SYNCHROS

Strategy brief on ethical and legal issues in the optimisation of cohort data in Europe

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The SYNCHROS project has received funding from the *European Union's Horizon 2020 Research and Innovation Programme* under Grant Agreement No. 825884

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Acknowledgements

SYNCHROS would like to thank all the stakeholders involved in the consultation phase and key informant interviews for valuable contributions that have resulted in this Strategy Brief.

Publication date

31st of December 2020

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1 CONTEXT

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1.1 SYNCHROS OBJECTIVES AND SPECIFIC OBJECTIVES

SYNCHROS (SYNergies for Cohorts in Health: integrating the Role of all Stakeholders) is an EU-funded Coordination and Support Action (H2020, ref. no. 825884), aimed at developing a sustainable European strategy for the next generation of integrated cohorts. It was inspired by an urgent need for a global, universal approach to the challenge of optimising the use of health cohorts that are population-based, patient and clinical trial cohorts across Europe and the rest of the world.

SYNCHROS aims to create a strategic agenda for an enhanced international coordination and sustainable recommendations for better collaboration of cohorts globally. In particular, SYNCHROS addresses the practical, ethical, legal, and methodological challenges in optimising the exploitation of current and future cohort data. In so doing, SYNCHROS supports developments for a stratified and personalised medicine approach and facilitates health policy.

The project further aims:

- To map the cohort landscape in Europe and large international initiatives.
- To identify the best methods for integrating cohort data in order to enable the harmonisation of past and future data collection
- To identify solutions for addressing practical, ethical and legal challenges in integrating data across patient, clinical trial and population cohorts
- To take stock of emerging and new data collection technologies and types of data, including new exposures and health risks, and their potential impact on the development of future cohort studies and the need to optimise the integration of data

More information on the SYNCHROS project can be found on www.synchros.eu

SYNCHROS

1.2 STRATEGY BRIEF

The Strategy Brief (alternatively evidence brief or policy brief) is an internationally-recognized strategic tool of modern implementation science – which itself has developed from evidence-based medicine and knowledge-transfer methodologies to become the foundation for promoting the adoption and integration of practices and policies for individual clinical care, public health and health research.

One of SYNCHROS' overall objectives is to address the practical, ethical and legal, and methodological challenges to optimising the exploitation of current and future cohort study data. Because of this aim, it is essential that SYNCHROS relies on implementation science to transfer what tends to be abstract and theoretical issues into practical solutions that can be accomplished in the context of existing research infrastructures and practice. Strategy briefs are the essential first step in implementation, as they provide both the scientific basis and agenda focus for the consensus-based, sustainable and strategic resolution by means of stakeholder dialogues.

The current strategy brief follows a well-established format. We begin describing and contextualizing the central issues and a case is made, both for their relationship to the overall objective of the project but also their significance and priority. This is followed by an identification and prioritization of the key issues involved, in this case the methodological obstacles to optimisation and integration of data harmonization. Relying on the evidence that is set out in previous SYNCHROS reports, each issue is presented in terms of potential options for realistic and feasible solution. Each option is motivated and evidence and argument presented. Finally, a recommendation for the best option is provided. Although for reasons provided below, it is often difficult to distinguish between ethical and legal issues in the context of cohort data integration (e.g. preservation of confidentiality is both an ethical requirement and a legal duty), we have chosen to describe these issues separately in what follows.

1.3 COHORT STUDIES

Generally, a cohort study is an epidemiological study in which subsets of a defined population are identified who are, have been, or in the future may be exposed, or exposed in different degrees, to factors hypothesized to influence the probability of occurrence of a given disease or other outcome. Characteristically involving observations of a large number of cases over a long period, cohort studies may be either retrospective or prospective, follow-up or longitudinal. In terms of the individuals observed, population cohort studies (including birth cohorts) examine what happens to a group of people as they age, while patient cohorts focus on a specific health condition and follow its natural history over time, or, if a clinical trial characterizes its patient population in terms of specific interventions and examines disease and other outcomes, addressing intervention efficacy and/or the factors responsible for differential outcomes. In the traditional, epidemiological, cohort study, the outcomes of interest are incidence of disease, death or general health status; but in principle any observable and at least in principle measurable outcome – be it situational, psychological, behavioural, or social – can be a valuable study outcome. In some instances, outcomes of interest may only become apparent over time, altering or expand the initial focus of the study.

Although biobanks and other repositories can be involved in cohort studies, these research tools are not the focus of SYNCHROS as they can raise quite distinct ethical and legal problems (and, in the case of biobanks, are already incorporated within a well-established cooperation network between biobanks in Europe, namely BBMRI-ERIC). Similarly, genomic research or research involving very large data sets – as in so-called 'big data' studies utilizing machine learning and other sophisticated techniques) can overlap with cohort studies, they too raise specific ethical and legal issues that, although not dissimilar to, are nonetheless distinct from those found in cohort studies.

1.4 VALUE OF COHORT STUDIES

Population and patient cohort studies, including those from clinical trials, are particularly valuable sources of data because they can detect and quantify changes in health-related parameters, including a wide variety of disease onset and course determinants – pathogenic, environmental and social. Identifying patterns in the specific disease outcomes and their determinants across these diverse population groups offer a robust evidence-base for improving medical science and practice. The strength of a cohort study is that it allows us to make sense of one or a complex set of diverse outcomes as the result of the cumulative, or even emergent, dynamic interplay between diverse, phenotypical, biological, behavioural and sociocultural or even political influences on human health. By relying on temporal

sequencing, cohort studies ensure that exposure to these factors precedes, rather than coincides, with outcomes. Importantly, the researcher is able to examine both multiple effects of a single exposure as well as single outcomes of multiple and diverse exposures. Arguably, no other study design could accommodate the researcher's need to understand how genetic, biological, behavioural and social determinant could, singly or in complex interactive association produce health outcomes in a population over time. This makes cohort studies particularly valuable in ageing studies where distinct patterns of 'normal' ageing can be discerning despite the somewhat bewildering number and diversity of potential determinants to which a person is exposed over the life-course.

1.5 COHORT STUDIES AND POLICY-DEVELOPMENT

Cohort studies are well-suited to provide relevant information about the diversity of determinants and the dynamics of change over time. Policy-makers benefit from information about disease trajectories and the impact of a variety of psychosocial and environment determinants insofar as they are also factors that influence how people behave (including how they might react to policy changes). Because cohort studies are longitudinal, they address the dynamics that create the most salient challenges for policy-makers: anticipating new or emerging future trends and predicting short-, medium- and long-term outcomes of policies (including the policy decision not to address a potential social trend). Evidence of long-term impacts of environmental or economic shocks and crises help to anticipate the best political tools to apply and at what stage. These data provide policy-makers with both breadth and depth of knowledge, showing not only what demographic or social trends are responsible, but also how previous policies affected their impact. Cohort studies also have the potential to expand the policy evidence base, not only for specific social problems (say, an unexpected rise in an indicator of population ill-health) but also for the higher-level policy concerns of scalability, equity and sustainability.

1.6 OPTIMISING COHORT STUDIES: HARMONISATION AND DATA INTEGRATION

Europe is extremely well served by a rich variety of population, patient and clinical trial cohorts. Integrating data from studies involving similar cohort populations exponentially increases the longitudinal power and range of health-related parameters from heterogeneous data sources. For health research generally, integrating data from existing cohort studies would increase sample size and improve statistical power to more accurately describe health outcomes and determinants, facilitating comparison across study populations that vary by geography, composition, or socioeconomic status.

Looking forward to data collection platforms that can create very large datasets, the impact of data integration on health research and the effectiveness, and efficiencies, of healthcare provision is enormous. To achieve these benefits and integrate data across cohort studies with different patient and population cohorts requires data harmonisation (building a common data base by adapting variables across studies) and data integration (defining common variables for analysis and developing methods to efficiently collect or merge data). Although the optimization of health-related data from patient and population cohort studies has been an EU priority since 2014, [1] there are substantial challenges to integrating cohort data across studies. The goal of SYNCRHOS is to identify these challenges and, by an extensive investigation into the literature and best practices, and collaborative input from stakeholders, propose solutions.

