from the Council of Mosques felt that the men would not agree. After an extensive correspondence and various telephone conversations, the Mufti agreed that he could be contacted if fathers were to agree to provide a sperm sample and needed guidance. In fact, he provided a letter which could be sent out with leaflets when asking fathers to participate. The provision of sperm is known to be a quite common taboo subject for Moslems.

Another pitfall that can be identified is the status of the person providing information. For example, the authority of a medical doctor shapes his, though trustful, relationship with the participants and may not be underestimated. This implies a degree of power inequality that prevents a patient to refuse participation in a study. In this context an explicit instead of implicit consent in research practice often boils down to formal documents that will reduce later uncertainty about the limits of the consent given and may forestall subsequent dissatisfaction, complaint or litigation. It may be considered problematic to what extent a formal consent issuing out of a context of power inequality is really autonomous and if such a procedure really safeguards the dignity and integrity of the participants.

Finally, it seems that in modern day society the balance tilts over very strongly towards the individual, while in a public health context society's interests should be taken to heart as well. Obviously it is very important to protect the participants participating in a research study. An appropriate balance should be struck between these possibly conflicting interests of individual autonomy and public health. One way to go about would be to establish a moral framework with a more important role for social justice and solidarity. The notion of institutional solidarity is based on the idea of reciprocity — the idea that being a community member creates a responsibility towards other members and an obligation to contribute to their needs — but also on the idea of equity in treating citizens. Both ideas can create a strong moral basis for the state to justify consent procedures which diverge from the classical standard of prior, free, informed and explicit consent (45).

To what extent, in a public environmental health context is individual consent always a necessity? Evidently people can not be obliged to donate samples for health and environment studies. Exemptions on the need for informed consent relate mostly to secondary use of samples and related data that were previously obtained for other purposes. As discussed earlier, these exemptions exist already in current legislation (see 1.2) and foresee in such cases alternative ways of protecting human dignity: approval from REC and DPA and transparency through a public register of data treatment. An additional way can be the involvement of representatives. For example, in the case of specific groups of individuals like ethnical minorities (see also case above), employers or patients suffering from a certain affection, their representative bodies (like patient groups) could be asked for support to request informed consent at individual level. Such a procedure may not only increase societal approval, but may also sustain policy impact.

Communication at recruitment

An effective communication at recruitment is strongly connected with the engagement of the recruiter to obtain an authentic consent. For an authentic consent, ideally, the study participant should understand what the research is about and should feel absolutely free in his decision to participate and should feel equal in his relationship with the recruiter. He must feel understood and should receive answers to his questions at his own level of comprehension. It should be emphasized that communication and the informed consent procedure are intensive, time-consuming two-way processes through which the study participant will gain insight in what the study concretely entails (46).

However, 100% authenticity is not feasible. Unfortunately, information is never 100% complete. Moreover, each actor in the process has his own personality, intellectual properties and personal history. Each recruiter is limited by his own degree of empathy and skill to inspire trust and confidence. The result of a recruitment conversation depends on the complex interaction between two personality types. It is very important to avoid exclusion of certain personality types, not only out of respect for individuals, but also to reduce possible sampling bias and its possible consequences for the results. Indeed, personality type, biological factors and psychological and social experiences are interrelated; excluding certain personality types may therefore hinder the representativeness of the sampling strategy. Training and education of the people providing information is thus paramount — although frequently neglected — and will eventually lead to substantially higher inclusion rates, which will only be beneficial for science.

Example case 2.10. Recruitment of mothers for a perception study

Mothers who have consented to donate the placenta after birth for studies on carcinogen transfer through the placenta (placental study) were invited to participate anonymously in a perception study (47). A nurse specialized in prenatal care carried out the interviews pertaining to their perception about i.a. informed consent, comprehension of research ethics etc. At the pilot interview study, it became apparent that the recruitment process was not optimal: six out of nine mothers refused to participate. The mothers were asked for participation by a nurse not involved in the placental study itself. According to the modified strategy for the actual study, the nurse carrying out the interviews was closely involved in the placental study, implying that she was acquainted with the mothers and could answer much more questions about the study in detail. Consequently, the refusal rate dropped so that from the following ten mothers asked to participate, only one refused (48).

Withdrawal from research

Legislation concerning research with human subjects states that the right to withdraw from a study at any moment should be included in the informed consent procedure and should be well explained to potential study participants, as well as the possible consequences of withdrawal: what will happen with samples or data already collected?; will withdrawal have consequences for health status or health care?, etc. No one will dispute the necessity of the right to withdraw. Nevertheless, however correct the ethical and formal juridical principle, one should be aware that at the same time the proposition of this

right at recruitment may not be used (by the recruiter) to convince the study participant to participate. In the long run, this may be counterproductive. With a more substantial basis for commitment the participation of the study participant will prove much better for science: if the study participant is not truly committed to his participation in the study, it is probable that he withdraws at some point. Moreover, if the right to withdrawal is the main argument to convince someone to participate, the volunteer's trust in science can be jeopardized, ultimately causing more damage for science in general than what is gained from a onetime participation. Again, this illustrates the significance of good communication since such a genuine participation will be primarily dependent on the communicative approach.

Children and informed consent

Many issues regarding informed consent and the protection of autonomy exist in public health research. This is the case for adults, but even more so for children. However, the participation of children is much needed in certain environmental health studies. Knowledge on the toxicity of contaminants in children is a necessary scientific basis for possible further (European) regulatory activities. However, since children differ from adults in the sense that their bodily systems are continuously developing, they eat, drink and breathe more in proportion to their body size, their behavior may expose them more to chemicals and organisms, and they differ from adults in their intake and transformation of (toxic) chemicals, results of studies performed on adults cannot simply be transposed onto children (41,49).

Currently, a variety of large mother-child cohorts (50)⁵⁴ is set up or being set up in many European countries to study and increase awareness of long-term health effects from early life exposure throughout childhood and adolescence. Research involving children needs to be carefully set up because, as explained above, the child is extremely vulnerable. Research should be done in children only if comparable research in adults could not answer the same question. A research procedure which is not beneficial for the individual child is not necessarily unethical or illegal, if it is likely to yield generalized knowledge of vital importance. All proposals involving medical research in children should be submitted to a research ethics committee involving experts in pediatric research (51).

The principles behind informed consent presuppose that only adults are presumed to have the capacity to act autonomously, whereas children are not presumed to have this capacity. In general, consent is given on their behalf by parents or legal guardians, usually supplemented by the positive affirmation (or assent) of the child where possible (52). In EU countries, the age of majority is generally 18 years, although exceptions exist, and it is the age that any competent person is legally able to refuse treatment as well as to consent to it. It is important to involve parents in the decision making process, thus building up a trustful relationship between parents and scientists. Certainly, age is an important determining factor and while under aged, children will be submitted to their parents' power to decide about participation.

⁵⁴ <http://www.birthcohorts.net/About.asp>.

But surely age cannot be the only criterion to attribute decisional autonomy upon. Competence has often been associated with cognitive capacity, rationality and age e.g. a concept of “mature minor” includes groups of children between 14 to 18 years; in children with relapses of leukemia, the “experience of the illness” is taken into account and age of competence can be decreased to 12, even 9 years. Studies suggest that children over 9 years of age can understand quite complex metabolic processes (52) whereas other results indicate that children’s ability to understand the nature and purpose of research and their research rights begins to emerge in early childhood reaching adult levels by mid-adolescence (53).

In any case, regardless of the cognitive and experiential maturity, children’s non adult status and vulnerabilities do not justify ignoring their privacy rights. It is important to be aware of the power inequality that exists between children, their parents and researchers and to reduce this as much as possible in practice. Researchers should strive to create a goodness of fit between children’s maturing skills and the research context by approaching child assent as a process of research education fitted to the child’s age and abilities (54). Indeed, it should be borne in mind that the relationship between competence and information is a complex one. Therefore, all children, even those not judged as competent, have the right to receive information given in a way they can understand and give assent or dissent (52). A reasonable practice is to provide children with simple information sheets written in age-appropriate language that sets out exactly what will be expected of them and what will happen to them in the research. This information should also explain in simple and explicit language that the child has the right to change his or her mind at any time and withdraw from the research without fear of consequence (55).

2.3.2. Decision making and communication after research

2.3.2.1. At collective level

Communication of results

The ultimate goal of gathering knowledge on the impact of the environment on health is to take actions based on this knowledge and to establish preventive measures to protect citizens’ health. To allow this, spreading information about research outcomes is essential and has come more in the focus of attention, also in the major ethical guidelines. The Oviedo Convention requires researchers to make public their research results. Findings of studies should be made publicly available and disseminated within an appropriate time scale once they come to an end⁵⁵. This information can be communicated through a variety of channels.

