EU-STANDS4PM
standards for in silico models for personalised medicine

A European standardization framework for data integration and data-driven *in silico* models for personalized medicine – EU-STANDS4PM

Legal and ethical review of in silico modelling

Deliverable 3.1

Imprint

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Using this content

Table of content

Executive summary

The development of in silico models for personalised medicine in the EU requires lawful and ethical data integration. The ultimate use of these models will also require the use of information in these automated systems in a fair and transparent way, which respects patients' rights.

This report therefore surveys the legal landscape for health data integration, and the challenges which arise when information is re-used to develop analytical or predictive models, which are then re-applied to a patient population. Particular attention is paid to the nature and role of consent in data integration and use within in silico models. Consent has a role within the Clinical Trials Regulation, the General Data Protection Regulation, and more broadly as authorising the use of private or confidential information. It also has key limitations, particularly when it cannot easily be revoked, or where it is not sufficient to allow significant decisions to be made in the context of automated processing.

These key features of the landscape help identify avenues for harmonisation and integration of Big Data for personalised medicine models, which will be the next point of focus for our Work Package.

1. Introduction

1.1 Aim and delimitations

This report is the first deliverable from WP3 in the EU-STANDS4PM project. WP3 is responsible for providing guidance on the legal, ethical and policy considerations arising from data integration for *in silico* modelling for personalised medicine. The key data sources to be used for in silico modelling will be data both collected in a clinical context (in the healthcare services) or in clinical trials and other research projects. Consequently, the main focus of WP3 is on data protection issues (task 3.1), issues related to clinical trials and other research projects (task 3.2) and questions related to basic patients' rights (task 3.3). WP3 collaborates closely with the other WPs to ensure alignment between the scientific, legal and ethical issues risen in the EU-STANDS4PM project.

The aim of this report is to provide:

(1) a survey of the international and European data protection and clinical trials regulation as well as legal and ethical regulation relevant for protection of equal access to health, and right to information and self-determination relevant for harmonization and integration of data in in silico modelling, and

(2) an assessment of the challenges and options this regulation provides for harmonization and integration of data for in silico modelling. The legal and ethical analyses provided in the report are closely related to the data sources relevant for the development of in silico models.

As the project´s survey on data sources is still ongoing, the present report cannot, at this point, go into more detailed analyses of all relevant specific examples of potential data sources. Instead, it will use emblematic examples of data sources, to highlight particular concerns raised by selected data sources. The guidance strives at being as comprehensive as possible – given the number of potential data sources as well as *in silico* models that are being analysed in WP1, 2, and the associated legal issues. As well as considering data integration to support the development and review of in silico models, this report also outlines legal and ethical issues arising as these models are deployed within a healthcare context.

1.2 Data sources for in silico modelling

Personalised medicine represents a therapeutic aspiration that can be understood in different ways. At a more ambitious end of the spectrum, it is a multi-omic tailoring of healthcare to the specific needs of the individual patient.[1] Alternatively, a less individual-centred version envisages personalised medicine as a more refined system of grouping patients into smaller treatment groups, otherwise referred to as 'stratified' medicine.[2] The version of personalised medicine implemented will have implications for patients in receipt of the therapy, and may also have implications for the type of data needed to develop, validate, test and adapt the models in question.

For example, personalised medicine that groups patients more accurately, and more promptly, into risk categories could be developed using electronic healthcare records. I Glenn Cohen and colleagues

[1] European Science Foundation, *ESF Forward Look: Personalised Medicine for the European Citizen*, (Strasbourg, 2012).

[2] European Commission, *Biobanks for Europe: A Challenge for Governance*, (2012, Brussels).

envision a system which, for example, predicts which hospital inpatients would most benefit from admission to the Intensive Care Unit. This could be developed, tested and implemented through the secondary use of hospital data.[3] Elements of this vision of predictive analytics are already in place in national healthcare systems. In the UK, the 'streams' application has been launched in one hospital to alert clinicians to patients at risk of acute kidney injury; the algorithms for which were developed[4] and peer-reviewed[5] using patient record data (although government data such as the Indices of Multiple Deprivation were also cross-referenced for peer review).

Electronic health records thus emerge as one key resource in the development of personalised medicine models, albeit potentially supplemented by other social data when the impact of the models comes to be evaluated. However, other in silico models may require data collected specifically for their development. For example, the AgeAbility mobility forecast tool, designed to support tailored support for hypertension,[6] was developed using data from 296,051 residents of US veteran nursing homes, amounting to 1.8 million assessments (similar to the 1.6 million patient records used for the streams app[7]). Where these large-scale studies meet the definition of a clinical trial, participants in the EU will have the protection of the Clinical Trials Regulation; if not external oversight of data collections will be more limited.

Clinical trial data (CTD) encompass different types of data such as clinical reports, processing data and patient level data[8], including pharmacogenomic data, which may be highly relevant for personalised medicine. If compared to clinical data from clinical practice (health care records), CTD represent much more homogeneous aggregated sets of data and, as such, provide a useful starting point for data integration, potentially more so than research data more generally. Efforts are being made, however, to create file types to make clinical and research data more interoperable, for example the 'phenopacket' model endorsed by the Global Alliance for Genomics and Health,[9] but while these initiatives are still in their infancy, a more standardized category of data is of particular utility for data integration.

Biobanks have also been acknowledged as an important source of information for personalised medicine. The European Commission recommended in 2012 that biobanks should be embedded within

[3] I Glenn Cohen, Ruben Amarasingham, Anand Shah et al, 'The Legal and Ethical Concerns that Arise from Using Complex Predictive Analytics in Health Care' (2014) 33 Health Affairs 7.

[4] Information Commissioner's Office, 'Royal Free - Google DeepMind trial failed to comply with data protection law', 3 July 2017, available at: <https://ico.org.uk/about-the-ico/news-and-events/news-and-blogs/2017/07/royal-free-google-deepmind-trial-failed-to-comply-with-data-protection-law/> accessed 27 November 2019.