1.7 ETHICAL AND LEGAL OBSTACLES TO OPTIMIZATION OF COHORT DATA

This Strategy Brief addresses a set of ethical and legal obstacles and challenges to the goal of optimizing the use of cohort data. At the outset it is important to note that the distinction between ethical and legal obstacles can at times be fluid: the key legal issues of consent, confidentiality, and social justice, for example are at the same instant key ethical issues. The legal sphere is distinguished from ethics primarily in terms of authoritative enforceability. Unless ethical concerns are codified and given legal status, these concerns are persuasive only. Legal requirements, such as those set out in the General Data Protection Regulation (GDPR)[2], can be enforced, in a manner consistent with and subject to the provisions of the regulation and jurisdictional considerations.

Although not enforceable, ethical concerns can be genuine obstacles to the optimization of cohort studies: 1) like any study, cohort studies require ethical approval by a research ethics board, and in some jurisdictions may require ethical monitoring as the study progresses. Since boards in different jurisdictions will have different ethical assessments, they may not be consistency in enforcement, which is an obstacle to integration; 2) more generally, ethical issues affect the perceived legitimacy of studies – either by funders, government agencies, or the general public – and studies that lose perceived legitimacy may not survive for long. We begin with ethical concerns before briefly outlining the legal issues.

2 THE ETHICAL DOMAIN

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2.1 THE PHILOSOPHICAL SOURCE

There are fundamentally two sources of ethical issues that arise in the context of studies that, as is generally the case with cohort studies in health sciences, directly or indirectly involve human beings. The first is philosophical, and more specifically from standard bioethical resources. The international standard text is the *Principles of Biomedical Ethics* by Beauchamp and Childress [3], in which the authors set out four principles that govern all particular ethical concerns found in the domain of the health sciences. These are:

- Respect for autonomy (ensure that individual choice over matters concerning themselves is respected);
- Beneficence (act in a manner that benefits the individual);
- Non-maleficence (avoid causing harm to the individual); and
- Justice (ensure that the benefits of health care are fairly distributed to everyone).

The underlying values expressed are both individual-oriented (autonomy) and societally-oriented (justice).

Of necessity, these principles are very general, but in the context of health care generally, and health research specifically, they can quickly be made more concrete. For example, the principle of autonomy in health research supports the requirement that people who participate in research freely consent to do so in light of sufficient information to make an informed decision, and that information derived from their participation is confidential. The principles of beneficence and non-maleficence come into play when determining whether and to what extent the individual will benefit from research, or be harmed by it, either during research or afterwards. Finally, the justice principle requires consideration of the distribution of the value accrued from research (whether concrete benefits such as new diagnostic or therapeutic techniques or more abstract and far-reaching benefits such as new understanding or advancement of scientific knowledge) are shared with everyone.

In the vast philosophical literature on biomedical research, two central themes

emerge. First, although these principles are both intuitive and have been shown to be culturally universal, their application to particular cases is not automatic and requires careful interpretation. Secondly, and more significantly, is that ethical issues in actual settings tend to arise because two or more principles clearly apply to the situation, but provide different, even incompatible, ethical guidance about what should be done. To take a classic example, relevant to research on human subjects, is it ethical to do research on an individual willing participate who will not in any way benefit from the outcome of the research (that is, is autonomy sufficient even if beneficence is not fulfilled). Or take an other common situation, is it ethically acceptable to violate confidentiality if that is the only way in which the value of the research, which will benefit the individual, can be realized (does beneficence outweigh autonomy). The point of these examples, and the primary message of modern bioethics, is that the four principles are not absolute and because they are frequently in conflict in particular instances ethical deliberation is required to determine how best to balance them and, through a compromise, come to the most defensible ethical decision.

2.2 INTERNATIONAL TREATIES AS AUTHORITATIVE SOURCE

In light of the primary aim of SYNCHROS to contribute to a sustainable European strategy to optimize the scientific and social value of cohort studies, it is important to seek a more universal and authoritative source of ethical considerations relevant to data integration. Although in principle the philosophical discussions are rationally authoritative, to implement change at the policy level, it is more appropriate to seek these principles from international treaties that express and confirm agreement over salient ethical considerations among the European community (and beyond). Although the underlying rationale and justification for the specific provision of these quasi-legal international treaties is fully embedded in the philosophical literature (and in many instances merely expresses philosophical consensus), they are in this context authoritative expressions of agreement.

Common provisions of the following international declarations, conventions and treaties were used to extract the most salient ethical issues pertaining to cohort data integration (see Appendix 1 for specific provisions):

- UNESCO Universal Declaration on Bioethics and Human Rights, 2005.[4] (IDBHR)
- CoE. (Oviedo Convention) 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. [5] (CoE)
- OECD. Recommendation of the Council on OECD Legal Instruments Health Data Governance, 2017. [6] (OECD)
- CIOMS/WHO. International Ethical Guidelines for Health-related Research Involving Humans Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the

World Health Organization (WHO), 2016. [7] (CIOMS/WHO)

(Although it does not provide specific recommendations, another relevant document is Ethics of New Health Technologies and Citizen Participation (2016) produced by the European Group on Ethics in Science and New Technologies, a body that advises the European Commission [8].)

Table 1 shows the three common ethical issue areas relevant to data integration in cohort studies these authoritative documents identify:

Table 1 Identified common ethical issue areas relevant to data integration in cohort studies from authoritative documents

	Consent	Confidentiality	Justice
UNESCO	A3, A5, A6, A7	A8	A4, A9, A10, A11, A12, A13, A14, A15, A16
CoE	A2, A5, A6, A7, A9, A16-19	A10, A11, A12, A13	A3, A16
OECD	PIII(5)	PI, PIII(2,3,6,7)	
CIOMS/WHO	G5, G9, G10, G16, G17	G11, G12, G22	G3, G4, G7, G3, G15, G18, G19, G24

(A= Article; P= Part; G=Guideline)

2.3 THREE SALIENT AREAS OF ETHICAL CONCERN IN THE CONTEXT OF DATA INTEGRATION

CONSENT:

the most obvious ethical concern about research on human subjects is that participants must be treated with dignity and respect, rather than as mere objects of research. Here the underlying values are that of autonomy and dignity, and these play out concretely as the ethical requirement that participant's in research knowingly and willingly consent to participation and the foreseeable consequences of participation – usually termed informed consent. The preconditions of 'knowingly' and 'willingly' tend to generate the specific ethical dilemmas that can create obstacles both to the initiation and progress of cohort-based research (especially for populations who have limited capacity to understand or consent to research).

CONFIDENTIALITY:

an equally familiar ethical concern, namely that data and information that results from participation in research must only be used or disseminated in a manner that respects confidentiality. The underlying values in this area are also autonomy and respect: generally, information about oneself as an individual should be under the control of the individual, and information that is disseminated without permission may be embarrassing or otherwise disadvantageous, and in either case the act of ignoring these considerations disrespects the inherent dignity of the person. The underlying value of confidentiality is more commonly thought to be privacy.

JUSTICE:

the philosophical literature has traditionally emphasized that scientific research must produce benefit (of some variety) for society and if possible the individual participants as well, but if nothing else, it must 'do no harm' (i.e. the principles of Beneficence and Non-maleficence). Research that yields no benefit of any sort is not only socially irresponsible and wasteful of resources, arguably it is also disrespectful as it treats the time and effort of research participants as of no inherent value. In much health research, the underlying ethical issue involving a balance of both benefit and harm between the individual participant and the greater society; and it is in the determination of the balance that ethical issues arise.

This dynamic of health research raises the last area of ethical concern that moves from a primarily individualist ethics to a social ethic in which the underlying social value is fair treatment for the population as a whole. Justice is historically divided into two domains: procedural and distributive justice. Procedural justice involves the fairness of processes and protocols underlying decisions that may have consequences for individuals. If an individual is prohibited from participating in research because of a consideration that in the context of the research is scientifically and ethically irrelevant (gender, race, religious belief), then the sampling frame is unjust as it is discriminatory. Distributive justice, as the name implies, means in the context of research, that the benefits and burdens of research are fairly distributed across the population. [4: Article 15] Arguably, research that ignores the interests of future generations or of the biosphere or environment at large, is similarly unjust.