As research productivity and researchers’ careers are heavily dependent on the usage and application of research findings — as enshrined in the academic mandate to “publish or perish” and in the reward system of academic research — communication towards the scientific world is in principle guaranteed. Nevertheless, many results also remain unpublished, for several reasons. Many negative data (“no outcome”) are not published because of a — misconceived —

⁵⁵ Art. 28 of Additional Protocol to Oviedo Convention.

lack of scientific relevance. In contrast, certain positive data can be prevented from being published because of pressure executed by industry or governmental institutions to avoid financial losses, political loss of face or so-called unnecessary panic (56,57). Although not directly related to public health research, it is worth mentioning the results here of a survey conducted by a REC in Spain, assessing the output of all protocols for clinical trials submitted in one year. A worrisome finding was that results of only 27% of started trials were presented at scientific meetings, and only 31% of closed clinical trials published or in-press in peer-reviewed journals. The authors concluded that research ethics committees should devote more effort and resources to assess public dissemination of results of clinical trials (58).

Pushed by scientists everywhere, government agencies (including the EU) are increasingly exploring the open access (OA) model for spreading knowledge (59). Open access journals guarantee that all research is freely accessible online immediately, to anyone around the world. This guarantee of access, however, is not purchased by any compromise in academic standards. There is still a peer-review process. The primary rationale for such “open access movement” is researcher-to-researcher access and not public access (nor even educational access). It is indeed assumed that the vast majority of peer-reviewed research is not of direct interest to the lay public and that the greatest public benefit is the potential research progress that results from maximizing researcher-to-researcher access. OA should allow an improved uptake and use of information which should be built upon in further research and applications for the benefit of the public that funded it — not in order to generate revenue for the peer-reviewed journal publishing industry (60).

Overall the information reported should be clear and truthful. Especially with respect to communication to the public, both raising panic and unjustified reassurance are to be avoided: there is no need for exaggeration, but the consequences of scientific findings should not be minimized either. At the same time, one should always be aware of possible pitfalls of reporting back: stigmatization may occur. Indeed, it was found that a study, in which breast milk was analyzed for the presence of environmental chemicals, resulted in the undermining of the confidence of mothers, parents and health professionals in breast feeding. This was due to the fact that, when communicating the results, the situational context was overlooked: focus was on “polluted” breast milk and avoidance of breastfeeding was seen as a possible option, rather than that there was a focus on the fact that the detection of residues in breast milk is an indicator of the body burden of all human beings and that breast milk still remains the best possible nutrition for a healthy development of young children. The results should therefore be used as an exhortation to political action for strong legislation on the production, release and use of the chemicals detected in breast milk. The inclusion of specialists (communication specialists, lactation specialists) could be of help in this matter (61). Stigmatization can occur at other levels: e.g. the plunging of real estate values when the word gets out that a certain region is contaminated.

Risk communication has long been dominated by “top down” technocratic approaches that can be characterized as “expert to public” monologues. However, a significant gap may exist between the risk perception of experts and that of the public. Moreover, risk

communication restricted to conveying “technical” information will ultimately fail to communicate because it ignores the complex determinants of risk perception; risks have different meanings to different people. A more “open” approach based on concepts such as partnership and dialogue is therefore advisable. Citizens, civil society organizations and other stakeholders (such as local communities, interest groups and industry) should work together with an interdisciplinary group of scientists and experts through processes of co-operative inquiry. To account for the social component of risk perception and communication, a social scientist in the expert group might significantly facilitate the process (62).

Nevertheless, even in such more open approaches, language problems may still arise. Situation analysis in a comparative case study of three organizations undertaking environmental health research revealed that language played a significant role in the divisions between local and university communities. The dominant language of meetings was science, and time constraints limited the translation of this language needed to ensure equal participation in the process by all participants (i.e. community members and researchers). Members of the local community were not enabled to introduce their language or ideas into the working groups.

To increase community involvement in research (from decision making to recruitment to communication of results) the complex structural issues affecting communication among diverse groups must be addressed, amongst which is the lack of shared scientific knowledge and the lack of respect for community spokespersons’ knowledge. Scientists, ethicists and community representatives should be informed about one another’s languages and perspectives. This could be achieved a.o. through the organization of training in science for the community representatives and in local issues for the researchers (43).

Translation to action

For researchers, it is also a moral duty to communicate scientific results that are relevant for public health to policy makers and to assist in translation into policy actions. Interviews with study participants have clearly shown that an important reason for participation to research projects is that they believe that their participation is helpful for society in general (63). This belief should not be wasted.

In practice, however, many studies with relevant information are never passed on to policymakers and the gap between science and policy still remains to be bridged despite declarations of good intentions from both sides. This is often the case because there is an obvious discrepancy in issue framing between experts and policy makers, to a large extent due to uncertainties regarding the research results and due to the need for quick political actions. Often the results do not offer an immediate opportunity for remediation since for instance the source of contamination remains unknown, which leaves policy makers with bare hands to come up with proposals to reduce exposure. Moreover, there is the internal split scientists are forced into by political authorities. The research product must be of the highest scientific standard and able to survive all possible criticism on a very specific level. At the same time, the product must be delivered quickly and the message should be simple.

In order to bridge this gap, again, the involvement of social scientists could be helpful. Moreover, time should be spent on different actors (environmental health scientists,

social scientists, policy makers) getting used to work together, which requires trust-building, a time and effort consuming challenge. And, since different scientific disciplines and policy makers use different (technical) language, common vocabularies need to be developed to enable communication (64). Expert and lay opinions need to be perceived as complementing rather than competing with each other (62). The most effective way to achieve this is to make the public a partner in the communication process.

Participatory processes (6) are needed to combine technical expertise, rational decision making, and public values and preferences. Mutual understanding and participation are necessary to create trust in order to solve problems that are both scientifically and socially complex. According to Keune et al. there are three main goals for involving public participation in decision-making processes and policy relevant research (65,66). First, the value of a final decision is higher when non-scientific (e.g. local) expert knowledge is included, since science itself suffers from many uncertainties and unknowns, especially in the complex relationship between environment and health. Second, the legitimacy of the final outcome is higher when potentially affected parties can state their own case before their peers and have an equal chance to influence the outcome. Participation is therefore likely to increase public support for the policy decision-making process. Third, it is a way of implementing democracy. Public participation is identified with the way democratic government should conduct itself in public decision-making activities.

An example of public participation is the Boston Consensus Conference on Human Biomonitoring (67). Involvement of a lay panel showed that the public is fully capable of understanding technical issues and making unique valuable contributions to discussions about policy relevant science and technology. This process was effective in bringing perspectives from the public to bear on scientific research and public health practice, an important element of simultaneous research translations. Research translation should be a reciprocally informative process that allows for mutual education, with products that are strengthened by the diversity of voices and perspectives that creates them.

RECs may contribute to closing the existing gap between the publication of research results and their translation into policy. They could encourage and invite the scientific community to reflect on how to use the expected results already at the stage of designing the research protocol. Also striving for public participation in decision making processes and policy relevant research may be promoted within the RECs efforts with respect to communication.

Secondary use of material⁵⁶

Secondary use of research data or samples refers to the use for purposes other than those for which these were originally collected. In the field of environment and health it finds its ground in that it makes economic and ethical sense to use all relevant data and samples as much as possible in the interest of all for research leading to identifying causes of disease, identifying populations at risk, protecting public safety in relation to environmental hazards, supporting and evaluating policies, health education of the public and health professionals.

⁵⁶ For the purpose of this paragraph secondary use does not entail the setup of a biobank.

The secondary use of biological material or data can occur both spatially and temporally: in the case of collaborations between research groups at different locations, one group can get access to the data and samples obtained by the other for other purposes. In time, data or samples collected at one time point may prove valuable for future research purposes unforeseen and not included in the original study design or informed consent.

For current regulations on secondary use, we refer to the ethical and legal framework described in Chapter 1 (1.2.). In essence, data and samples may nowadays only be used on the condition that informed consent was obtained for a specific purpose. No further use of data and samples is allowed without consent of the donor involved. However, several exemptions exist and circumstances in which this is allowable are defined in for instance the Data Protection Directive, the Oviedo Convention and its Additional Protocol, Rec(2006)4, etc. (see 1.2.) for reasons of public interest, or when processing of personal data for scientific purposes is not considered incompatible with the purposes for which the data have previously been collected and/or providing information would be impossible or involve disproportionate effort. Rec(2006)4 attempts to formulate recommendations for “secondary use”. It applies to research activities in the health field that involve the removal of biological materials of human origin to be stored for research use or to research activities that involve the use of residual biological materials of human origin that were originally removed for clinical or forensic purposes or for a previous research project.

Questions surrounding the secondary use of data or samples have become more pressing with the advent of new technologies. Data can easily be shared by a click on the mouse, bringing up new concerns for privacy aspects. While legally data may only be used for the purpose for which they were collected — being the specified, explicit and legitimate purpose described in the informed consent⁵⁷ and not stored longer than is necessary for the purposes for which the data were collected, in practice, data is often stored as long as possible.