[5] Alistair Connell, Hugh Montgomery, Peter Martin et al, 'Evaluation of a digitally-enabled care pathway for acute kidney injury management in hospital emergency admissions' (2019) 2 npj Digital Medicine 67, available at: <https://www.nature.com/articles/s41746-019-0100-6#Sec2> accessed 27 November 2019.

[6] Sonia Verma, 'Are you sure you don't have a background in medicine?' 27 October 2019available at: <https://brighterworld.mcmaster.ca/articles/manaf-zargoush/> accessed 27 November 2019 .

[7] Note 4.

[8] Timo Minssen, Neethu Rajam and Marcel Borgers, 'Clinical trial data transparency and GDPR compliance: Implications for data sharing and open innovation.' Science & Public Policy (forthcoming, 2019), available at: https://papers.ssrn.com/sol3/Papers.cfm?abstract_id=3413035 accessed 29 January 2020

[9] Global Alliance for Genomics and Health 'Phenopackets: Standardizing and Exchanging Patient Phenotypic Data' (22 October 2019) <https://www.ga4gh.org/news/phenopackets-standardizing-and-exchanging-patient-phenotypic-data/> accessed 13 December 2019.

public healthcare systems to ensure their sustainability and ability to support personalized medicine.[10] While this has not been universally implemented, it remains another option for data integration, alongside phenopacketing.

While large-scale data collection clearly fulfils an important role, some have also argued that N of 1 (single patient) studies will be particularly important for the development of personalised medicine.[11] Although smaller-scale studies may provide an easier context in which to manage relationships with data subjects,[12] the need to ensure appropriate consent and privacy remains a complex proposition. In particular, where individuals are more identifiable, and are subject to a greater number of interventions over time, this raises questions as to whether the generalizability of the results is sufficient to justify the burden placed on the participant.

Finally, the future of medical in silico modelling is connected to the trajectory of trends in Big Data more generally, which could include incorporation of novel sources of health-related information, such as that made available by subjects on social media,[13] but the legal and ethical parameters of data scraping are still largely unclear. In the US, for example, it has been ruled that individuals with public profiles do not have any expectations of privacy,[14] but within the EU the Polish Data Protection Authority has fined a company for failing to provide privacy notices to millions of individuals whose data they had scraped from public websites.[15]

With this in mind, we will focus in this report particularly on the law protecting privacy, autonomy and data protection rights, and in particular the various, overlapping laws which govern consent in clinical and research contexts.

1.3 Introduction to the legal framework

As established in the previous section, data generated in the context of healthcare services, as well as information collected in clinical trials, are key sources of data for in silico models for personalised medicine. In this report, we therefore concentrate on the rights that patients and research participants enjoy under international health law and practice, and the Clinical Trials Regulation (CTR),[16] as well as

[10] European Commission (2012), Note 2.

[11] Stephen Senn, 'Statistical pitfalls of personalized medicine' (2018) Nature <https://www.nature.com/articles/d41586-018-07535-2> accessed 27 November 2019.

[12] Harriet Teare, Joanna Hogg, Jane Kaye et al, 'The RUDY study: using digital technologies to enable a research partnership' (2017) European Journal of Human Genetics 25, 816–822.

[13] Heads of Medicines Agency and European Medicines Agency, 'HMA-EMA Joint Big Data Taskforce – summary report (2019)' available at: <https://www.ema.europa.eu/en/documents/minutes/hma/ema-joint-task-force-big-data-summary-report_en.pdf> accessed 27 November 2019.

[14] Emma Woollacott, 'Linkedin Data Scraping Ruled Legal' Forbes, 10 September 2019, <https://www.forbes.com/sites/emmawoollacott/2019/09/10/linkedin-data-scraping-ruled-legal/#17d263851b54> accessed 27 November 2019.

[15] President of the Personal Data Protection Office, Decision ZSPR.421.3.2018, 15 March 2019, available at: <https://uodo.gov.pl/decyzje/ZSPR.421.3.2018> accessed 27 November 2019.

[16] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance (hereafter referred to as 'Clinical Trials Regulation').

the protections afforded under the General Data Protection Regulation ('GDPR')[17]. These comprise key obligations, which must be met for data integration, development and use of in silico models for medical purposes. As will be clear, this legal landscape is complex and multi-layered, with regulations at national, European (regional), and international level (e.g. UN and WHO rules).

The numerous relevant legal instruments span hard law (e.g. Treaties and Conventions)[18] to soft law mechanisms (e.g. recommendations and guidelines). International treaties are binding on states that have ratified. Individuals, like companies and researchers, are furthermore expected to respect rights.[19] At European level, the regulatory framework also both consists of EU regulations and Council of Europe treaties and recommendations. The complexity gives rise to potential uncertainties and conflicts regarding the room for national discretion (and variations) and the relation between actors both at the same regulatory level (e.g. the EU and the Council of Europe) and at different regulatory levels (e.g. between EU law and national law).

The precise legal implications of international treaties and recommendations depends on the national legal order. For example, in dualist legal systems, such as the United Kingdom and Denmark, international treaties (of the UN or WHO for example) must be incorporated into domestic law before an individual can bring a complaint to court alleging non-compliance. With monistic legal systems, like the Netherlands, individuals can complain directly that a provision has been breached, provided the provision is sufficiently clear. However, all states that have ratified an international treaty are bound to respect, protect and fulfil the obligations into which they have entered.

EU law has a more direct steering effect on national legislation compared to, for example, UN and Council of Europe regulation. Treaties (regulations and directives) of the European Union have direct effect for EU Member States. Regulations aim for harmonisation while Directives require domestic implementation by Member States.