3 POTENTIAL ETHICAL OBSTACLES TO OPTMISING DATA INTEGRATION AND POTENTIAL SOLUTIONS

3 POTENTIAL ETHICAL OBSTACLES TO OPTIMIZING DATA INTEGRATION AND POTENTIAL SOLUTIONS

Although helpful, it is ultimately problematic to create separate domains or areas of ethical concern as was done above. In concrete settings, issues of consent, confidential, individual and social interests and justice not only overlap and merge, they conflict creating the standard ethical dilemma of not be able to satisfy all ethical requirements at the same time. To be able to drill down to the level of practice relevant to data integration, without ignoring the reality of overlapping and conflicting ethical demands, it is helpful to identify potential ethical obstacles associated with standard research practices involving data: **data collection**; **access and sharing of data**, and, finally **data integration** itself. In the end, all of the ethical (and the analogous legal) issues involved in data integration arise from these standard research modalities that involve data in cohort studies.

3.1 DATA COLLECTION

Continuity and scope of consent

The primary area of ethical concern associated with both initial and on-going data collection in cohort studies is that of consent to collect these data. In the standard case, in addition to the objective, aim and nature of the research and potential risks and benefits, the participant is informed of the uses of information about themselves that he or she could decide whether those uses are acceptable. But because cohort studies have a longitudinal nature and there is the potential for data integration with other cohort studies, obtaining informed consent raises the key question how a participant can meaningfully consent to potential uses of information that are unforeseeable at the time of consent. Future uses of data may not be known, or knowable, not just by the participant but the

researchers as well. If the participant is informed of this possibility, he or she may withhold consent, which creates an obstacle to research.

To address this problem, some have argued that cohort studies in principle create the ethical requirement that informed consent must be continuously renewed and updated in order to give participants the opportunity to respond to changes in the course of the research caused by unforeseen events, and in particular the perceived advantage of future data sharing or new uses of the data that the participant initially consented to. [9-10] This is sometimes called 'dynamic consent'. If the participant is convinced that he or she will retain this control over personal information, then initial consent may more readily be given. Although dynamic consent is sometimes recommended in limited cases, technologically assisted by consent apps that monitor consent continuity [11-14], other commentators have been sceptical [15] and in practice there are substantial practical problems of returning to the original participants in a study to renew consent and hence, it may not be a feasible solution.

To be clear, the issue here is not the frequently-heard objection that because the scientific research is highly specific, technical or requires expertise, participants in research do not have the intellectual capacity or scientific background to be able to understand the information that is presented to them, and so cannot 'knowingly' consent (e.g. [16-18]). This somewhat paternalistic complaint typically is raised to seek exception to, or sidestep, the ethical and legal requirement of informed consent.
But this stance ignores the fact that only information directly relevant to support the decision to participate is required: the participant does not need to become an expert in the background science. Moreover, researchers have access to established strategies – e.g. decision aids, workshops and training sessions – to ensure that participants fully understand the content of consent. [19-21] It is not plausible that, with patience and time, comprehensible information about the nature of the research, its risks and benefits cannot be communicated successfully. Techniques of 'supported decision-making' in which more active counselling and education is used can also overcome this informational inequality. [22]

The ethical problem is rather that for cohort studies that there may be no possibility to determine in advance what information should be presented since researchers may not themselves know how research objectives may evolve in the future in light of data integration with other or future cohort studies. [22-3] In other words, the kind and extent of information necessary to be informed for the purposes of autonomous consent cannot always be determined in advance since some applications and uses of data are unforeseeable. [13,24] Again, unless the participant agrees to waive consent (which is not legally possible in some European jurisdictions), this feature of data integration create an obstacle to optimization of data use for cohort studies.

Two options for dealing with this ethical obstacle have been suggested:

Option 1: Loosen autonomy restrictions in favour of social value and duty to participate

Without totally displacing the value of autonomy, it might be argued that this value is not absolute and must be balanced against the potential value, both for the participant and society as a whole, of the research. Individuals often, for the greater good, are required to limit their autonomy by, example, obeying the laws of the land. As long as these restrictions are reasonable and justifiable, and, most importantly, the individual can fully participate in this group decision to restrict autonomy (e.g. by means of democratic processes that are open to all and fully transparent), then the individual has in effect consented to having his or her autonomy limited. (A stronger, and more contentious, version of this argument is that, under these conditions of full participation, that if research has a good chance of producing genuine value for everyone, then the individual participant has a duty to consent.)

In the specific case of cohorts, commentators have made the case for Option 1 in a variety of ways:

- Autonomy must always be linked to the public good, and while participants may plausibly argue that they should be fully autonomous over some highly personal information, that does not mean they are over all information. [16,25-26]
- Unconditional autonomy can only be justified by an implausible application of methodological individualism that in practice can lead to health inequalities and stigmatization. [27] Researchers should instead adopt a communitarianism perspective that balances the recognition that participants are able to take fully rational decisions against their responsibilities in relation both to societal conditions and to the individual members of society as a whole. [28-31]
- We regularly limit autonomy for consent, for example, when participants because of intellectual impairments or mental health problems do not have the full decision-making capacity. [31] As long as the research promises to produce social value and the participant is not harmed, then consent can be presumed.
- Limiting the impact of autonomy in the case of cohort research makes sense because participants are not only limited in their capacity to understand scientific information, they do not necessarily have an adequate idea of what constitutes their best interests, or to evaluate the risks and benefits of their participation. [28] They are thus not necessary qualified to evaluate the *risks and benefits* of their participation. They may thus over-estimate the likelihood of potential benefits to research and underestimate the risks of research procedures. Hence, the researcher has to decide whether he or she should mention only those benefits and risks that are very likely to be achieved.
- A related issue is the therapeutic *misconception problem* where participants accept to take part in clinical research because they expect to receive the same individually focused treatment that they would receive in a non-research clinical context. [33] The question therefore, is whether researchers should specify that the research is calibrated for gaining generalisable knowledge rather than for patients' benefits. For example, the participant might be under the 'therapeutic

misconception' that he or she as a participant in a study receive the same kind of clinical treatment as he or she should would under treatment. [33]

- Given the increase use of 'big data' data collection tools, such as wearable devices, where in effect the participant is creating the data it is increasingly unlikely that a participant can be informed of the extent of the data that will be collected [34] or the future uses of their data. [35] In the world of new technology, informed consent is simply an unrealistic requirement that cannot be implemented in practice. [21, 23]

Option 2: Broad or enduring consent

Although international bioethical conventions often speak about the requirement that consent be expressly given and 'specific' [5: Articles 5 and 16], the consent requirement has been interpreted to allow for a range of clinical and research interventions, on a spectrum from high to relatively low strictness on the scope of consent. For example, in the case of consenting to potential dangerous research or therapeutic intervention, consent requires specificity so that the individual is fully aware of what he or she is consenting to. Arguably, when this level of harm or vulnerability is not present, then the requirement of specificity can be removed. When consent is sought only with respect to the storage, maintenance or secondary research involving private information by means of cohort data integration, then perhaps a less stringent version of consent is ethically acceptable.