Not optimally using data and samples may be considered irrational or even irresponsible, leading to additional procedures for which again study participants need to be recruited for obtaining data and samples. However, the act of obtaining new consent frequently involves insurmountable economic and practical difficulties. Furthermore, the requirement to obtain new consent involves a significant potential for selection bias due to dropouts, decreasing the scientific value of a study (68). The anonymization alternative can generally not be recommended since it also risks losing scientific value, prevents retroactive validation and demonstration of reproducibility and irrevocably excludes further influence from study participants (69).

On the other hand, establishing research routines on secondary use that disregard participants’ views on how their samples should be handled and what they will be used for may on the long term result in loss of trust in science. So, a conflict arises between the legal requirement to obtain a specific informed consent — preventing the future unforeseen use of data — and the optimal utilization of data for scientific progress.

⁵⁷ Art. 6 of the EU Data Protection Directive.

In general, a right balance should be found between the rights of the participant and the rights of society as a whole or between the need for individual protection and the need for facilitating research progress. The appropriate balance between protection of the study participants and research progress may also depend on the nature (sensitivity) of the data and samples. In genetic analysis for example, criteria for more or less generic consent may differ depending on the possibility of identification of data indirectly revealing properties on other family members or the degree of intrusion of private lives. Different situations may call for different praxis. To balance the interests at stake, each information and consent form should be carefully assessed by both researchers and ethics committees. Wishes of donors that their samples should not be used for some specific study should always be respected.

Facilitation of secondary use

In fact, many study participants may not pose serious concerns about the further use of their data and/or samples, on the condition that they feel protected in their dignity and integrity and that confidentiality is guaranteed. Complementary assurance to protect the rights and dignity of the research participant and facilitation of research should be explored out of a double loyalty of duty from the researcher. This double loyalty towards both components (individual and science) should subsequently be assessed for its validity by an ethics committee.

To anticipate to the problems surrounding secondary use, a longer term vision could be adopted when drawing up the informed consent form and at the time of data and sample collection. One option to achieve this, is the introduction of a partially restricted informed consent model, as proposed by the WHO (70)⁵⁸. It would allow study participants to make informed decisions about the handling of their data and samples for specific research and related (but mostly unplanned) future investigations. It should for example contain the consent (i) to store samples and related data, (ii) to use the data for specific purposes or (iii) for all kinds of researches that directly or indirectly relate to the specific purpose (71). Such a form would respect individual autonomy while facilitating and proceeding research using biological materials. The model is situated between a restricted and a broad consent. A too broad consent would not truly be an informed consent since the study participant can no longer overlook the range of his decision and mainly serves the interests of research.

⁵⁸ Donors of human tissues, cells and fluids for clinical research are, as a rule, volunteers who participate in the research of their own free will and have given prior informed consent in accordance with established local, national or other regulations and practices. The nature and extent of the information provided to such volunteers, and on which their consent is subsequently based, is becoming increasingly important and complex in the light of recent medical and technical developments. In particular, recent advances in the fields of diagnostics and genomics have highlighted the need for donors to be given the opportunity to indicate whether or not they want the samples they are donating for a particular research purpose to be stored for use in future research and, if so, whether they want to place any limitations on the storage time or restrictions on the use to which their samples can be put in such future research. This WHO Guideline has been drawn up to assist researchers in dealing with the ethical issues relating to how clinical research materials are obtained, used and eventually disposed of, and the corresponding informed consent requirements. While this guideline is intended for the future collection of samples, many of the ethical considerations in this guideline are relevant also to previously collected human biological materials stored in repositories.

Fully restricted informed consent formally protects the study participant's decision at the expense of research.

The sensitivity of the data and samples and the probability of being able to re-contact the participants, as well as the potential harm caused by such a contact should be considered in decision making for obtaining consent for new research purposes. When a study does not involve particularly sensitive data and on the condition that (i) the research addresses an important scientific interest possibly resulting in the improvement of collective health, (ii) there is no evidence that the person concerned has expressly opposed such research use, (iii) strict confidentiality procedures are in place, and (iv) that the decision has been carefully validated by an ethics committee, re-use of identifiable samples might be facilitated without individual new consent.

The essence is that data and samples are handled by the researcher with the highest respect for confidentiality and that ethics committees are able to assess these conditions taking into account a view on the improvement of community health and have the power for sanctioning if certain conditions are not met. In specific situations, public health or the common interest may exceed the individual interest (for example national cancer registers can be used for research purposes, for example to track cases or to obtain specific samples). In such cases it is still necessary and morally obliged, to communicate truthfully and transparently with the study participants and other relevant parties. Availability of transparent institutionalized competent bodies (such as ethics committees and data protection authorities) which must ensure respect of confidentiality in order to optimally use the obtained personal data and/or biological material is required.

Overall, decision making processes may not entirely shift the responsibility towards the individual volunteer based on the fact that, in the end, it is the individual study participant who autonomously decides about his/her participation. Also, many decisions on secondary use are made on an ad hoc decision level by local researchers. A more streamlined decision making process, like the one suggested above, is certainly desirable, and should be implemented in clearly articulated policies at higher level ensuring that decisions are based on ethical principles rather than simply on pragmatic ways of overcoming practical problems. Ethics committees have an important role to play regarding this decision making process. To increase consistency, it is important that they form part of a larger (international) structure, in which other groups including the supervisory authority can collectively decide and control secondary use.

Research ethics approval could require a process for coding, storing and providing access to the data in a uniform fashion. The settlement of these issues at a higher level may result in a larger preparedness amongst researchers to voluntarily share their data and maintain them in a format which is easily accessible to third parties. Added to this, research education may be expanded to include improved understanding about the advantages, processes and barriers in data sharing. Furthermore, an information professional, such as a librarian or an archivist, could be added to the research team (72). His responsibilities could include the verification of the informed consent in accordance with the protocol, advising the local ethics committee on coding the samples, giving a secondary code to the stored samples

and being the key-holder of the secondary code (73). Also, the implementation of clear and enforced standards for citation of data files and sources of samples for publication may facilitate data sharing.

Finally, it is strongly recommended that public awareness is increased in general by informing about the significant impact that secondary analysis of data can have on science. This implies the concrete implementation of the embedded European value of democratic participation. Ways to go about are the organization of public meetings and focus groups. But also funding agencies and policy statements could more strongly advocate secondary use. Similar to environmental education, they have a strong position to promote changes in behavior (74). By facilitating secondary use through adapted legal requirements and implementations in daily practices, sharing data should be the practice unless there are specific objections.

2.3.2.2. At individual level

Study participants always have to right to know individual results as well as the right not to know their results. The right not to know should be documented at the start of a research project. Often however, results are not communicated to individual study participants, despite the legally embedded right to know⁵⁹. There are several reasons for this. It is in the nature of environmental health research results that many uncertainties remain⁶⁰ and that different interpretations are possible⁶¹. In addition, when the results are of relevance at community level only and not at the individual level, researchers may not see the need for individual reporting and may find it an inefficient allocation of time and resources and even an unethical way of working. Moreover, the transnational dimension of many studies generates practical difficulties to get back to the study participants in their own language.

⁵⁹ Data Protection Directive, art. 12, a) point 2: Member States shall guarantee every data subject the right to obtain from the controller: "communication to him in an intelligible form of the data undergoing processing".

⁶⁰ In environmental health research a shift occurs from relatively simple to more complex issues. Single effect studies have been expanded with more complex environmental exposures in different economic, social and political settings when assessing the gap between the environmental burden and its health impact. Because of this multi-factorial environmental burden, knowledge and data is often incomplete and diverging interpretations exist regarding the results, but also regarding the prioritization of the problems to handle. The interdisciplinary character of these kinds of assessments adds to the problem.

⁶¹ According to Harrison (40) if study participants want to learn their individual results, two principles from the classical paradigm, nonmaleficence and autonomy, seem to give different answers. A careful balancing of risks and benefits by the investigators may argue against sharing individual data in the early stages of investigating a biomarker. This is an ethically supportable position as long as the study participants are informed before participation of the decision not to disclose personal results. Reference is made to the U.S. Center for Disease Control's (CDC) National Exposure Report as a good example of how biomonitoring information can be generated and communicated with high scientific and ethical standards. Individual test results are not given unless the concentration is markedly above population means. Notification in these rare cases is ethically justified because an individual may be able to identify the source of exposure and correct it. The principle of beneficence argues for disclosure. At the same time, the CDC is careful to emphasize that mere presence of the chemical, even at multiple standard deviations above the group mean does not imply health risk (the principles of nonmaleficence and veracity are thereby satisfied).

However, providing individual results can be very important for the individual. It is conceivable that people simply are curious to know their results, and participants after all do exhibit the solidarity to participate, so informing them about their results is the least a researcher can do in return. Moreover, even though data may be hard to interpret at the individual level at a certain time, sharing and keeping individual results in a medical file may turn out useful later on. Also, with human biomarkers in environmental health, pollution and exposure become personal and can instigate awakening or changes in behavior (75,76). Moreover, sharing as much knowledge as possible may have an impact that goes beyond purely individual health and might empower initiatives for preventive actions in favor of community health (77). The particular power of human biomarkers in environmental health in this context should be stressed. This became already clear in occupational health where repeated biomonitoring was a driving force for preventive actions at collective and individual level (78).