Separately, the Council of Europe has adopted several important binding treaties, although implementation depends on member state law. The European Convention on Human Rights (ECHR) however, stands out among Council of Europe and UN treaties as the Convention grants individuals the right to bring complaints to the European Court on Human Rights.

Beyond conventions, recommendations and declarations are advisory and therefore of non-binding status. However, non-binding recommendations can also be effective at shaping practices, particularly if they enjoy support from states and other stakeholders.[20] Recommendations in this field are intentionally broadly phrased to leave room for national variation. Consequently, domestic legislation varies among states parties, when implementing European and international patients' rights legislation.

[17] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ 2016 L 119/1 (hereafter cited as GDPR).

[18] International Statute of Court of Justice, Article 38.1.

[19] UN Human Rights Council, Protect, respect and remedy : a framework for business and human rights : report of the Special Representative of the Secretary-General on the Issue of Human Rights and Transnational Corporations and Other Business Enterprises, John Ruggie, 7 April 2008, A/HRC/8/5.

[20] Helen Busby, Tamara Hervey and Alison Mohr, 'Ethical EU Law? The influence of the European Group on Ethics in Science and Technology', (2008) 33 E.L. Review 803.

Data protection and *clinical trials* regulation are areas of EU law undergoing significant transition: the Clinical Trials Regulation is expected to be brought into force in 2020; while member states have completed the initial implementation the GDPR, clarification is needed at European level on a number of key issues. The GDPR applies to personal data collected and used in the context of research, requiring us to examine the interplay of the GDPR and the Clinical Trials Regulation, particularly in light of the current uncertainty as to the scope of the GDPR's presumption of compatibility of research use, which has been the source of disagreement between the European Commission and the European Data Protection Board (see section 2.4.1).

In the absence of complete clarity of new GDPR provisions, there is some evidence that member states have come to different interpretations on, for example, appropriate bases for processing data for research.[21] As well as differences in national interpretation, the GDPR provides scope for national derogation from data subject rights for scientific research and statistical purposes, and not all member states have taken full advantage of these derogations.[22] As such, even though the GDPR applies directly across member states, and was intended to create an internal market for personal data across the EU,[23] scientific research is an area of national derogation, making the seamless international integration of data for research or statistical purposes a less straightforward endeavour, requiring accommodation of different national provisions.

Although *patients' rights* are not going through the same sea change, as the development and application of medical in silico models begins and ends with patients, these rights are a cornerstone of legal and ethical use of models for personalised medicine. The rights of patients and research subjects are codified in several international treaties. International conventions set minimum standards and governments are free to enshrine greater protections in national law.[24] Besides binding treaties, there are copious recommendations, spanning intergovernmental declarations from the Council of Europe and World Health Assembly, as well as expert recommendations, such as from the Council of Europe Committee of Ministers and the European Group on Ethics in Science and New Technologies (EGE).[25]

1.4 Basic legal and ethical values

Basic human rights principles, such as respect for dignity, integrity and privacy, are closely related to general principles within medical ethics and bioethics. The seminal bioethical principles developed by Beauchamp and Childress on autonomy, beneficence, non-maleficence and justice are clearly reflected

[21] Consortium of European Social Science Data Archives ('CESSDA-ERIC'), 'GDPR and research one year on – Experiences across Europe'**,** webinar 27 June 2019 <https://www.cessda.eu/content/download/4729/53224/file/CESSDA_GDPR_webinar_2019.pdf> accessed 27 November 2019.

[22] Santa Slokkenberga, Olga Tzortzatou and Jane Reichel (eds), *Individual Rights, the Public Interest, and Biobank Research: Article 89 GDPR and European Legal Responses*. (Springer, Law, Governance and Technology Series) (Forthcoming).

[23] GDPR, Recital 10.

[24] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Biomedicine Convention), ETS no. 164, Oviedo, 4.IV.1997, Article 27.

[25] For EGE recommendations, see a list on this link < http://ec.europa.eu/archives/bepa/european-group-ethics/publications/opinions/index_en.htm> for opinions until 2014 and on this link < https://ec.europa.eu/research/ege/index.cfm?pg=reports> for later opinions (accessed 29 January 2020).

in a number of legal instruments.[26] Common legal rights and principles in the field of the rights of patients and research subjects have emerged at a European and international level. These centre on respect for dignity and the inherent worth of the human beings. Rights to autonomy, privacy, data protection, and confidentiality also have a prominent position. Critically, several statements underscore the primacy of the individual: "the interests and welfare of the human being shall prevail over the sole interest of society or science".[27] Similarly, research should not prevail over respect for human rights, fundamental freedoms and human dignity of individuals or groups.[28] In the case of children, the *best interests* of the child shall prevail over the "interest of general society or scientific advancement".[29] Ultimately, in applying biomedical research, 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.[30] Furthermore, in research involving human subjects, it has been suggested that the following ethical principles should be of guidance: respect for persons, beneficence, non-maleficence and justice.[31] The American Society of Human Genetics (ASHG) also references researchers' ethical obligation of *veracity or truth telling*.[32]

1.5 Importance of data sharing (for in silico modelling) and public attitudes

Sharing data collected in the course of health care or health research is a basic condition for the successful development of personalized medicine and in silico modelling. Therefore, current initiatives on sharing clinical trial data (CTD) that might facilitate the use of this data for in silico modelling should also be briefly discussed. Sharing of CTD has recently been suggested as an "ethical obligation" or "expected norm"[33]. This initiative has been prompted by international guidelines, funding agencies, journals and international organizations (International Committee of Medical Journal Editors[34]

[26] Tom L Beauchamp and James F. Childress, *Principles of Biomedical Ethics* (8th ed., OUP, 2019).

[27] Biomedicine Convention, Article 2; Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes, Council of Europe Treaty Series - No. 203, Strasbourg, 27.XI.2008, Article 3.

[28] UNESCO, Universal Declaration on the Human Genome and Human Rights (11 November 1997), Article 10.