This is the argument for broad consent, or consent that extends beyond the explicit research objectives of the study to which the participant gives consent (sometimes called 'prospective consent'). The ethical acceptability of broad consent has recently been incorporated into the 2018 US Department of Health and Human Services criteria for Institutional Research Board approvals of research. [36] In addition to the standard requirements for consent – the objective, aim and nature of the research, potential harms and benefits – broad consent also requires the researcher to provide the participant with: a) a description of the types of secondary research that may be conducted; b) a description of the private information that might be used in research, whether sharing of the information might occur, and the types of institutions or researchers that might conduct research with the information; c) information on how long the information will be stored, maintained, and used; d) a statement that the participant will or will not be informed of the details of any subsequent research and research results. (As we shall see, there are provisions of the GDPR that imply that some of these provisions may be included for valid consent when it is not possible to fully identify how personal data will be used in the future. [2: Article 33]

While the first options invites use to balance autonomy against social benefits of research (or even against the individual's own obligation to contribute to social benefit by participating) this second option suggests that the value of autonomy is in part a function of what is at risk from consenting. If one is consenting to some form of bodily interventions in a clinical setting, then the case for the individual to be fully in charge of the decision whether to have the treatment or not is very strong:

being able to freely make decisions about what happens to one's own body is the clearest example of what autonomy protects. When the issue is information however, it is not as clear that we have complete autonomy over this information. Information, so to speak, resides more in the public than the private sphere, and a person does not necessarily 'own' information, even personal information, especially when the public use of that information is of scientific, and so societal, value. Broad consent, in short, may be sufficient to fully protect the value of autonomy.

Other arguments for this option have been suggested:

- At least with respect to non-biological and de-identified information, parents of children in birth cohorts appear to prefer non-specific consent for use of research data, as long as there are governance practices in place that are both highly detailed and rigorous. [37] This confirms the general point that the right to consent, and the underlying value of autonomy, is not univocal but depends on the nature of the information at issue.
- Some have argued that the doctrine of informed consent is not the only manner in which the value of autonomy can be preserved while allowing, and encouraging, the widest use of data. Looking to novel governance structures in which, for example, data is owned by individuals collectively by agreement, autonomy protection without the need for specific consent is provided. [38,39] So far, these proposals have concentrated on genomic research and biobanks, where the notion of ownership has more purchase than might be the case for population cohort studies generally. If such solidarity-based approaches to governance reflect future trends, it is significant that broad consent is in fact a pre-cursor to such an approach, and may be more acceptable as a first step.

3.2 ACCESS AND SHARING OF DATA

Preserving confidentiality

The underlying ethical values of confidentiality are autonomy and respect: we respect an individual's presumptive right to keep information about themselves private, or at least subject to the individual's control. Privacy is the manifestation of respect in the informational domain. Of course, individuals live with and have obligations to others, organized into social organization. Because individuals live with others, it is rare when information is exclusively about one single individual or only impacts on the interests of a single individual. Most information is about shared events and concerns shared interests. Because we have obligations to others, often enforced by society, there are occasions in which private information has public significance and public interest overrides privacy: the fact that one is showing symptoms of a highly infectious disease, and can readily affect others, is in one sense private information, but the interests of all in limiting exponential contagion overall the harm to the individual of invading privacy. In short, when accessing and sharing data from individuals, the privacy consideration will always be potentially offset by the consideration of public interest. [23]

With cohort studies, data sharing and integration requires interoperability – by means of ex ante or ex post harmonization – and while this improves accessibility it also increases the changes that confidentiality is breached, either directly or by means of de-anonymization and incidental re-identification. In cohort research, generally, protecting privacy is evaluated by parameters that determine the flow and pathway of information, [40] and the potential for breach of confidentiality by unintentional or inappropriate access depends very much on the type of data collected and means of collection. [20,23,24] Advanced mobile and wearable technology and web-based modes of data collection, to take the obvious example, limit individual control over data because participants become part of an interacting system that enhances connectivity while diluting individual control. [16, 41-6] Independently of policies designed to support 'free data flow' and 'open science', [30] or terms of funding, peer-review requirements or ethical committee approvals, [47] or even the complexities of determining intellectual property rights to data, [32] the potential for the requirement to preserve confidentiality may have the effect be an obstacle to optimizing the value of cohort data would be stymied.

Two options have been proposed to deal with this potential obstacle:

Option 1: Federated structures that allow data to be shared in a de-identified form

Growing out of international efforts to ensure data comparability in registry databases and biobanks, several mechanisms have been suggested to preserve confidentiality while benefiting from access to integrated data. One component of this was to reach agreement on principles of good data management and stewardship. The well-known FAIR data principles, first published in 2016, address this international concern. [48] Data should be Findable, Accessible, Interoperable, and Reusable in order to maximize the added-value of the enormous volume of scientific data in the literature. These principles were motivated and designed to serve the interest of 'contemporary e-science' and point to both infrastructural and methodological solutions to data management, consistent with many special-purpose data repositories as well as repository software such as Dataverse, FAIRDOM and others. In the domain of cohort studies specifically, the federated approach has been strongly recommended as a way of solving methodological problems in harmonization of data. [49-51]

But the resulting FAIR-compliant platforms and federated facilities often claim to resolve the ethical issue of confidentiality as well. At the outset, the FAIR principles were directly linked to the promise of ‘machine actionable’ endeavours, in which "a digital object provides increasingly more detailed information to an autonomously acting, computational data explorer." [48:3] What is being referred to here are technologies of 'distributed analytics' in which data collected from numerous sources – researchers, healthcare institutions, or generated by individuals by apps and wearable devices – can be used and re-used without data owners losing control or breaching confidentiality. [52]

For example, the Personal Health Train is a federated, cooperative infrastructure in which the original data steward – fully implementing the FAIR principles – can maintain control over data without sacrificing any confidentiality promises that have been arranged with the individual who provided the data. Should a researcher member of the federation request access to the data for analysis, the data does not move to the researcher but is shifted to a secure data repository where the machine-based analytics executes whatever tasks the researcher has requested. If the original data steward – the owner of the database – feels that there is a potential for de-anonymization or re-identification in the proposed analysis, then that use can be prevented. [52] Similarly, the UK Data Service Secure La, UK SERP, DataSHIELD and ViPAR are all software infrastructures for distributed analysis that facilitate the direct analysis of repository data from multiple studies simultaneously without sacrificing confidentiality or other data-use restrictions. [53-56]

It should be noted that this option depends on technical and methodological issues that are covered in the Strategy Brief on methodological issues. Moreover, the feasibility of this option depends on the participation in one or more of these federated structures among the community of cohort study researchers and others who have ownership over the data.

Option 2: Governance structures to coordinate public and private interests

The second option builds on the insight mentioned about that private and public interests are fundamentally interconnected, in the sense that it is both a private and a public concern to maintain privacy and, equally, it is both a private and public interest to optimize the responsible use of data that is compatible with this ethical value. [57:154] In the domain of confidentiality, the issue is not so much 'balancing' privacy against public interest, but coordinating these interests.

Institutionally, this suggests the option of creating sustainable, governance structures, potentially international in scope, that can act both as a neutral data custodian and intermediary between competing or uncoordinated interests of relevant stakeholders: researchers, health practitioners, governments, and individual citizens in their role as data sources. The primary role of these structures would be to transparently decide on how best to coordinate these interests, either on a case-by-case basis or as a matter of policy. As articulated in the 2015 Nuffield Council on Bioethics report on biomedical data use for research and health care, the task of such an agency would not be to establish rules that set some basic threshold of acceptability for data initiatives, but to 'permeate' these initiatives with ethical reflection throughout the process of establishing and implementing a data initiative. Recognizing that there are ethical arguments on both sides of the issue of confidentiality of personal data, the aim is to continuously seek better solutions rather than set forth permanent rules or guidelines. [57:155]

An example of such an agency is the UK Health and Social Care Information Centre (HSCIC), which in the language of the legislation that created it in 2012, is meant to be "a national focal point for information collection across health and social care that is responsible for collecting, transporting, storing, analysing and disseminating the nation’s health and social care data. [58] The remit of the HSCIC is to collect and store all health care information from the country's care centres, including GP practices, and to determine whether the data is open or limited access. The agency has the authority to determine whether, in the public interest, data can be disclosed even if it potentially can identify individuals who have withheld consent from such disclosure. Although the Nuffield Report ultimately finds fault in various features of the governance structure and day-to-day operations of HSCIC, the agency shows that the potential for this option is not unrealizable. Ethically, the acceptability of this option depends on a commitment not only to transparency but also to active public engagement in decisions about how to balance, or coordinate, the individual's concern about confidentiality and the public's interest in deriving as much value from research data as possible. [23,57]

3.3 DATA INTEGRATION

Benefit for patients and society: the domain of justice

So far, the ethical issues that raise potential obstacles to the optimal use of cohort studies, by means of data sharing and integration, have concerned the ethical values of autonomy and respect, and the derivative value of privacy. In classical research bioethics, one of several balancing exercises is to ensure that for the individual the balance of potential benefit from participating in research outweigh the potential harm. The source of this issue is two-fold, first that research must 'do no harm' and secondly that research should benefit, either directly or indirectly, the participating individual. These are obviously important issues, although rarely raised in the context of data integration. Another classical concern of research ethics, however, is more pertinent, and that is the social value of the research itself. Here the underlying point is that research that lacks social value lacks ethical rustication as well, for the simple reason that, in light of scare resources, socially valueless research is a waste of resources. Again, this consideration does not involve the individual values of autonomy and privacy, rather it involves the social value of justice.