The same effect is showing in environmental health: human biomarkers alter public understanding of chemical pollution at collective and individual level. In this respect, Altman et al. report on interviews conducted with participants in a study about environmental chemicals in body fluids and household air and dust. The interviews reveal how personal and collective environmental history influence the interpretation of exposure data, and how participants fashion an emergent understanding of environmental health problems from the articulation of science and personal experience (76).

Again, clear strategies and proactive measures need to be included in the protocol. Because of the possible uncertainties in and the diverse interpretations of research results, the question how not to raise unnecessary concern whilst at the same time not minimizing results needs to be cautiously reflected on. Concerns or even anxiety can be reduced by providing sufficient information. Expectations about the outcome of a study need to be framed in a realistic perspective and presented to the study participant already at the time of recruitment. This way, the participant can adapt his expectations accordingly.

Options like the right to know or the right not to know should be well explained and documented before data or sample collection starts. Overall, three possible strategies to communicate results can be envisaged: (i) never communicate results at individual level; (ii) communicate individual results on request only; and (iii) communicate results as a general rule, unless specified otherwise by the study participant. In most EU countries option (i) would be illegal given the requirements of the EU Data Protection framework Directive and its implementation in domestic laws. In options (ii) and (iii) communication of individual results should be encouraged with an emphasis on explaining scientific uncertainties and addressing all concerns present.

Research has shown that it is advisable to frame individual results within the aggregated results or even within comparable results from other studies (9). This is particularly so if results can not be set against accurate background results and health based values indicating more information on the risk associated with the result. While acknowledging the importance of statistic or probabilistic information, people still want to know where they stand in relation to some reference point. Passive reporting may not be sufficient.

Reporting of results is most efficient when written material is provided in combination with the possibility for conversation with experts. To cope with unexpected results or pathological findings, a procedure needs to be established at the start of each relevant study. It is recommended to envisage counseling services from the start of the project. Integration of counseling would not be superfluous when dealing with very specific personal information, such as individual genetic risk. Contact information of the individual's medical doctor should be documented from the start and used when required.

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3. Concluding remarks

Human biomarker studies in environmental health are essential tools to study the relationship between health and environment. The development of relevant research potential and the setup of biomonitoring surveys should ultimately lead to a better understanding and prevention of environmentally induced adverse health effects. The use of biomarkers involves the donation of tissues or fluids by healthy volunteers and leads to sensitive ethical questions.

To ensure the protection of the rights and dignity of study participants a complex legal and ethical framework has to be applied, consisting of several international directives, conventions, and guidelines, whether or not transposed into domestic laws. Nowadays, within an EU context, the probably most important international references in this respect are the Data Protection Directive (95/46/EC), the Oviedo Convention, more in particular its Additional Protocol concerning biomedical research and Rec(2006)4 on research on biological material of human origin.

The Data Protection Directive, which is subject to transposition in all EU Member States, concerns the processing of personal data and imposes the practice of informed consent, including the right to know one's own individual results, and notification of the research to the national supervisory authority. The Oviedo Convention and its Additional Protocol are documents open for signature and ratification by all Member States of the Council of Europe. They also emphasize the necessity of obtaining informed consent and require that a research project is submitted to an ethics committee for independent examination in every country where any research activity is to take place. Rec(2006)4 builds on the principles embodied in the Oviedo Convention and its Additional Protocol, but where the Additional Protocol covers interventions to remove biological materials for *specific* research projects and other interventions on human beings for *specific* biomedical research projects, or data collected for and resulting from these research projects, Rec(2006)4 focuses on the study of biological materials that have been *stored after originally being collected* in a diagnostic or therapeutic setting, during research projects with human subjects or during autopsy.

Together with the better sensitivity, the decreased cost of analytical techniques and the increased possibilities for application of human biomarkers, the attention for, and interest in, the ethical and legal aspects has increased. In this volume we reviewed ethics and data protection in environmental health studies using human biomarkers. The key question at stake is whether study participants involved in human biomarker studies are adequately and equally protected throughout the whole of Europe and whether at the same time the possibilities for environmental health related research to progress are safeguarded.

Besides presenting the general conditions in the current EU regulative and ethical framework, a critical analysis of a number of research experiences in various EU Member States has been used as a basis to show that difficulties, ambiguities or even inconsistencies exist in the way ethical challenges are being dealt with. Example cases were used to highlight particular aspects. Their analysis may help readers to gradually become more familiar with the application and implementation of the regulatory context and may enrich the public debate.

3.1. Challenges

Inconsistencies and fragmentation

In the current regulatory context, inconsistencies and difficulties are reported due to the different interpretations which can be given — within and across countries — to key terms or concepts used in the regulations of concern such as “research”, “anonymization”, “controller”, “substantial public interest”, “disproportionate efforts”, “compatibility of purposes”.

Moreover, the differences across countries in the transposition and implementation of EU regulations or guidelines in domestic law have consequences for transnational research. For example, when data and/or samples are exchanged between Member States for laboratory analysis, approval from a local ethics committee is required in some but not in all of the Member States, often causing confusion for the researcher.

A reason for the sometimes not easily applicable concepts of the Data Protection Directive could be the fact that this Directive adopted a horizontal approach and applies to a very broad range of societal domains. Since not every domain and its specificities can be covered, certain societal concerns can unwillingly become isolated, such as the progress in research fields which contribute to people’s health protection. It was of course impossible to foresee the implications of the Directive for each domain of society; and certainly for a particular domain such as human biomarkers studies.

The creation of clarity and consistency in the interpretation of legal documents and in the implementation of an ethical and legal framework is not straightforward in the EU. Conflicting opinions exist regarding the need for more consistency. On the one hand, a call is launched for a more harmonized approach, including the use of standardized procedures, which increase comparability of results, but also tend to overlook local characteristics — while on the other hand the principle of subsidiarity is strongly recognized, thus promoting the development of procedures at a more local level, resulting in differences in approaches between Member States or research centers. Advancement of consistency is justified, but is not an easy endeavour. It should not necessarily entail a full or even partial standardization of methods or procedures. On the contrary, national traditions should be respected, though the level of protection of the participants should be equal throughout the Member States and the procedures transparent and unambiguous.

Individual and public concerns

A major issue for the specific field of human biomarker studies is the balancing of two different — and sometimes perceived as opposite — concerns: the need for the protection of the individual's privacy and the societal need for scientific progress. The tension between these two concerns should however not be overemphasized, as several studies highlight the willingness of study participants and populations to participate in studies with a view to promote scientific knowledge in the interest of all.

Secondary use of data

The secondary use of data or samples that were collected in previous research projects for other purposes sometimes remains very difficult or almost impossible. However, there are strong and recognized arguments for facilitation of such further use in the context of environmental health research where risks for improper use of data or samples are minimal, where public interest comes to the forefront and where adequate collective protection and control can be installed, so that breach of confidentiality or any use of data which would not be in line with the participant's moral stakes can be excluded.

According to the Data Protection Directive, data may be re-used for a new (historical, statistical or scientific) purpose without renewed consent if “disproportionate efforts” are required to obtain such consent. The Additional Protocol to the Oviedo Convention specifies conditions for a research project designed for a specific purpose and does not foresee guidelines for the re-use of data and/or material. The Rec(2006)4 clarifies that if the original consent does not include the specified purpose for the re-use of data, all reasonable efforts should be made, both in terms of means and time, to re-contact the participant to request new consent. If re-contacting the participant is not possible despite reasonable efforts, Rec(2006)4 formulates specific conditions to comply with for the re-use of data.

In practice, the decision whether a study objective is to be considered in line with the original purpose and whether the call for a new consent would require disproportionate efforts remains at first instance with the individual researcher. Such decision making process obviously add to differences in practices within and across countries and may hinder consistency and ultimately may delay and impede important research beneficial to all.

Between the two extremes of application of the current regulation, either following it in its strictest possible sense — making it sometimes impossible to process further valuable study material and thus hindering scientific progress — or adopting opportunistic strategies - more ignoring the view of study participants — a more formal facilitation may increase the strengths of EU regulations. However, caution should also be taken not to over-formalize research conditions because scientific progress might ultimately be hampered, without any real gain regarding the protection of the (potential) study participant.

When risks for the individual study participant are minimal and study results are expected to be profitable for the whole community, facilitation of secondary use can be implemented better, though based on firm conditions guaranteeing a full respect for human dignity through measures related to data confidentiality and regarding compliance with

what can reasonably be assumed the motives of the participant for his or her original consent and his or her moral stakes.