[29] Committee on the Rights of the Child, General comment No. 15 (2013) on the right of the child to the enjoyment of the highest attainable standard of health (art. 24), (17 April 2013), para 85.

[30] Universal Declaration on Bioethics and Human Rights, adopted by UNESCO's General Conference on 19 October 2005.

[31] Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organisation, , 'International Ethical Guidelines for Health-related Research Involving Humans' (Geneva. 2016) https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. Accessed 29 January 2020

[32] 'ASHG Position Statement: The Responsibility to Recontact Research Participants after Reinterpretation of Genetic and Genomic Research Results' (2019) 104 The American Journal of Human Genetics 578–595, p. 582.

[33] Nicola Howe, et al, 'Systematic review of participants' attitudes towards data sharing: A thematic synthesis' (2018) 23 Journal of Health Services Research & Policy. 123-133; Darren Taichman, et al, 'Sharing Clinical Trial Data: A Proposal from the International Committee of Medical Journal Editors' (2016) 29 The National medical journal of India 6-8.

[34] Nicola Howe et al, ibid.

(ICMJE)[35], European Medicines Agency (EMA)[36,37], US Institute of Medicine (IOM)[38] just to mention a few) and pharmaceutical companies[39]. New US/European policy initiatives and new legislation, such as the European Medicine Agency's (EMA) policy 00702 and the EU's new clinical trial regulation 536/20143 (CTR), have considerably increased public access to CTD. The new disclosure rules not only encompass the results of clinical studies, but also pertain to anonymized patient level data and other detailed information from clinical trials' dossiers.[40]

On the other hand, adoption of GDPR as well as recent US litigation,[41] and Facebook and Cambridge Analytica scandals[42] have drawn the attention of the general public to the misuse of data. They have increased citizens' and patients' awareness of their data rights and have highlighted the fact that the use of healthcare records and CTD need to be controlled and regulated.[43.]

However, current studies show that general population still has a positive attitude towards sharing personal data for healthcare purposes.[44] The main findings of consultation activities carried out by the European Commission show that over 93% of more than 1400 respondents to an online questionnaire believe that "*Citizens should be able to manage their own health data".* Furthermore, 83% of all respondents either agree or strongly agree with the statement that "*Sharing of health data could be beneficial to improve treatment, diagnosis and prevention of diseases across the EU*". The overwhelming majority of all respondents (73.6%) identify improved possibilities for medical research as a reason for supporting cross border transfer of medical data, which was higher than for their purpose of their own

[35] Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors. available at: < http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf> accessed 29 January 2020

[36] European Medicines Agency. Data anonymisation - a key enabler for clinical data sharing. Workshop report available at: <https://www.ema.europa.eu/en/documents/report/report-data-anonymisation-key-enabler-clinical-data-sharing_en.pdf> accessed 29 January 2020

[37] European Medicines Agency. European Medicines Agency policy on publication of clinical data for medicinal products for human use. Available at: <https://www.ema.europa.eu/en/documents/other/european-medicines-agency-policy-publication-clinical-data-medicinal-products-human-use_en.pdf> accessed 29 January 2020

[38] Institute of Medicine, *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk* (2015, Washington, DC: The National Academies Press)**.** Available at: <https://www.nap.edu/read/18998/chapter/1#xiv. accessed 29 January 2020

[39] Richard E Kuntz, et al, 'Individual patient-level data sharing for continuous learning: A strategy for trial data sharing' *NAM Perspectives.* (2019, Discussion Paper, National Academy of Medicine, Washington, DC). Available at: <https://nam.edu/individual-patient-level-data-sharing-for-continuous-learning-a-strategy-for-trial-data-sharing/> accessed 29 January 2020

[40] Note 8.

[41] Robins, Rebecca, 'Potential class action lawsuit accuses the University of Chicago of sharing identifiable patient data with Google', available at: https://www.statnews.com/2019/06/26/potential-class-action-lawsuit-accuses-theuniversity-of-chicago-of-sharing-identifiable-patient-data-with-google/// Dinerstein v. Google (2019), LLC, 1:19-cv-04311. available at: < https://digitalcommons.law.scu.edu/historical/1973/>

[42] Confessore N., (2018) 'Cambridge Analytica and Facebook: The Scandal and the Fallout So Far', New York Times, available at: <https://www.nytimes.com/2018/04/04/us/politics/cambridge-analytica-scandal-fallout.html

[43] Note 8.

[44] European Commission, *Synopsis Report Consultation: Transformation health and care in the digital single market* (European Union, 2018) Available here: https://publications.europa.eu/en/publication-detail/-/publication/b9699d62-4122-11e8-b5fe-01aa75ed71a1/language-en. Accessed 14 January 2020.

treatment (67.8%). This suggest that citizens support data sharing, but at the same time wish to have control when doing so.

Positive public attitudes towards data sharing may also be regarded as an important precondition for effective sharing of CTD. In addition to what was already mentioned, research data shows that attitudes towards CTD sharing is even more positive than for the clinical data. For example, a survey of clinical trial participants in the United States showed that 93% of respondents were likely to allow their data to be shared with university scientists, and 82% with scientists at for-profit companies — a better acceptance rate than for the sharing of hospital data or biological samples.

2. Consent

2.1 Introduction

Consent is a concept which features in a number of areas of law, and can have a subtly different meaning in these different legal contexts. Consent can e.g. be seen as a means of showing respect for individual autonomy and the right to self-determination (including informational self-determination[45]), as a way to legitimise bodily interventions, or as a means to establish transparency and trust.[46] It is therefore important to recognise that consent can play different roles and may have different requirements depending on the purposes for which it is obtained.

In the case of data integration, development and use of in silico models for personalised medicine, consent may fulfil any of the following roles:

- It is almost always a precondition for participation in a clinical trial,[47] or the donation of tissue (for example for biobanks);
- It is also, more generally, a precondition for a medical intervention;[48]
- Crucially, consent may or may not be a GDPR ground for the further use of data obtained from medical or clinical trial contexts for a new purpose;
- Where identifiable information of a private or confidential nature is used, consent can be a key way of authorising this interference with the right to privacy.