This ethical consideration is clearly reflected in international ethical conventions and guidelines. The opening guideline of *the International Ethical Guidelines for Health-related Research Involving Humans*, for example, states that "The ethical justification for undertaking health-related research involving humans is its scientific and social value: the prospect of generating the knowledge and the means necessary to protect and promote people's health." [7: Guideline 1] Social value can be undermined by poor science. But it can also be undermined by respectable science that perpetuates social stereotypes and stigma, or whose sampling frame privileges some populations (e.g. Western, Educated, Industrialised, Rich and Democratic (WEIRD) societies, while ignoring others, or whose benefits are not equally shared across society.

Although it is not controversial that ethically acceptable research must have social value, evaluating the social value of research is fraught with controversy, and scepticism about whether, and how, social value can be ascertained is a potential ethical obstacle to the aim of optimizing the value of cohort data through data integration.

There are two options to circumvent this obstacle, one that trades on the possibility of ascertaining the social value of research at all, and the other that suggests a mechanism for doing.

Option 1: Determination of social value through scientific consensus

The case for this option is that no procedure or process can plausibly determine the social value of research and our best option is to use appropriate blind peer-reviewing by relevant and conflict-free scientific experts to make a decision to approve or fund research solely on scientific merit. Scientific consensus becomes a proxy indicator of social value. This scepticism may be fuelled either by examples of research that did not initially appear to further any social aim, but later did, or more bluntly, by the view that social value is unknowable and the best we can do is rely on scientific consensus utilizing objective criteria of scientific soundness.

Option 2: Agency to negotiate the social value of research

Most middle- and high-resources countries rely on research councils, institutes or funding agencies that seek to evaluate both the scientific and social value of research, especially in the health area in which the potential for direct implementation at the clinical level, or even commercialization, is often a requirement of funding. Details of governance structure for such agencies are not as important as the underlying principles involved. First and foremost is the need for full participation by all stakeholders, including the public at large. And this may involve active participation in the sense of ethical engagement, rather mere representation of positions. The point is to describe what is in the public interest and participatory involvement is a pre-requisite. As is full transparency: hidden agendas or special interests do not reflect the public interest, or identify public goods. Finally, determination of the social value of research inevitably involves reconciling and negotiating relevant interests of individuals and groups that often are conflict. [57:153]

The CIOMS/WHO Guidelines recognizes in Guideline 7 the importance of community engagement in the determination of the social value of research, putting the responsibility for ensuring this with state authorities. Engagement to be effective needs to be encouraged at the outset, for example when research funding objectives are being developed, so that the public is not brought in after the research is a fait accompli. Guideline 8 further acknowledges that engagement is only possible if the public has the capacity to review and evaluate health research. At the same time, it would be naïve to assume that the general public would have the ability to be able to fully understand the scientific background or have the specialized knowledge to be able competently evaluate all examples of health research. [43] Equally problematic is the phenomenon of patient advocacy groups whose interests in promoting research to benefit specific groups may complicate agreement on the ultimate social value of health research. [59-61]

The feasibility of such an agency, therefore, very much depends on several open questions, perhaps the most important of which is the extent to active participation and ethical engagement is possible for a wide range of stakeholders, with potentially conflicting agendas in the case of health research. [41,60] Unlike models of participatory research in the social sciences in which issues of value are more easily addressed, and indeed participants in research can contribute to the design of studies

themselves, in health science research this level of engagement is rare. [62-4]. So, the agency would not be able to call upon experienced and engaged members of the public to contribute to the determination of the social value of research, especially where there are conflicting interests. At the same time, the authority of such an agency need not depend on a 'track record' of popular judgments about which research is socially valuable and which is not. It might suffice if the agency has the public perception of neutrality, fairness and respect for different interests.

3.4 ETHICAL ISSUES: SUMMARY

A review of the major international ethical conventions and guidelines indicates that the most salient ethical considerations relevant to the issue of optimizing the potential impact and social value of cohort research through data integration are: Consent, Confidentiality, balancing individual and social interests in the context of Justice. The most relevant analysis of the impact of these values on cohort research focuses on the collection, access, sharing and integration of data. This accords with the intuition that the primary concern with cohort research is how data is collected from human subjects and how it is manipulated to achieve both the optimal scientific use of data and to achieve the ultimate social value of the research.

Focusing on the methodological stages of data collection, the access and sharing of data and data integration yields potential ethical obstacles to optimizing cohort study data. These obstacles, it should be clear, all arise from the apparent conflict between adherence to ethical principles and carrying the research from inception onwards. For each area of ethical concern, options were proposed and arguments from the literature summarized in Table 2:

Table 2 - Summary of ethical issues and options

Methodological stage	Ethical concern	Option 1	Option 2
Data collection	Continuity and scope of consent	Loosen autonomy restrictions in favour social value and duty to participate	Broad or enduring consent
Access and sharing of data	Preserving confidentiality	Federated structures that allow data to be shared in a de-identified form	Governance structures to coordinate public and private interests
Data integration	Benefit for patients and society: the domain of justice	Determination of social value through scientific consensus	Agency to negotiate the social value of research

4 LEGAL CONCERNS AND ISSUES

4 LEGAL CONCERNS AND ISSUES

4.1 CONTEXT

There will always be a conceptual parallel between ethical and legal issues in the domain of scientific research, since all attempts at legal codification are essentially codifications of ethical conclusions about the same issues – primarily consent and confidentiality. Inevitably, critiques of legal solutions – whether 'soft' international guidelines or hard national, enforceable legal provisions – will conceptually involve ethical considerations of balancing conflicting interests. Yet, since they deal with concrete matters of practice, legal provisions are detailed and complex, and the interpretation of legislative provisions inevitably is a fluid process that depends on the pace of litigation and other factors. For that reason, for this Strategy Brief, we will outline the major categories of legal issues rather than try to summarize the state of play at the national level in the EU countries or at the transnational level with the central piece of legislation from the European Parliament and the Council of the European Union – namely the General Data Protection Regulation (GDPR). [2]

It perhaps goes without saying that the literature on legal regulations that, in the eyes of researchers, are 'constraints' on science tends to be more aggressively opposed to legal obstacles than the more flexible ethical obstacles: the law proceeds at a much slower pace than advances in data collection technologies, biotechnologies and bioscience, [28] and legal frameworks more easily become obsolete in relation to scientific development. [65,66]

Yet if scientists are often frustrated by legal constraints on consent and confidentiality, it is important to put research into a the wider social context: without public support and financing – including indirect supports such as financing higher education institutions in which cutting-edge research is conducted – research activity would either not exists or would be restricted to the private sphere where the benefits of research would no longer be public goods, but rather private commodities that would be sold to the highest bidder. Society clearly benefits from scientific research, and in particular health research; but scientists also benefit from society. Legal constraints regarding consent and confidentially that are imposed on

scientific research cannot easily be cast aside as in principle objectionable, even if each constraint needs to be negotiated in terms of potential, competing social values.
As in the ethical sphere, the potential legal obstacles to scientific research in general, and the optimisation of cohort study data in particular, will always be a matter of balancing values and obligations. For legal obstacles it is less important to separate out the distinct issues surround consent and confidentiality, as not only do these issues interact within the legal sphere, but they typically are governed by rules or regulations from a signal legal source.