Communication

Whilst human biomarker research may entail less or no risk for the study participant as compared to other applications that were at the origin of the establishment of the regulatory context of concern, and whilst it has its biggest merits in a common interest perspective, it requires an adapted approach to communication. More attention is needed — at the initiation of a study, during the study, as well as at the time of dissemination of results — for instance to the explanation of the meaning of the results at both individual level and collective level. At individual level this is important a.o. to deal with side findings related to health properties of the participants or indirectly of his or her relatives. At the collective level, this is important a.o. to express that the researchers are not sampling individual participants just for their own research interest, but with a view to contribute to the well-being of the population under study, encouraging their involvement also as a collective endeavour in eventual subsequent decision making on preventive action and policy measures.

Further assessment of the ethical and legal aspects of human biomarker research in environmental health may be called for, taking into account the specific context of benefit for the society as well as the possibilities to guarantee the full respect of the individual's privacy concerns. In this frame, principles put forward here (respect for human dignity, social justice, solidarity and democratic participation) may be appealing reflections of European values and should be included in weighing the four conventional bioethical principles (autonomy, beneficence, non-maleficence, and justice) that have gained wide use for evaluating policies, programs or activities that may entail risk to human health and the four additional bioethical principles which Beauchamp and Childress refer to as “secondary principles” (veracity, utility, fidelity, and confidentiality).

3.2. Steps to solutions

Information and education

Even though many improvements regarding the legal and ethical challenges in human biomarker research have already been implemented in the EU in the last years and possibilities have been created for allowing exemptions to the law for reasons of “substantial public interest” (art. 8 Data Protection Directive), thereby overruling the primacy of the individual in certain circumstances, the general need for a right balance between respect for the privacy of the individual and the need for scientific progress in the field of environmental health protection remains and improvements in the field are needed.

As said above, in some cases, there is a lack of clarity on the interpretation to be given to some key terms in the regulations. However, knowing that an all-embracing definition of terms such as “research”, “disproportionate efforts” etc. does not exist, the fact that improved definitions could lead to a substantial facilitation of human biomarker studies

may be seriously questioned. For example, the creation of a clear and all-encompassing definition of “substantial public interest” (mentioned in the Data Protection Directive) in the context of research is a difficult, if not an impossible, task.

Nevertheless, it should also be mentioned that degrees of specification or definition may exist. For example, regarding the definition — or rather description — of “reasonable efforts”, it can be said that whilst the Data Protection Directive and the Oviedo Convention and its Additional Protocol do not elaborate at all on what is to be understood under this term, Rec(2006)4 initiates a first attempt of a more specific description. Also, instances such as the Article 29 Working Party, the independent advisory body on data protection and privacy, set up under Article 29 of the Data Protection Directive, try to examine questions covering the application of the national measures adopted under the EU directives in order to contribute to their uniform application. The Article 29 Working Party carries out this task by issuing recommendations, opinions and working documents.

However these issues and instances are not well known among the actors involved and efforts should be devoted to better education and dissemination of information and improved transparency targeting researchers but also the general public, the media and the policymakers. One way will obviously be the improvement of the communication processes related to human biomarker studies.

Communication and raising trust

The main endeavour is the reconciliation between respect for the individual privacy and the progress of science. Whilst respect for data protection regulations could wrongfully be reduced to a simple administrative ritual, limiting oneself to a formal informed consent that may lack “authenticity”, the key to make both privacy concerns and the concern for scientific progress not contradictory is building trust amongst (potential) participants and the general public in science and thus in scientists, in their goals and in the context they are working in. Confidence can first of all be established by correct and respectful communication. Respectful communication requires professionalism in many aspects, including the understanding by the recruiter how the confrontation of particular personalities may affect the (degree of authenticity of) the outcome of an informed consent procedure. Striving for an authentic informed consent, even knowing one can never reach 100% authenticity, is an ethical duty and highly valuable as such.

It is important to realize that it is the way the study participant perceives the situation that will determine his attitude, his trust in science and thus his decision to participate or not. Correct communication presupposes both the willingness and ability or competence to communicate by those involved in executing a research project. Commitment and involvement of recruiters are preconditions for good communication, which should on its turn be a prerequisite and an integral part of an ethically sound decision making process. The vital role of communication is obvious: each communicative act of a researcher or any other person otherwise involved in human biomarker research may induce trust or distrust in a study participant. These experiences will be shared by the participant with others and eventually affect the perception of future potential participants.

Involvement of communication experts in human biomarker studies is strongly advised. Researchers should organise and promote, and be actively involved in democratic participation processes. These must be inseparable key principles in human biomarker research. Communication at a collective level with the population to which the study participants belong may be another key requirement in most biomarker studies. Informed consent of individual participants can never substitute for, and should be complemented by this elementary step in a democratic participatory decision making process.

The role of Research Ethics Committees

Good communication in combination with confidentiality agreements alone will not be sufficient to make a research project ethically acceptable. Here is where the ethics committees should come in. Whilst the rules from the Data Protection Directive guarantee notification and transparency, ethics committees should play a key role in assessing any problem which may arise regarding what might be called the reconciliation of privacy regulations and scientific needs. Ethics committees can fill in the regulatory gap regarding the assessment of the collective “societal” interest. They can provide clarification on what, for example, are “disproportionate efforts” or what should not be subject to the requirement of informed consent. Such decisions should indeed not be totally left to the researchers alone.

Ethics committees should have the authority and moral imperative to act for the good of study participants and their communities. They are in a crucial position to advocate thorough communication to diverse stakeholders, including the process of translation of research results into policy, thereby helping the concrete implementation by other social science expert groups. And, while focusing on different aspects, ethics committees should closely relate to and be in contact with national data protection authorities in order to benefit from each other’s knowledge and competence. Ethics committees could substitute for individual informed consent in specific cases of secondary use of data and/or samples.

This role could for example be made dependent upon the inclusion of a clause in the initial individual informed consent document in which the participant delegates the agreement for secondary use to an ethics committee. Questions like: “Do participants want to be re-contacted for re-use? Would an approval of an ethics committee suffice whilst participant is informed through an information letter?” should then be included in the informed consent form.

A Research Ethics Committee at the European level

Ethics committees will weigh ethical principles against their reference regulations, which in most cases will be national regulations. Specifically for transnational research projects, to achieve a better consistency in the research conditions, the establishment of an ethics committee at the level of the “European research area” could be envisaged. Its main mission would be to give advice and/or decide on the interface between individual privacy regulations and concerns on the one hand and public health research needs on the other. Such a committee should have a permanent staff and ethical subcommittees or groups consisting of experts familiar with specific research domains. One expertise subgroup may for example involve human biomarker research in environmental health. The overall committee should survey consistency in the

advising or decision making processes of the subcommittees. The overall committee should report periodically to international institutions such as the European Parliament and the Council of Europe. Investment in such an effort could prevent loss of time, energy and research money.

The analysis and evaluation of different cases in different situations will lead to a build-up of an extensive knowledge and experience that may serve as an inspiring starting point for a well informed societal debate. This way, gradually, consistency in the handling of proposals and transparent decision making will be reached at the EU level, lifting the daily practices to a higher level. A formulated advice is one deepened advice, possibly criticized or sharpened by national advices, and should be considered as a well thought utterance of distilled jurisdiction and ethics. The European ethics committee would mainly be in place for transnational research, though it should be open for advice or opinion on national research projects as well. At the same time, the decision making process should occur in a manner that provides access and participation to any person involved.

Through the implementation of such an EU research ethics committee, the inconsistencies in regulations across EU Member States regarding ethical acceptability of practices could be overcome. The very same initiative may also create opportunities for the elimination of unnecessary bureaucratic burden for international research projects, and may considerably aid in avoiding irregular practices, while creating precedents which scientists can take into account when planning future research projects.

Participatory approaches

A way of increasing the possibilities for the inclusion of arguments from the societal perspective lies in the current movement of participatory approaches. Participatory processes make the public a partner in the communication process and are needed to combine technical expertise, rational decision making and public values and preferences. Mutual understanding between all actors involved and participation are necessary to create trust in order to solve problems that are both scientifically and socially complex. Striving for public participation in decision making processes may promote policy relevant research and the related translation of study results into action.

Political decision making

Solutions might be found following a political decision making process. Politics should aim at the identification of societal problems and take the necessary measures to guarantee societal development, among which public health and scientific progress. Although elaboration on and the adoption of laws may seem the way forward, reality is very complex and no law or regulation will ever fully cover this complexity. Laws should therefore never be regarded as dogmas and should be continuously evaluated with respect to the basic societal and ethical concerns and principles which guided the legislator in the first place. Indeed, blind application of the law in cases of conflicting societal interest may lead to undesirable situations. Respect for legal provisions is necessary, but a critical attitude towards current legislation and the identification of drawbacks are equally important. This should lead to a societal debate and adaptation of the framework in place if appropriate.