The above roles are essentially either a legitimation of a physical interference (1 and 2) or of an interference with what has been termed 'informational privacy'[49] (3 and 4).

Informational consent differs from consent to bodily interventions. There are very limited circumstances where consent to a physical clinical intervention is not required—for example in emergencies or where the patient lacks the relevant mental capacity and a decision is made for them on the basis of their best interests. Informational privacy is more complex, however, as a person does not necessarily 'own' information relating to them in any absolute sense, and their consent to data use may therefore be broader, more implicit or even not solicited for secondary use of information. The status of biobank

[45] See .e.g. Alan Westin, *Privacy and Freedom*, (New York: Athenum, 1967).

[46] Onora O'Neill, *Autonomy and Trust in Bioethics*, (Cambridge University Press, 2002).

[47] Clinical Trials Regulation, Article 28.1(c)

[48] Biomedicine Convention, Article 5.

[49] Graham Laurie, *Genetic Privacy: A Challenge to Medico-Legal Norms* (Cambridge University Press, 2002).

samples is more blurred. The bodily intervention has already taken place, but there may be legal (and ethical) regulation regarding the further use and the donors rights in this respect. Some countries, like Denmark, consider tissue samples as personal data and apply GDPR and national data protection regulation to the use of biobank samples. In other countries, such as the UK, the samples are not perceived as personal data, and they fall outside the scope of data protection regulation.

We will focus, in this section on 'informational privacy,' and in particular what we will refer to as 'informational consent.' This is, broadly speaking, consent to use information relating to oneself, as opposed to consent for a physical intervention or other form of medical treatment. This encompasses the legal and bioethical principle of 'informed consent,' as well as statutory consent under the Clinical Trials Regulation and the General Data Protection Regulation. Interventional consent is considered more in the context of patients' rights in section 4.

The implementation of the GDPR has highlighted the distinction between physical and informational consent, and helped to spark a controversy as to when, and whether, consent is an appropriate basis for re-using a person's information, particularly in the context of clinical trial data used outside the trial protocol. In order to cover this, and the other aspects of consent relevant to in silico modelling, this section will address the following:

- The evolution of informed consent as a key principle in bio-medicine;
- Recent developments of the concept as occasioned by the Clinical Trials Regulation and the GDPR;
- Evidence as to what data subjects want from consent, and how this might be implemented;
- How consent should be used for the development of in silico models

2.2 Informed Consent & Patients' Rights

The principle of informed consent is fundamental to international treaties and recommendations on the patients' rights.[50] Free and informed consent is a prerequisite for any medical intervention. Informed consent is furthermore needed for "preservation and use of all substances of the human body", and it is, thus, extended to the disposal of human body parts after a medical intervention.[51] The legal obligation to obtain informed consent supports patients' right to self-determination. However, international law provides that right to informed consent can be abrogated by national law in certain situations, provided such limitations are in line with, *inter alia*, international human rights law. This could e.g. be justified in cases of coercive psychiatric treatment and coercive testing and treatment of epidemic diseases.[52]

The importance of patients' right to self-determination is also relevant for processing of health data.[53] The duty of confidentiality is an important principle in clinical practice, which expresses the obligation of health care professionals not to reveal information shared with them by their patients in the context

[50] Biomedicine Convention, Article 5; Patient Rights Declaration, paragraph 3.1; European Union, Charter of Fundamental Rights of the European Union, 26 October 2012, 2012/C 326/02 (EUCFR), Article 3.1(a).

[51] Patient Rights Declaration, paragraph 3.8.

[52] Biomedicine Convention, Article 8.

[53] See further, Council of Europe, Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data as it will be amended by its Protocol CETS No. 223.

of medical treatment. Confidential information may therefore only be disclosed where provided for by law, or where the patient consents.[54] This implies that consent may also be relevant in regard to the processing of health data for purposes outside the scope of medical care.

2.3 Informed Consent in Human Research

2.3.1 Informed consent in international treaties and research ethics guidelines

As within patients' rights, the principle of informed consent is fundamental to international treaties and recommendations on the rights of research subjects. No research on a person may be carried out "without the informed, free, express, specific and documented consent of the person".[55] Crucially, medical experimentation without consent is a human rights violation.[56] It is important, however, to briefly address historical developments of this fundamental concept in the post-World War II period.

International human subject research guidelines, such as Nuremberg code (1949)[57] and first versions of the WMA Declaration of Helsinki[58] (1964), mainly concentrated on consent to bodily intervention. According to these guidelines, voluntary informed consent has been absolutely essential to begin clinical trials on human subjects, however, it explicitly covered only interventional aspects of human subject research. Informed consent implied consent for a particular research project and particular interventions carried out in the framework of this research. The importance of consent to bodily interventions has been followed in the subsequent and legally binding regulations. For example, the Convention on Human Rights and Biomedicine (1997) reinforces the need of consent that should not only be freely-given, informed, revocable but "*express, specific and written consent". The words "specific consent" are to be understood here as meaning consent which is given to one particular intervention carried out in the framework of research*."[59] The content of consent in the context of biomedical research has been further specified in the Additional Protocol concerning Biomedical Research. This instrument also covers only interventional aspects of research and in this respect, it follows the tradition of the first research ethics guidelines mentioned above. Its scope is limited to physical intervention or intervention with a risk of psychological harm.[60] To sum up, in all the mentioned binding legal documents and soft

[54] Patient Rights Declaration, paragraph 4.2.

[55] Council of Europe, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, CETS No.195 (2007), Article 14.1.

[56] UN General Assembly, International Covenant on Civil and Political Rights, 16 December 1966, United Nations, Treaty Series, vol. 999, p. 171, Article 7.