5 POTENTIAL LEGAL OBSTACLES TO OPTMISING DATA INTEGRATION AND POTENTIAL SOLUTIONS

5 POTENTIAL LEGAL OBSTACLES TO OPTIMIZING DATA INTEGRATION AND POTENTIAL SOLUTIONS[1]

5.1 CONFLICT BETWEEN NATIONAL LEGAL REGIMES GOVERNING RESEARCH

Scientific research, and especially cohort studies, is rarely restricted to a single jurisdiction. Although there are of course purely national birth cohorts, registries and biobanks, most large-scale cohort studies involve at their initiation a consortium of researchers from different countries. And national registries and biobanks profits from international organizations to establish common rules. When research is international, however, researchers inevitably face the problem of the interplay and potential contradiction between legal rules governing consent and confidentiality. [66] Across Europe in particular, there are significant tensions and outright contradictions between national legal frameworks, most of which are themselves bound by the international and European conventions and guidelines, such as the EU Clinical Regulation no: 536/2014, and those mentioned above – the Council of Europe Oviedo Convention and the 2004 Universal Declaration on Bioethics and Human Rights. [67]

There are various and differing study approval procedures on the local level. There are also variations in rules governing access to cohort data. Various jurisdictions across the EU countries have different (and sometimes contradictory) expectations about how cohort data was collected in the first place. This can block or hinder open access and open sharing between cohort studies because they are in opposition to local legal provisions or case law interpretations. There are important variations for informed consent and consent exemptions. All of this results in difficulties in choosing between narrow and general consent and generates confusion for re-contacting procedures. There is also a lack of consensus on data

[1] The SYNCHROS consortium is currently working on a more comprehensive Strategy Brief only on legal issues in the optimisation of cohort data in Europe

protection norms and requirements for the protection of privacy.

5.2 TECHNICAL SOLUTION TO NATIONAL LEGAL CONFLICTS

One solution is to borrow from human genome research the practical technique of bringing computation to data. [68] 'Compute-to-Data' is a technical means for exchanging data while preserving privacy by allowing the data to stay with the data controller (the individual or individual responsible for the generation, harmonization and storage of data) and allowing data consumers to run computations tasks on the data: rather than sending data to the algorithm, the algorithm runs where the data is. Client-server architecture such as DataSHIELD for cohort studies [55] or for biobanks BioSHaRE-EU [69]. This is a useful solution in case the governance scheme in place prevents data release or forbids the combination of multiple datasets. [70] 'Compute-to-data' frameworks allow researchers, not only to more easily resolve methodological problems in harmonization, but also to combine individual level analysis of harmonized data from various EU cohorts (regardless of whether they were held by cohort custodians or requested remotely). [40]

5.3 GENERAL DATA PROTECTION REGULATION (GDPR)

The GDPR was approved by the European Parliament and the Council of the EU on 27 April 2016 and came into general force in May, 2018. It applies to all European institutions, companies and individual researchers. It was the result of several years of EU debate over increasing concerns for participants' privacy and data protection, especially in the case of health research. [70] The GDPR was, inevitably, also a response to the previous issue, namely lack of consistent direction across Europe on issues of consent and confidentiality. As a solution to this problem, the GDPR has been not been wholly successful in practice, in no large part because all of its 99 articles and 173 recitals are open to interpretation. The GDPR is extraordinarily complex legislation that will keep lawyers busy.

As a general matter, the GDPR "strengthens individual control of data subjects over their data in this digital age" especially in light of growing scepticism about the reliability of anonymisation as a technique for protecting confidentiality. [71] The intention was to harmonize data privacy laws across Europe and specify the legitimate modalities of data collection, storage, sharing and use for categories of data that are potentially 'private'. [67] There was also an intention to ensure the protection of vulnerable communities' rights. [72] The general principles of the GDPR – Lawfulness, fairness

and transparency; Purpose limitation; Data minimisation; Accuracy; Storage limitation; and Integrity and confidentiality – all underscore the need to strengthen individual data subjects' control over their data. In this sense the GDPR is fully consistent with the general thrust of all international ethical conventions and guidelines concerning the central role of consent.

The GDPR only applies to personal data – and hence to the bulk of the data found in health cohort studies – but not to fully anonymous data [66,73] and the principle of data minimization requires that data be fully anonymised when it no longer serves any scientific or statistical purposes. Yet remains unclear whether so-called 'pseudoanonymised' data (data that could identify an individual but to do so requires a key that is safely kept by the data controller) is personal data or not. [71] If data is personal data under the terms of the GDPR – and all health data is in principle personal data – then collection, storage, sharing and use require informed consent that is "freely given, specific, informed and unambiguous by a clear and affirmative act". [2: Article 7]

Some commentators have argued that by making explicit informed consent the primarily pre-condition for research involving personal data, the GDPR constitutes an obstacle to innovative health research in the EU. [67] The requirement might exclude persons from participating in research who should have benefited from it the most. [22] By focusing on the risk of re-identification, data integration across cohort studies, and longitudinal research in general may be jeopardized [74] nothing else the insistence on explicit consent might increase research costs. [75] On the other hand, some researchers suggest that informed consent may not be a sufficient protection of the rights of individuals, when for example, the data controller is a public authority with sufficient power to convince the data subject that he or she would suffer some detriment were they to refuse. [76]

Despite GDPR's strong statement about the centrality of informed consent, and in particular the requirement that it be 'specific', the Regulation qualifies this approach in two ways. First, there is a recognition in one of the Recital, that there may be a role for 'broad consent' (or potentially even 'dynamic consent' [73]) when "The specific purposes of data processing for research cannot be fully identified at the start of data collection.

Therefore, data subjects should be allowed to consent for certain areas of research'. [2: Recital 33; 71] Secondly, GDPR's general operating principle of 'no personal data processing or use without inform consent' is subject to four widely-ranging exemptions:

- Necessary to protect the vital interests of the data subject;
- Necessary for preventive or occupational medicine, medical diagnosis, provision of healthcare etc.…;
- Necessary for the public interest in public health, such as protection against serious cross-border health threats, assuring high standards of quality and safety etc.…;
- Necessary for scientific, historical or statistical purposes … based on Union or member state law which must be

> proportionate to the aim pursued and provides suitable and specific measures to safeguard the rights and freedoms of the data subject. [2: Article 9.2]

Although some have concluded that these exceptions should be welcome to the researchers since it suggests that "there is considerable flexibility afforded to data processing for scientific research or statistical purposes under the GDPR", [76:37], that may be too optimistic a conclusion. One does not have to be a lawyer to see the enormous potential for both interpretative leeway and alternative approaches to balancing public health, scientific and broadly social benefits of research from data sharing on the one hand and the privacy rights of study participants. [66,67]
If the GDPR opens the door to broad consent (although this remains controversial [71]), and given the spectrum of potential countervailing social interests that might modulate the requirement of informed consent, then it is difficult to be fully confident that the GDPR will send a consistent and clear message to researchers. A legal document with considerable potential interpretative fluidity might not be one that researchers can confidently rely on. Some Member States may react by not applying the GDPR to the healthcare context at all, or seek specific national exemptions for certain categories of data, as allowed by the Regulation. In the end, guidance on the interpretation of the GDPR is the hands of the European Data Protection Board at the EU level and individual national supervisory authorities at the Member States level, and ultimately, the Court of Justice of the European Union. Unfortunately, interpretative questions are complex and need to be dealt with on a case-by-case basis, and this take times.

Cohort studies that rely on standard data collection tools such as surveys, medical examinations, and self-report questionnaires to collect personal information are difficult enough to assess in terms of the security of data; but with new technological data collection tools such wearable sensors and social media dominate the data collection toolbox, the clarifying role of the GDPR may be further limited in practice. Unfortunately, there is no solution to this legal obstacle other than those that are provided by the terms of the Regulation itself.