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Appendix 1. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data

Public health, medical data, public interest

(Rec.) (34) Whereas Member States must also be authorized, when justified by grounds of important public interest, to derogate from the prohibition on processing sensitive categories of data where important reasons of public interest so justify in areas such as public health and social protection — especially in order to ensure the quality and cost-effectiveness of the procedures used for settling claims for benefits and services in the health insurance system — scientific research and government statistics; whereas it is incumbent on them, however, to provide specific and suitable safeguards so as to protect the fundamental rights and the privacy of individuals.

(Rec.) (42) Whereas Member States may, in the interest of the data subject or so as to protect the rights and freedoms of others, restrict rights of access and information; whereas they may, for example, specify that access to medical data may be obtained only through a health professional.

Article 7

Member States shall provide that personal data may be processed only if:

- (e) processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller or in a third party to whom the data are disclosed.

Article 8

The processing of special categories of data

1. Member States shall prohibit the processing of personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life.
2. Paragraph 1 shall not apply where processing of the data is required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, and where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy.
3. Subject to the provision of suitable safeguards, Member States may, for reasons of substantial public interest, lay down exemptions in addition to those laid down in paragraph 2 either by national law or by decision of the supervisory authority.

Definitions

Article 2

Definitions

For the purposes of this Directive:

- (a) 'personal data' shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity;
- (b) 'processing of personal data' ('processing') shall mean any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organization, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction;
- (c) 'personal data filing system' ('filing system') shall mean any structured set of personal data which are accessible according to specific criteria, whether centralized, decentralized or dispersed on a functional or geographical basis;
- (d) 'controller' shall mean the natural or legal person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data; where the purposes and means of processing are determined by national or Community laws or regulations, the controller or the specific criteria for his nomination may be designated by national or Community law;
- (e) 'processor' shall mean a natural or legal person, public authority, agency or any other body which processes personal data on behalf of the controller;
- (f) 'third party' shall mean any natural or legal person, public authority, agency or any other body other than the data subject, the controller, the processor and the persons who, under the direct authority of the controller or the processor, are authorized to process the data;
- (g) 'recipient' shall mean a natural or legal person, public authority, agency or any other body to whom data are disclosed, whether a third party or not; however, authorities which may receive data in the framework of a particular inquiry shall not be regarded as recipients;
- (h) 'the data subject's consent' shall mean any freely given specific and informed indication of his wishes by which the data subject signifies his agreement to personal data relating to him being processed.

Scope

Article 1

Object of the Directive

1. In accordance with this Directive, Member States shall protect the fundamental rights and freedoms of natural persons, and in particular their right to privacy with respect to the processing of personal data.
2. Member States shall neither restrict nor prohibit the free flow of personal data between Member States for reasons connected with the protection afforded under paragraph 1.

Article 3

Scope

1. This Directive shall apply to the processing of personal data wholly or partly by automatic means, and to the processing otherwise than by automatic means of personal data which form part of a filing system or are intended to form part of a filing system.
2. This Directive shall not apply to the processing of personal data:
 - in the course of an activity which falls outside the scope of Community law, such as those provided for by Titles V and VI of the Treaty on European Union and in any case to processing operations concerning public security, defence, State security (including the economic well-being of the State when the processing operation relates to State security matters) and the activities of the State in areas of criminal law,
 - by a natural person in the course of a purely personal or household activity.

Principles relating to data quality

Article 6

1. Member States shall provide that personal data must be:
 - (a) processed fairly and lawfully;
 - (b) collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes. Further processing of data for historical, statistical or scientific purposes shall not be considered as incompatible provided that Member States provide appropriate safeguards;
 - (c) adequate, relevant and not excessive in relation to the purposes for which they are collected and/or further processed;
 - (d) accurate and, where necessary, kept up to date; every reasonable step must be taken to ensure that data which are inaccurate or incomplete, having regard to the purposes for which they were collected or for which they are further processed, are erased or rectified;
 - (e) kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the data were collected or for which they are further processed. Member States shall lay down appropriate safeguards for personal data stored for longer periods for historical, statistical or scientific use.
2. It shall be for the controller to ensure that paragraph 1 is complied with.

Conditions for data processing for the purpose of scientific research

Article 6

- (b) collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes. Further processing of data for historical, statistical or scientific purposes shall not be considered as incompatible provided that Member States provide appropriate safeguards;
- (e) kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the data were collected or for which they are further processed. Member States shall lay down appropriate safeguards for personal data stored for longer periods for historical, statistical or scientific use.

(Rec.) (33) Whereas data which are capable by their nature of infringing fundamental freedoms or privacy should not be processed unless the data subject gives his explicit consent; whereas, however, derogations from this prohibition must be explicitly provided for in respect of specific needs, in particular where the processing of these data is carried out for certain health-related purposes by persons subject to a legal obligation of professional secrecy or in the course of legitimate activities by certain associations or foundations the purpose of which is to permit the exercise of fundamental freedoms.

Informed consent

Article 7

Member States shall provide that personal data may be processed only if:

- (a) the data subject has unambiguously given his consent; or

Article 8

The processing of special categories of data

1. Member States shall prohibit the processing of personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life.
2. Paragraph 1 shall not apply where:
 - (a) the data subject has given his explicit consent to the processing of those data, except where the laws of the Member State provide that the prohibition referred to in paragraph 1 may not be lifted by the data subject's giving his consent; or

Right to refuse consent or to withdraw

Article 14

The data subject's right to object

Member States shall grant the data subject the right:

- (a) at least in the cases referred to in Article 7 (e) and (f), to object at any time on compelling legitimate grounds relating to his particular situation to the processing of data relating to him, save

where otherwise provided by national legislation. Where there is a justified objection, the processing instigated by the controller may no longer involve those data;

- (b) to object, on request and free of charge, to the processing of personal data relating to him which the controller anticipates being processed for the purposes of direct marketing, or to be informed before personal data are disclosed for the first time to third parties or used on their behalf for the purposes of direct marketing, and to be expressly offered the right to object free of charge to such disclosures or uses.

Member States shall take the necessary measures to ensure that data subjects are aware of the existence of the right referred to in the first subparagraph of (b).

Anonymization

(Rec.) (26) Whereas the principles of protection must apply to any information concerning an identified or identifiable person; whereas, to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person; whereas the principles of protection shall not apply to data rendered anonymous in such a way that the data subject is no longer identifiable; whereas codes of conduct within the meaning of Article 27 may be a useful instrument for providing guidance as to the ways in which data may be rendered anonymous and retained in a form in which identification of the data subject is no longer possible.

Article 2

- (a) 'personal data' shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.

Notification of supervisory authority

Article 18

Obligation to notify the supervisory authority

1. Member States shall provide that the controller or his representative, if any, must notify the supervisory authority referred to in Article 28 before carrying out any wholly or partly automatic processing operation or set of such operations intended to serve a single purpose or several related purposes.
2. Member States may provide for the simplification of or exemption from notification only in the following cases and under the following conditions:
 - where, for categories of processing operations which are unlikely, taking account of the data to be processed, to affect adversely the rights and freedoms of data subjects, they specify the purposes of the processing, the data or categories of data undergoing processing, the category or categories of data subject, the recipients or categories of recipient to whom the data are to be disclosed and the length of time the data are to be stored, and/or

- where the controller, in compliance with the national law which governs him, appoints a personal data protection official, responsible in particular:
 - for ensuring in an independent manner the internal application of the national provisions taken pursuant to this Directive,
 - for keeping the register of processing operations carried out by the controller, containing the items of information referred to in Article 21 (2),
 - thereby ensuring that the rights and freedoms of the data subjects are unlikely to be adversely affected by the processing operations.
3. Member States may provide that paragraph 1 does not apply to processing whose sole purpose is the keeping of a register which according to laws or regulations is intended to provide information to the public and which is open to consultation either by the public in general or by any person demonstrating a legitimate interest.
 4. Member States may provide for an exemption from the obligation to notify or a simplification of the notification in the case of processing operations referred to in Article 8 (2) (d).
 5. Member States may stipulate that certain or all non-automatic processing operations involving personal data shall be notified, or provide for these processing operations to be subject to simplified notification.

Article 19

Contents of notification

1. Member States shall specify the information to be given in the notification. It shall include at least:
 - (a) the name and address of the controller and of his representative, if any;
 - (b) the purpose or purposes of the processing;
 - (c) a description of the category or categories of data subject and of the data or categories of data relating to them;
 - (d) the recipients or categories of recipient to whom the data might be disclosed;
 - (e) proposed transfers of data to third countries;
 - (f) a general description allowing a preliminary assessment to be made of the appropriateness of the measures taken pursuant to Article 17 to ensure security of processing.
2. Member States shall specify the procedures under which any change affecting the information referred to in paragraph 1 must be notified to the supervisory authority.

Article 21

Publicizing of processing operations

1. Member States shall take measures to ensure that processing operations are publicized.
2. Member States shall provide that a register of processing operations notified in accordance with Article 18 shall be kept by the supervisory authority.