[57] 'Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law

No. 10', Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949 (The Nuremberg Code).

[58] World Medical Association, Declaration of Helsinki: Recommendations guiding doctors in clinical research,

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Available at: <https://www.wma.net/wp-content/uploads/2018/07/DoH-Jun1964.pdf> Accessed 14 January 2020.

[59] Council of Europe, Explanatory Report to the 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.

[60] Additional Protocol concerning Biomedical Research, Article 2.

laws the preference was in favour of specific, informed and written consent to intervention, while personal data processing has not been explicitly addressed.[61]

However, the most recent versions of international research ethics guidelines, such as Declaration of Helsinki (2013), art. 32, and the Council for International Organizations of Medical Sciences ('CIOMS') guidelines (2016)[62], in addition to "interventional" consent have also introduced provisions of consent and derogations from consent requirement in case of research on personal data and biological materials.

The Clinical Trials directive[63] in its implementing documents, and the CT Regulation, also clearly distinguish informational and interventional elements of informed consent for the use of clinical trial data for particular research purposes. For example, in the *Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use*[64] it was stated that the form to be used to verify that information has been given and that the trial subject has consented (the informed consent form) should contain at least three elements:

- consent to participate in the trial;
- consent to make confidential personal information available (direct access) for quality control and quality assurance by relevant personnel from the sponsor, a nominated research organisation on behalf of the sponsor, and inspection by the competent authorities/institutions assigned this task in the Member State or, if applicable, the Ethics Committee;
- consent to archive coded information, and for its transmission outside the Community if applicable.

It should also be noted that under the CT Directive and CT Regulation, similarly to other documents and guidelines presented in this section, informed consent means a subject's free and voluntary expression of their willingness to participate in a particular clinical trial after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate (Article 2(j) CT Directive; Article 2(21) CT Regulation). However, derogations from specific consent for the use of data in future research has been explicitly introduced in the upcoming CT regulation – an issue that will be addressed below (see 2.4.2).

[61] Ciara Staunton, Santa Slokenberga and Deborah Mascalzoni, 'The GDPR and the research exemption: considerations on the necessary safeguards for research biobanks' (2019) European Journal of Human Genetics 27**,** 1159–1167.

[62] Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organisation, , International Ethical Guidelines for Health-related Research Involving Humans (Geneva. 2016) available at: <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf> accessed 29 January 2020

[63] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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. Official J Eur Commun 2001;L121:34–44.

[64] European Commission, Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (2006, Brussels,

ENTR/CT 2) Available at: <https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/12_ec_guideline_20060216_en.pdf>. Accessed 14 January 2020

2.3.2 Consent to research exclusively based on tissue samples and personal data

The principle of informed consent does not necessarily apply to all such research projects; there are recognized *exceptions* to the principle of consent in scientific research exclusively based on data and tissue samples (which do not involve any physical intervention). Such exceptions should only be made in accordance with ethical and legal standards adopted by States, consistent with the principles and provisions set out in the Universal Declaration on Bioethics and Human Rights, and international human rights law.[65] Limitations should be specified in law and can include purposes such as, the interests of public safety, for the investigation, detection and prosecution of criminal offences, for the protection of public health or for the protection of the rights and freedoms of others.[66] For instance, exceptions to consent can be made if the proposed use of genetic material corresponds to an "important public interest" is provided for by domestic law and consistent with international law on human rights.[67]

The role of consent to research on human biological materials and personal data has especially attracted attention in regard to:

- collection of tissue samples and data for *future research* (section 2.3.3) and
- secondary use of *previously collected* tissue samples and personal data (section 2.3.4)

2.3.3 Collection of biological materials and data for future research

Biological material and data obtained in a research project may be of interest for future research. If this is envisaged *when initiating the research project*, it raises the question about *consenting to future research*. In the context of future secondary use of biomedical research data, the distinction between consent to take part in a particular biomedical research and future use has been addressed in various legal instruments.

For example, the Explanatory report to the Additional Protocol to the Convention on Human Rights and Biomedicine,[68] states that,

> *"although the research use of biological materials which have been previously removed in the course of a clinical intervention are beyond the scope of this Protocol, it should be noted that if there is an intention to utilise biological materials or personal data obtained during a medical intervention for research purposes after the medical intervention, it is good practice for specific consent to be obtained for such research uses not related to the medical intervention."*

However, it should be noted that specific consent may not always fit the purpose of data sharing. In such cases, we have to find other grounds justifying the use of data for personalised medicine. Whereas the Explanatory Report Additional Protocol refers to a 'good practice' of obtaining a *specific consent*, more recent soft law and legal regulations have introduced the concept of a *broad consent* to use data and

[65] UNESCO. Universal Declaration on Bioethics and Human Rights, 19 October 2005, article 6.2.

[66] Ibid, article 12.

[67] UNESCO, International Declaration on Human Genetic Data, Adopted unanimously at UNESCO's 32nd General Conference on 16 October 2003, Article 16(a).

[68] Council of Europe. Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (Strasbourg, 25.I.2005). Available at: <https://rm.coe.int/16800d3810.>accessed 29 January 2020.

tissue samples for future research. For example, a soft law instrument that recommends unspecified future use of personal data is the Council of Europe Recommendation on research on biological materials of human origin (2016).[69]

The upcoming Clinical Trial Regulation 2014/536 also specifically addresses further use of clinical trials data based on broad consent. Its Recital 29 states that,

> *"it is appropriate that universities and other research institutions, under certain circumstances that are in accordance with the applicable law on data protection, be able to collect data from clinical trials to be used for future scientific research, for example for medical, natural or social sciences research purposes".*

Art. 28 (2) provides a clarification that the sponsor may ask the subject or, where the subject is not able to give informed consent, his or her legally designated representative at the time when the subject or the legally designated representative gives his or her informed consent to participate in the clinical trial to consent to the use of his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That consent may be withdrawn at any time by the subject or his or her legally designated representative. (See the interpretation of broad consent under GDPR further below in section 2.4.1.