5.3 LEGAL ISSUES: SUMMARY

Essentially there are two kinds of potential legal obstacles to the optimalisation of cohort data through harmonization and data integration: the lack of consistency between legal standards for protection of confidentiality and the terms of informed consent for health research generally across the EU countries; and the fact that the potential solution to this diversity, the General Data Protection Regulation is an extraordinarily complex, and relatively new, regulatory document that is inherently subject to a high degree of interpretative fluidity that – perhaps in time but not at the moment -- has been resolved to produce transparent clarity that researchers can rely on with confidence.

To be sure, as mentioned above there are certain technical solutions such as 'compute to data' that in limited cases, can serve the interests of the researchers, data subject providing personal data, and society at large. But as a general matter, the legal situation remains unclear. Unclarity in this context is an obstacle that poses a challenge for the future.

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APPENDIX

UNIVERSAL DECLARATION ON BIOETHICS AND HUMAN RIGHTS

19 October 2005

Article 1 – Scope

1. This Declaration addresses ethical issues related to medicine, life sciences and associated technologies as applied to human beings, taking into account their social, legal and environmental dimensions.
2. This Declaration is addressed to States. As appropriate and relevant, it also provides guidance to decisions or practices of individuals, groups, communities, institutions and corporations, public and private.

Article 2 – Aims

The aims of this Declaration are:

(a) to provide a universal framework of principles and procedures to guide States in the formulation of their legislation, policies or other instruments in the field of bioethics;

(b) to guide the actions of individuals, groups, communities, institutions and corporations, public and private;
(c) to promote respect for human dignity and protect human rights, by ensuring respect for the life of human beings, and fundamental freedoms, consistent with international human rights law;
(d) to recognize the importance of freedom of scientific research and the benefits derived from scientific and technological developments, while stressing the need for such research and developments to occur within the framework of ethical principles set out in this Declaration and to respect human dignity, human rights and fundamental freedoms;

(e) to foster multidisciplinary and pluralistic dialogue about bioethical issues between all stakeholders and within society as a whole;

(f) to promote equitable access to medical, scientific and technological developments as well as the greatest possible flow and the rapid sharing of knowledge concerning those developments and the sharing of benefits, with particular attention to the needs of developing countries;

(g) to safeguard and promote the interests of the present and future generations;

(h) to underline the importance of biodiversity and its conservation as a common concern of humankind.

Principles

Within the scope of this Declaration, in decisions or practices taken or carried out by those to whom it is addressed, the following principles are to be respected.

Article 3 – Human dignity and human rights

1. Human dignity, human rights and fundamental freedoms are to be fully respected.

2. The interests and welfare of the individual should have priority over the sole interest of science or society.

Article 4 – Benefit and harm

In applying and advancing scientific knowledge, medical practice and associated technologies, direct and indirect benefits to patients, research participants and other affected individuals should be maximized and any possible harm to such individuals should be minimized.

Article 5 – Autonomy and individual responsibility

The autonomy of persons to make decisions, while taking responsibility for those decisions and respecting the autonomy of others, is to be respected. For persons who are not capable of exercising autonomy, special measures are to be taken to protect their rights and interests.

Article 6 – Consent

1. Any preventive, diagnostic and therapeutic medical intervention is only to be carried out with the prior, free and informed consent of the person concerned, based on adequate information. The consent should, where appropriate, be express and may be withdrawn by the person concerned at any time and for any reason without disadvantage or prejudice.

2. Scientific research should only be carried out with the prior, free, express and informed consent of the person concerned. The information should be adequate, provided in a comprehensible form and should include modalities for withdrawal of consent. Consent may be withdrawn by the person concerned at any time and for any reason without any disadvantage or prejudice. Exceptions to this principle should be made only in accordance with ethical and legal standards adopted by States, consistent with the principles and provisions set out in this Declaration, in particular in Article 27, and international human rights law.

3. In appropriate cases of research carried out on a group of persons or a community, additional agreement of the legal representatives of the group or community concerned may be sought. In no case should a collective community agreement or the consent of a community leader or other authority substitute for an individual's informed consent.

Article 7 – Persons without the capacity to consent

In accordance with domestic law, special protection is to be given to persons who do not have the capacity to consent:

(a) authorization for research and medical practice should be obtained in accordance with the best interest of the person concerned and in accordance with domestic law. However, the person concerned should be involved to the greatest extent possible in the decision-making process of consent, as well as that of withdrawing consent;

(b) research should only be carried out for his or her direct health benefit, subject to the authorization and the protective conditions prescribed by law, and if there is no research alternative of comparable effectiveness with research participants able to consent. Research which does not have potential direct health benefit should only be undertaken by way of exception, with

the utmost restraint, exposing the person only to a minimal risk and minimal burden and, if the research is expected to contribute to the health benefit of other persons in the same category, subject to the conditions prescribed by law and compatible with the protection of the individual's human rights. Refusal of such persons to take part in research should be respected.

Article 8 – Respect for human vulnerability and personal integrity

In applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected and the personal integrity of such individuals respected.

Article 9 – Privacy and confidentiality

The privacy of the persons concerned and the confidentiality of their personal information should be respected. To the greatest extent possible, such information should not be used or disclosed for purposes other than those for which it was collected or consented to, consistent with international law, in particular international human rights law.

Article 10 – Equality, justice and equity

The fundamental equality of all human beings in dignity and rights is to be respected so that they are treated justly and equitably.

Article 11 – Non-discrimination and non-stigmatization

No individual or group should be discriminated against or stigmatized on any grounds, in violation of human dignity, human rights and fundamental freedoms.

Article 12 – Respect for cultural diversity and pluralism

The importance of cultural diversity and pluralism should be given due regard. However, such considerations are not to be invoked to infringe upon human dignity, human rights and fundamental freedoms, nor upon the principles set out in this Declaration, nor to limit their scope.

Article 13 – Solidarity and cooperation

Solidarity among human beings and international cooperation towards that end are to be encouraged.

Article 14 – Social responsibility and health

1. The promotion of health and social development for their people is a central purpose of governments that all sectors of society share.

2. Taking into account that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition, progress in science and technology should advance:

(a) access to quality health care and essential medicines, especially for the health of women and children, because health is essential to life itself and must be considered to be a social and human good;
(b) access to adequate nutrition and water;

(c) improvement of living conditions and the environment;

(d) elimination of the marginalization and the exclusion of persons on the basis of any grounds;

(e) reduction of poverty and illiteracy.

Article 15 – Sharing of benefits

1. Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries. In giving effect to this principle, benefits may take any of the following forms:

(a) special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research;

(b) access to quality health care;

(c) provision of new diagnostic and therapeutic modalities or products stemming from research;

(d) support for health services;

(e) access to scientific and technological knowledge;

(f) capacity-building facilities for research purposes;

(g) other forms of benefit consistent with the principles set out in this Declaration.

2. Benefits should not constitute improper inducements to participate in research.

Article 16 – Protecting future generations

The impact of life sciences on future generations, including on their genetic constitution, should be given due regard.

Article 17 – Protection of the environment, the biosphere and biodiversity

Due regard is to be given to the interconnection between human beings and other forms of life, to the importance of appropriate access and utilization of biological and genetic resources, to respect for traditional knowledge and to the role of human beings in the protection of the environment, the biosphere and biodiversity.

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

Chapter I – General provisions

Article 1 – Purpose and object

Parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine.

Each Party shall take in its internal law the necessary measures to give effect to the provisions of this Convention.

Article 2 – Primacy of the human being

The interests and welfare of the human being shall prevail over the sole interest of society or science.

Article 3 – Equitable access to health care

Parties, taking into account health needs and available resources, shall take appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate quality.

Article 4 – Professional standards

Any intervention in the health field, including research, must be carried out in accordance with relevant professional obligations and standards.

Chapter II – Consent

Article 5 – General rule

An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time.

Article 6 – Protection of persons not able to consent

1 Subject to Articles 17 and 20 below, an intervention may only be carried out on a person who does not have the capacity to consent, for his or her direct benefit.