The register shall contain at least the information listed in Article 19 (1) (a) to (e).
The register may be inspected by any person.
3. Member States shall provide, in relation to processing operations not subject to notification, that controllers or another body appointed by the Member States make available at least the information referred to in Article 19 (1) (a) to (e) in an appropriate form to any person on request.

Member States may provide that this provision does not apply to processing whose sole purpose is the keeping of a register which according to laws or regulations is intended to provide information to the public and which is open to consultation either by the public in general or by any person who can provide proof of a legitimate interest.

Information to be given to the data subject

Article 10

Information in cases of collection of data from the data subject

Member States shall provide that the controller or his representative must provide a data subject from whom data relating to himself are collected with at least the following information, except where he already has it:

- (a) the identity of the controller and of his representative, if any;
- (b) the purposes of the processing for which the data are intended;
- (c) any further information such as:
 - the recipients or categories of recipients of the data,
 - whether replies to the questions are obligatory or voluntary, as well as the possible consequences of failure to reply,
 - the existence of the right of access to and the right to rectify the data concerning him,
 - in so far as such further information is necessary, having regard to the specific circumstances in which the data are collected, to guarantee fair processing in respect of the data subject.

Article 11

Information where the data have not been obtained from the data subject

1. Where the data have not been obtained from the data subject, Member States shall provide that the controller or his representative must at the time of undertaking the recording of personal data or if a disclosure to a third party is envisaged, no later than the time when the data are first disclosed provide the data subject with at least the following information, except where he already has it:
 - (a) the identity of the controller and of his representative, if any;
 - (b) the purposes of the processing;
 - (c) any further information such as:
 - the categories of data concerned,
 - the recipients or categories of recipients,
 - the existence of the right of access to and the right to rectify the data concerning him in so far as such further information is necessary, having regard to the specific circumstances in which the data are processed, to guarantee fair processing in respect of the data subject.
2. Paragraph 1 shall not apply where, in particular for processing for statistical purposes or for the purposes of historical or scientific research, the provision of such information proves impossible or would involve a disproportionate effort or if recording or disclosure is expressly laid down by law. In these cases Member States shall provide appropriate safeguards.

Article 12

Right of access

Member States shall guarantee every data subject the right to obtain from the controller:

- (a) without constraint at reasonable intervals and without excessive delay or expense:
 - confirmation as to whether or not data relating to him are being processed and information at least as to the purposes of the processing, the categories of data concerned, and the recipients or categories of recipients to whom the data are disclosed,
 - communication to him in an intelligible form of the data undergoing processing and of any available information as to their source,
 - knowledge of the logic involved in any automatic processing of data concerning him at least in the case of the automated decisions referred to in Article 15 (1);
- (b) as appropriate the rectification, erasure or blocking of data the processing of which does not comply with the provisions of this Directive, in particular because of the incomplete or inaccurate nature of the data;
- (c) notification to third parties to whom the data have been disclosed of any rectification, erasure or blocking carried out in compliance with (b), unless this proves impossible or involves a disproportionate effort.

Exemptions and restrictions

Article 13

Exemptions and restrictions

1. Member States may adopt legislative measures to restrict the scope of the obligations and rights provided for in Articles 6 (1), 10, 11 (1), 12 and 21 when such a restriction constitutes a necessary measure to safeguard:
 - (a) national security;
 - (b) defence;
 - (c) public security;
 - (d) the prevention, investigation, detection and prosecution of criminal offences, or of breaches of ethics for regulated professions;
 - (e) an important economic or financial interest of a Member State or of the European Union, including monetary, budgetary and taxation matters;
 - (f) a monitoring, inspection or regulatory function connected, even occasionally, with the exercise of official authority in cases referred to in (c), (d) and (e);
 - (g) the protection of the data subject or of the rights and freedoms of others.
2. Subject to adequate legal safeguards, in particular that the data are not used for taking measures or decisions regarding any particular individual, Member States may, where there is clearly no risk of breaching the privacy of the data subject, restrict by a legislative measure the rights provided for in Article 12 when data are processed solely for purposes of scientific research or are kept in personal form for a period which does not exceed the period necessary for the sole purpose of creating statistics.

Secondary use of data

Article 6

1. Member States shall provide that personal data must be:
 - (b) collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes. Further processing of data for historical, statistical or scientific purposes shall not be considered as incompatible provided that Member States provide appropriate safeguards;
 - (e) kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the data were collected or for which they are further processed. Member States shall lay down appropriate safeguards for personal data stored for longer periods for historical, statistical or scientific use.

Article 11

Information where the data have not been obtained from the data subject:

1. Where the data have not been obtained from the data subject, Member States shall provide that the controller or his representative must [...] provide the data subject with at least the following information, except where he already has it: [...].
2. Paragraph 1 shall not apply where, in particular for processing for statistical purposes or for the purposes of historical or scientific research, the provision of such information proves impossible or would involve a disproportionate effort or if recording or disclosure is expressly laid down by law. In these cases Member States shall provide appropriate safeguards.

(Rec.) (29) Whereas the further processing of personal data for historical, statistical or scientific purposes is not generally to be considered incompatible with the purposes for which the data have previously been collected provided that Member States furnish suitable safeguards; whereas these safeguards must in particular rule out the use of the data in support of measures or decisions regarding any particular individual.

Transfer of personal data to third countries

Article 25

Principles

1. The Member States shall provide that the transfer to a third country of personal data which are undergoing processing or are intended for processing after transfer may take place only if, without prejudice to compliance with the national provisions adopted pursuant to the other provisions of this Directive, the third country in question ensures an adequate level of protection.
2. The adequacy of the level of protection afforded by a third country shall be assessed in the light of all the circumstances surrounding a data transfer operation or set of data transfer operations; particular consideration shall be given to the nature of the data, the purpose and duration of the proposed processing operation or operations, the country of origin and country of final destination, the rules of law, both general and sectoral, in force in the third country in question and the professional rules and security measures which are complied with in that country.

3. The Member States and the Commission shall inform each other of cases where they consider that a third country does not ensure an adequate level of protection within the meaning of paragraph 2.
4. Where the Commission finds, under the procedure provided for in Article 31 (2), that a third country does not ensure an adequate level of protection within the meaning of paragraph 2 of this Article, Member States shall take the measures necessary to prevent any transfer of data of the same type to the third country in question.
5. At the appropriate time, the Commission shall enter into negotiations with a view to remedying the situation resulting from the finding made pursuant to paragraph 4.
6. The Commission may find, in accordance with the procedure referred to in Article 31 (2), that a third country ensures an adequate level of protection within the meaning of paragraph 2 of this Article, by reason of its domestic law or of the international commitments it has entered into, particularly upon conclusion of the negotiations referred to in paragraph 5, for the protection of the private lives and basic freedoms and rights of individuals.

Member States shall take the measures necessary to comply with the Commission's decision.

Transnational research

Article 4

National law applicable

1. Each Member State shall apply the national provisions it adopts pursuant to this Directive to the processing of personal data where:
 - (a) the processing is carried out in the context of the activities of an establishment of the controller on the territory of the Member State; when the same controller is established on the territory of several Member States, he must take the necessary measures to ensure that each of these establishments complies with the obligations laid down by the national law applicable;
 - (b) the controller is not established on the Member State's territory, but in a place where its national law applies by virtue of international public law;
 - (c) the controller is not established on Community territory and, for purposes of processing personal data makes use of equipment, automated or otherwise, situated on the territory of the said Member State, unless such equipment is used only for purposes of transit through the territory of the Community.
2. In the circumstances referred to in paragraph 1 (c), the controller must designate a representative established in the territory of that Member State, without prejudice to legal actions which could be initiated against the controller himself.

Working party

Article 29

Working Party on the Protection of Individuals with regard to the Processing of Personal Data

1. A Working Party on the Protection of Individuals with regard to the Processing of Personal Data, hereinafter referred to as 'the Working Party', is hereby set up.
It shall have advisory status and act independently.

2. The Working Party shall be composed of a representative of the supervisory authority or authorities designated by each Member State and of a representative of the authority or authorities established for the Community institutions and bodies, and of a representative of the Commission. Each member of the Working Party shall be designated by the institution, authority or authorities which he represents. Where a Member State has designated more than one supervisory authority, they shall nominate a joint representative. The same shall apply to the authorities established for Community institutions and bodies.
3. The Working Party shall take decisions by a simple majority of the representatives of the supervisory authorities.
4. The Working Party shall elect its chairman. The chairman's term of office shall be two years. His appointment shall be renewable.
5. The Working Party's secretariat shall be provided by the Commission.
6. The Working Party shall adopt its own rules of procedure.
7. The Working Party shall consider items placed on its agenda by its chairman, either on his own initiative or at the request of a representative of the supervisory authorities or at the Commission's request.

Sanctions

Article 22

Remedies

Without prejudice to any administrative remedy for which provision may be made, inter alia before the supervisory authority referred to in Article 28, prior to referral to the judicial authority, Member States shall provide for the right of every person to a judicial remedy for any breach of the rights guaranteed him by the national law applicable to the processing in question.