Questions related to collection, storage and use of data for the future research purposes are also addressed in the CIOMS guidelines (2016).[70] According to these guidelines, consent should *anticipate* foreseeable plans for future use of the data in research[71], and Commentary on Guideline 12 defines 3 informed consent scenarios for the future use of data: *specific consent*, *broad consent* and *informed opt-out procedures*. The guidelines stipulate more specific requirements for each consent scenario. These guidelines do not have the same binding effect of legislation such as the GDPR or Clinical Trials egulation, however they have, throughout their history, been influential not only in informing best practice, but also in shaping the content of the CTR and the Directive which preceded it.[72]

2.3.4 Secondary use of previously collected data/biological materials

The interest in making use of previously collected data or biological material may also occur at a later stage and may include both data and material collected within a research project and in a clinical context. The issue of consent requirement for *secondary use* has in particular been addressed in regards to biological materials of human origin (including associated personal data).[73] The mentioned

[69] Recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin (Adopted by the Committee of Ministers on 11 May 2016 at the 1256th meeting of the Ministers' Deputies).

[70] Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organisation, , International Ethical Guidelines for Health-related Research Involving Humans (Geneva. 2016) available at: <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf> accessed 29 January 2020

[71] Ibid, Commentary on Guideline 4.

[72] The CTR makes multiple references in the recitals to 'international guidelines' which have shaped its core requirements, for example for consent to be in writing (recital 30 CTR & Guideline 9 CIOMS). The CIOMS guidelines are among these influences, along with World Health Organisation and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

[73] An older CoE recommendation also addresses the use of personal data obtained for research. It stipulates that personal data obtained for research should not be used for any purpose other than research or in connection with another research project substantially different in its nature or objects, without consent, Council of Europe, Committee of Ministers, Recommendation No. R (83) 10 of the Committee of Ministers to Member States on the

Recommendation on research on biological materials of human origin (2016)[74] states (Art. 21) that biological materials should – as a main rule – only be used in a research project if the latter is within the scope of the consent or authorisation given by the person concerned.

However, the Recommendation also introduces the so-called "research exemption" scenario providing options for use of identifiable biological materials in a research project that is not within the scope of the original consent or authorisation. In this situation, consent or authorisation to the proposed use should be sought by the person concerned, and, to this end, reasonable efforts should be made to contact the person, while still respecting the wish of the person concerned not to be contacted. If it has proven unsuccessful to contact the person concerned, the biological materials could only be used in the research project subject to an independent evaluation of the fulfilment of a number of conditions:

- evidence is provided that reasonable efforts have been made to contact the person concerned;
- the research addresses an important scientific interest and is in accordance with the principle of proportionality;
- the aims of the research could not reasonably be achieved using biological materials for which consent or authorisation can be obtained; and
- there is no evidence that the person concerned has expressly opposed such research use.

Any use of biological materials in an identifiable form should be justified in advance in the research protocol. Non-identifiable biological materials may be used in a research project provided that such use does not violate any restrictions defined by the person concerned before the materials have been rendered non-identifiable and subject to authorisation provided for by law.

Similarly, the CIOMS guidelines also allow the use of previously collected data and biological materials without consent. However, they recommend that waivers to informed consent should be regarded as "uncommon and exceptional" and must be approved by an ethical review committee.[75] The research design should entail "no more than minimal risk" and that a requirement of informed consent would make the research impractical.[76] Biological samples and medical records gathered during clinical care can be used for research without consent, provided the research entails minimal risk, the rights or interests of the patients are not violated, their privacy and confidentiality or anonymity is assured and the research is designed to answer "an important question", and the research would be impracticable without a waiver.

2.3.5 Summarising the role of consent in human research

To sum up, an overview of human research regulation and guidelines consistently shows that terminology of consent is still used as a prevalent paradigm of dealing with human subjects and their biological material and personal data. However, the need to broaden the justification of using biological materials and personal data, particularly to justify its secondary use or the collection of data and biological materials for future research, has been acknowledged both by the Council of Europe, EU instruments as well as recent versions of the Declaration of Helsinki and CIOMS guidelines. The

Protection of Personal Data used for Scientific Research and Statistics (Adopted by the Committee of Ministers on 23 September 1983), paras 4.1, 4.2.

[74] Recommendation CM/Rec (2016)6, note[69].

[75] CIOMS, Guideline 4. See also, Helsinki, para 32.

[76] CIOMS, Commentary on Guideline 4.

Declaration of Helsinki, CoE recommendations, as well as the CIOMS guidelines do not have a formal legal status; they are developed by professional organizations and not binding on governments. However, as mentioned above they have been influential in shaping the content of legally binding regulation such as the CoE Convention on Human Rights and Biomedicine, as well as the CTR and the Directive that preceded it.[77] The UNESCO Declarations are adopted by states parties, but belong to the category of international soft law, with less legal authority than the binding CoE conventions and EU instruments.

The European Data Protection Supervisor has highlighted the understandable confusion between consent as a principle of research involving human subjects, and consent as a provision within the General Data Protection Regulation.[78] Having outlined the evolution of the former, we will now focus on the latter. The adoption of GDPR and its interpretation in the field of human research has demonstrated different meanings of consent when applied to research interventions as compared to research use of data and biological materials. It has highlighted the distinction between physical intervention and the use of personal data in the context of research, and potentially introduced the concept of compatible use as an alternative to explicit consent.

2.4 Consent under GDPR

The GDPR requires both a lawful basis to process personal data, under Article 6, and a further 'condition' for processing special category data, such as genetic or health-related information.[79] Consent is one such basis, and explicit consent can be a relevant 'condition.' On its face, the GDPR's requirement for consent to be 'granular'[80] suggests that it requires a more specific consent to research than that accommodated within the Clinical Trials Regulation. The specificity or breadth of consent required under the GDPR is explored in this subsection.