2 Where, according to law, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law.

The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity.

3 Where, according to law, an adult does not have the capacity to consent to an intervention because of a mental disability, a disease or for similar reasons, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law. The individual concerned shall as far as possible take part in the authorisation procedure.

4 The representative, the authority, the person or the body mentioned in paragraphs 2 and 3 above shall be given, under the same conditions, the information referred to in Article 5.

5 The authorisation referred to in paragraphs 2 and 3 above may be withdrawn at any time in the best interests of the person concerned.

Article 7 – Protection of persons who have a mental disorder

Subject to protective conditions prescribed by law, including supervisory, control and appeal procedures, a person who has a mental disorder of a serious nature may be subjected, without his or her consent, to an intervention aimed at treating his or her mental disorder only where, without such treatment, serious harm is likely to result to his or her health.

Article 8 – Emergency situation

When because of an emergency situation the appropriate consent cannot be obtained, any medically necessary intervention may be carried out immediately for the benefit of the health of the individual concerned.

Article 9 – Previously expressed wishes

The previously expressed wishes relating to a medical intervention by a patient who is not, at the time of the intervention, in a state to express his or her wishes shall be taken into account.

Chapter III – 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.

Chapter IV – Human genome

Article 11 – Non-discrimination

Any form of discrimination against a person on grounds of his or her genetic heritage is prohibited.

Article 12 – Predictive genetic tests

Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling.

Article 13 – Interventions on the human genome

An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.

Article 14 – Non-selection of sex

The use of techniques of medically assisted procreation shall not be allowed for the purpose of choosing a future child's sex, except where serious hereditary sex-related disease is to be avoided.

Chapter V – Scientific research

Article 15 – General rule

Scientific research in the field of biology and medicine shall be carried out freely, subject to the provisions of this Convention and the other legal provisions ensuring the protection of the human being.

Article 16 – Protection of persons undergoing research

Research on a person may only be undertaken if all the following conditions are met: i. there is no alternative of comparable effectiveness to research on humans; ii. the risks which may be incurred by that person are not disproportionate to the potential benefits of the research; iii. 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 the research, and multidisciplinary review of its ethical acceptability; iv. the persons undergoing research have been informed of their rights and the safeguards prescribed by law for their protection; v. the necessary consent as provided for under Article 5 has been given expressly, specifically and is documented. Such consent may be freely withdrawn at any time.

Article 17 – Protection of persons not able to consent to research

1 Research on a person without the capacity to consent as stipulated in Article 5 may be undertaken only if all the following conditions are met:

i. the conditions laid down in Article 16, sub-paragraphs i to iv, are fulfilled;

ii. the results of the research have the potential to produce real and direct benefit to his or her health;

iii. research of comparable effectiveness cannot be carried out on individuals capable of giving consent;

iv. the necessary authorisation provided for under Article 6 has been given specifically and in writing; and

v. the person concerned does not object.

2 Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised subject to the conditions laid down in paragraph 1, subparagraphs i, iii, iv and v above, and to the following additional conditions:

i. the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition; ii. the research entails only minimal risk and minimal burden for the individual concerned.

Article 18 – Research on embryos *in vitro*

1 Where the law allows research on embryos *in vitro*, it shall ensure adequate protection of the embryo.

2 The creation of human embryos for research purposes is prohibited.

Chapter VI – Organ and tissue removal from living donors for transplantation purposes

Article 19 – General rule

1 Removal of organs or tissue from a living person for transplantation purposes may be carried out solely for the therapeutic benefit of the recipient and where there is no suitable organ or tissue available from a deceased person and no other alternative therapeutic method of comparable effectiveness.

2 The necessary consent as provided for under Article 5 must have been given expressly and specifically either in written form or before an official body.

Article 20 – Protection of persons not able to consent to organ removal

1 No organ or tissue removal may be carried out on a person who does not have the capacity to consent under Article 5.

2 Exceptionally and under the protective conditions prescribed by law, the removal of regenerative tissue from a person who does not have the capacity to consent may be authorised provided the following conditions are met:

i. there is no compatible donor available who has the capacity to consent;

ii. the recipient is a brother or sister of the donor;

iii. the donation must have the potential to be life-saving for the recipient;

iv. the authorisation provided for under paragraphs 2 and 3 of Article 6 has been given specifically and in writing, in accordance with the law and with the approval of the competent body;

v. the potential donor concerned does not object.

Chapter VII – Prohibition of financial gain and disposal of a part of the human body

Article 21 – Prohibition of financial gain

The human body and its parts shall not, as such, give rise to financial gain.

Article 22 – Disposal of a removed part of the human body

When in the course of an intervention any part of a human body is removed, it may be stored and used for a purpose other than that for which it was removed, only if this is done in conformity with appropriate information and consent procedures.

INTERNATIONAL ETHICAL GUIDELINES FOR HEALTH-RELATED RESEARCH INVOLVING HUMANS. PREPARED BY THE COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS) IN COLLABORATION WITH THE WORLD HEALTH ORGANIZATION (WHO), 2016

GUIDELINE 1: SCIENTIFIC AND SOCIAL VALUE AND RESPECT FOR RIGHTS

GUIDELINE 2: RESEARCH CONDUCTED IN LOW-RESOURCE SETTINGS

GUIDELINE 3: EQUITABLE DISTRIBUTION OF BENEFITS AND BURDENS IN THE SELECTION OF INDIVIDUALS AND GROUPS OF PARTICIPANTS IN RESEARCH

GUIDELINE 4: POTENTIAL INDIVIDUAL BENEFITS AND RISKS OF RESEARCH

GUIDELINE 5: CHOICE OF CONTROL IN CLINICAL TRIALS

GUIDELINE 6: CARING FOR PARTICIPANTS' HEALTH NEEDS

GUIDELINE 7: COMMUNITY ENGAGEMENT

GUIDELINE 8: COLLABORATIVE PARTNERSHIP AND CAPACITY-BUILDING FOR RESEARCH AND RESEARCH REVIEW

GUIDELINE 9: INDIVIDUALS CAPABLE OF GIVING INFORMED CONSENT

GUIDELINE 10: MODIFICATIONS AND WAIVERS OF INFORMED CONSENT

GUIDELINE 11: COLLECTION, STORAGE AND USE OF BIOLOGICAL MATERIALS AND RELATED DATA

GUIDELINE 12: COLLECTION, STORAGE AND USE OF DATA IN HEALTHRELATED RESEARCH

GUIDELINE 13: REIMBURSEMENT AND COMPENSATION FOR RESEARCH PARTICIPANTS

GUIDELINE 14: TREATMENT AND COMPENSATION FOR RESEARCHRELATED HARMS

GUIDELINE 15: RESEARCH INVOLVING VULNERABLE PERSONS AND GROUPS

GUIDELINE 16: RESEARCH INVOLVING ADULTS INCAPABLE OF GIVING INFORMED CONSENT

GUIDELINE 17: RESEARCH INVOLVING CHILDREN AND ADOLESCENTS

GUIDELINE 18: WOMEN AS RESEARCH PARTICIPANTS

GUIDELINE 19: PREGNANT AND BREASTFEEDING WOMEN AS RESEARCH PARTICIPANTS

GUIDELINE 20: RESEARCH IN DISASTERS AND DISEASE OUTBREAKS

GUIDELINE 21: CLUSTER RANDOMIZED TRIALS

GUIDELINE 22: USE OF DATA OBTAINED FROM THE ONLINE ENVIRONMENT AND DIGITAL TOOLS IN HEALTH-RELATED RESEARCH

GUIDELINE 23: REQUIREMENTS FOR ESTABLISHING RESEARCH ETHICS COMMITTEES AND FOR THEIR REVIEW OF PROTOCOLS

GUIDELINE 24: PUBLIC ACCOUNTABILITY FOR HEALTH-RELATED RESEARCH

GUIDELINE 25: CONFLICTS OF INTEREST

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The SYNCHROS project has received funding from the *European Union's Horizon 2020 Research and Innovation Programme* under Grant Agreement No. 825884