Article 23

Liability

1. Member States shall provide that any person who has suffered damage as a result of an unlawful processing operation or of any act incompatible with the national provisions adopted pursuant to this Directive is entitled to receive compensation from the controller for the damage suffered.
2. The controller may be exempted from this liability, in whole or in part, if he proves that he is not responsible for the event giving rise to the damage.

Article 24

Sanctions

The Member States shall adopt suitable measures to ensure the full implementation of the provisions of this Directive and shall in particular lay down the sanctions to be imposed in case of infringement of the provisions adopted pursuant to this Directive.

Appendix 2. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, 1997 Apr 4, Oviedo, Spain

Private life and right to information

Article 10

Private life and right to information

1. Everyone has the right to respect for private life in relation to information about his or her health.
2. Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed.
3. In exceptional cases, restrictions may be placed by law on the exercise of the rights contained in paragraph 2 in the interests of the patient.

Appendix 3. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 2005

What is research

Article 2

Scope

1. This Protocol covers the full range of research activities in the health field involving interventions on human beings.
2. This Protocol does not apply to research on embryos *in vitro*. It does apply to research on fetuses and embryos *in vivo*.
3. For the purposes of this Protocol, the term “intervention” includes:
 - (i) a physical intervention, and
 - (ii) any other intervention in so far as it involves a risk to the psychological health of the person concerned.

(Explanatory report) 15. In paragraph 1, it states that the Protocol covers the full range of research activities in the health field involving interventions on human beings. This includes all aspects of the research project from start to finish, including selection and recruitment of the participants. It lays out the principles for all types of biomedical research involving interventions on human beings. It is difficult to exactly delimit the health field. The Protocol covers research into molecular, cellular and other mechanisms in health, disorders and disease; and diagnostic, therapeutic, preventive and epidemiological studies involving interventions. This list is not meant to be exhaustive. Insofar as a human being is involved in research, this Protocol applies, notwithstanding the fact that provisions of other protocols could apply to research in specific spheres.

Informed consent

Article 14

Consent

1. No research on a person may be carried out, subject to the provisions of both Chapter V and Article 19, without the informed, free, express, specific and documented consent of the person. Such consent may be freely withdrawn by the person at any phase of the research.
2. Refusal to give consent or the withdrawal of consent to participation in research shall not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care.
3. Where the capacity of the person to give informed consent is in doubt, arrangements shall be in place to verify whether or not the person has such capacity.

Right to refuse consent or to withdraw**Article 13*****Information for study participants***

1. The persons being asked to participate in a research project shall be given adequate information in a comprehensible form. This information shall be documented.
2. The information shall cover the purpose, the overall plan and the possible risks and benefits of the research project, and include the opinion of the ethics committee. Before being asked to consent to participate in a research project, the persons concerned shall be specifically informed, according to the nature and purpose of the research:
 - (i) of the nature, extent and duration of the procedures involved, in particular, details of any burden imposed by the research project;
 - (ii) of available preventive, diagnostic and therapeutic procedures;
 - (iii) of the arrangements for responding to adverse events or the concerns of study participants;
 - (iv) of arrangements to ensure respect for private life and ensure the confidentiality of personal data;
 - (v) of arrangements for access to information relevant to the participant arising from the research and to its overall results;
 - (vi) of the arrangements for fair compensation in the case of damage;
 - (vii) of any foreseen potential further uses, including commercial uses, of the research results, data or biological materials;
 - (viii) of the source of funding of the research project.
3. In addition, the persons being asked to participate in a research project shall be informed of the rights and safeguards prescribed by law for their protection, and specifically of their right to refuse consent or to withdraw consent at any time without being subject to any form of discrimination, in particular regarding the right to medical care.

Article 14***Consent***

1. Refusal to give consent or the withdrawal of consent to participation in research shall not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care.

Undue influence**Article 12*****Undue influence***

The ethics committee must be satisfied that no undue influence, including that of a financial nature, will be exerted on persons to participate in research. In this respect, particular attention must be given to vulnerable or dependent persons.

Right to information**Article 26*****Right to information***

1. Study participants shall be entitled to know any information collected on their health in conformity with the provisions of Article 10 of the Convention.
2. Other personal information collected for a research project will be accessible to them in conformity with the law on the protection of individuals with regard to processing of personal data.

Article 27***Duty of care***

If research gives rise to information of relevance to the current or future health or quality of life of study participants, this information must be offered to them. That shall be done within a framework of health care or counselling. In communication of such information, due care must be taken in order to protect confidentiality and to respect any wish of a participant not to receive such information.

Duty to inform at collective level**Article 28*****Availability of results***

1. On completion of the research, a report or summary shall be submitted to the ethics committee or the competent body.
2. The conclusions of the research shall be made available to participants in reasonable time, on request.
3. The researcher shall take appropriate measures to make public the results of research in reasonable time.

Independent examination**Article 7*****Approval***

Research may only be undertaken if the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of research, and multidisciplinary review of its ethical acceptability.

Article 9***Independent examination by an ethics committee***

1. Every research project shall be submitted for independent examination of its ethical acceptability to an ethics committee. Such projects shall be submitted to independent examination in each State in which any research activity is to take place.

2. The purpose of the multidisciplinary examination of the ethical acceptability of the research project shall be to protect the dignity, rights, safety and well-being of study participants. The assessment of the ethical acceptability shall draw on an appropriate range of expertise and experience adequately reflecting professional and lay views.
3. The ethics committee shall produce an opinion containing reasons for its conclusion.

Secondary use

Article 11

Information for the ethics committee

1. All information which is necessary for the ethical assessment of the research project shall be given in written form to the ethics committee.

Article 24

New developments

1. Parties to this Protocol shall take measures to ensure that the research project is re-examined if this is justified in the light of scientific developments or events arising in the course of the research.
2. The purpose of the re-examination is to establish whether: (i) the research needs to be discontinued or if changes to the research project are necessary for the research to continue; (ii) study participants, or if applicable their representatives, need to be informed of the developments or events; (iii) additional consent or authorisation for participation is required.
3. Any new information relevant to their participation shall be conveyed to the study participants, or, if applicable, to their representatives, in a timely manner.
4. The competent body shall be informed of the reasons for any premature termination of a research project.

Transnational research

Article 9

Independent examination by an ethics committee

3. Every research project shall be submitted for independent examination of its ethical acceptability to an ethics committee. Such projects shall be submitted to independent examination in each State in which any research activity is to take place.

Sanctions

Article 30

Infringement of the rights or principles

The Parties shall provide appropriate judicial protection to prevent or to put a stop to an unlawful infringement of the rights or principles set forth in this Protocol at short notice.

Article 31

Compensation for damage

The person who has suffered damage as a result of participation in research shall be entitled to fair compensation according to the conditions and procedures prescribed by law.

Article 32

Sanctions

Parties shall provide for appropriate sanctions to be applied in the event of infringement of the provisions contained in this Protocol.

Appendix 4. Recommendation (2006)4 of the Committee of Ministers to Member States on research on biological material of human origin

Informed consent

Article 21

General rule

Research on biological materials should only be undertaken if it is within the scope of the consent given by the person concerned. The person concerned may place restrictions on the use of his or her biological materials.

Confidentiality and right to information

Article 25

The principles of chapter VIII (confidentiality and right to information) of the Additional Protocol concerning biomedical research should be applied to any research project using biological materials and associated personal data.

Independent examination

Article 24

Independent review

1. Research should only be undertaken if the research project has been subject to an independent examination of its scientific merit, including assessment of the importance of the aim of the research, and verification of its ethical acceptability. National law may additionally require approval by a competent body.
2. Member states should apply the provisions concerning ethics committees contained in chapter III of the Additional Protocol concerning biomedical research (CETS No. 195, 2005) to the review of research within the scope of this recommendation.
3. Review procedures may be adapted to the nature of the research and the extent to which the persons concerned could be identified from their biological materials or associated data.

Secondary use

Article 22

Identifiable biological materials

1.
 - i. If the proposed use of identifiable biological materials in a research project is not within the scope of prior consent, if any, given by the person concerned, reasonable efforts should be made to contact the person in order to obtain consent to the proposed use.
 - ii. If contacting the person concerned is not possible with reasonable efforts, these biological materials should only be used in the research project subject to independent evaluation of the fulfilment of the following conditions:
 - (a) the research addresses an important scientific interest;
 - (b) the aims of the research could not reasonably be achieved using biological materials for which consent can be obtained; and
 - (c) there is no evidence that the person concerned has expressly opposed such research use.
2. The person concerned may freely refuse consent for the use in a research project of his or her identifiable biological materials, or withdraw consent, at any time. Refusal to give consent or the withdrawal of consent should not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care.

Article 23

Unlinked anonymised biological materials

1. Unlinked anonymised biological materials may be used in research provided that such use does not violate any restrictions placed by the person concerned prior to the anonymisation of the materials.
2. Anonymisation should be verified by an appropriate review procedure.

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