2.4.1 Compatible Use—is a Lawful Basis Necessary?

As a preliminary point, we should acknowledge the potentially controversial question as to whether a further basis for processing is even necessary for research under the GDPR. It is helpful to clarify this point before proceeding on the assumption that a lawful basis (such as consent) is required to process data for research under the Regulation.

Ordinarily, the further processing of research data for another purpose would require a legal basis under Article 6 GDPR, and Article 9 for health data. This would either be the purpose for which the data were originally collected, or some new basis if the use is sufficiently different in nature. Whether this is the case in the context of scientific research and statistical purposes is a point on which the European

[77] The CTR makes multiple references in the recitals to 'international guidelines' which have shaped its core requirements, for example for consent to be in writing (recital 30 CTR & Guideline 9 CIOMS). The CIOMS guidelines are among these influences, along with World Health Organisation and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

[78] European Data Protection Supervisor, 'A Preliminary Opinion on data protection and scientific research' (Brussels, 6 January 2020), available at: < https://edps.europa.eu/sites/edp/files/publication/20-01-06_opinion_research_en.pdf> accessed 20 January 2020

[79] GDPR, Article 9

[80] I.e. separate consents for different processing operations, Recital 43 GDPR.

Commission's position has not been accepted by the national supervisory authorities, which make up the European Data Protection Board ('EDPB').

Recital 50 GDPR has been taken by some to mean that scientific research is also exempt from the first principle, and does not require a legal basis, stating as it does:

> *The processing of personal data for purposes other than those for which the personal data were initially collected should be allowed only where the processing is compatible with the purposes for which the personal data were initially collected. In such a case,* ***no legal basis separate from that which allowed the collection of the personal data is required****. […] Further processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes should be considered to be compatible lawful processing operations. (emphasis added)*

Some have taken this to mean that qualification as scientific research under the GDPR may be sufficient to satisfy the first and second principles.[81] This would omit the requirement for a lawful basis under Article 6, most likely consent, public interest or legitimate interest. It is perhaps a generous interpretation of the GDPR to suggest that no legal basis is required for processing as long as it was for scientific research with safeguards—not even demonstrable public or legitimate interest. This would undermine the logic of having two separate Articles (6 and 9) setting benchmarks for the validity of processing personal and special category data.

This issue has created a degree of initial divergence between the European Commission and the European Data Protection Board ('EDPB'). The former published a Question and Answers document, not for the purposes of offering any authoritative interpretation of the law, but rather to illustrate their state of play following discussion with the EDPB (without prejudice to future guidance from the Court of Justice of the European Union). The initial, preliminary position of the Commission on legal bases is that:

> *'If a sponsor/investigator would like to use the personal data gathered for any other purposes than the one defined by the clinical trial protocol (e.g. medical data collected to conduct a clinical trial on breast cancer used to run a study aiming to identify new biomarkers, but which was not foreseen in the clinical trial protocol), it would require a valid legal ground under Article 6 of the GDPR… The chosen legal basis may or may not differ from the legal basis of the primary use.' [82]*

This may appear to be a fair assessment, given that the first and second principles of the GDPR represent distinct legal obligations, and to satisfy one does not resolve the other. However, the EDPB has demurred in this regard, responding:

> *'the EDPB considers that this [the Commission's] approach excludes, in all circumstances, the applicability of the so-called presumption of compatibility provided under Article 5(1)(b) GDPR. […] These conditions, due to their horizontal and complex nature, will require specific attention and guidance from the EDPB in the future. For the time being, the presumption of compatibility,*

[81] Jessica Bell, et al., 'Balancing Data Subjects' Rights and Public Interest Research: Examining the Interplay between UK Law, EU Human Rights Law and the GDPR' (2019) 5(1) European Data Protection Law Review 43-53.

[82] European Commission Directorate-General for Health and Food Safety, 'Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation', page 7, available at: <https://ec.europa.eu/health/sites/health/files/files/documents/qa_clinicaltrials_gdpr_en.pdf>,

> *subject to the conditions set forth in Article 89, should not be excluded, in all circumstances, for the secondary use of clinical trial data outside the clinical trial protocol for other scientific purposes.'* [83]

This leaves the door open for data to be re-used for scientific research without an identified lawful basis, beyond the original basis for collection, which places great reliance on the capacity of Recital 50 GDPR to modify Articles 5 and 6. Although the EDPB has allowed scope for data to be re-used for Article 89 compliant purposes without an identified Article 6 legal basis, a cautious approach is justified. We will therefore proceed on the basis that Articles 6 and 9 GDPR still need to be satisfied, even for research and statistical purposes, and consider the nature of the consent the GDPR requires.

2.4.2 Specific Consent

The notion of 'consent' under the GDPR apparently goes beyond informed consent as defined in the Clinical Trial Directive (CT Directive) and upcoming CT Regulation.[84] As noted above, under the CT Directive and Regulation, informed consent means a subject's free and voluntary expression of their willingness to participate in a particular clinical trial after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate (Article 2(j) CT Directive; Article 2(21) CT Regulation). However, the GDPR imposes additional requirements as to what constitutes a valid consent, which go beyond the necessary characteristics of informed consent.

According to Recital 32 of the GDPR,

> *consent should be given by a clear affirmative act establishing a freely given, specific, informed and unambiguous indication of the data subject's agreement to the processing of personal data relating to him or her, such as by a written statement, including by electronic means, or an oral statement. Consent should cover all processing activities carried out for the same purpose or purposes. When the processing has multiple purposes, consent should be given for all of them.*

Consent is defined in the GDPR as *any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her.*[85] Consent needs to be clear, concise, specific and granular, a requirement that may be difficult in the context of research, where all processing may not be capable of anticipation at the outset.[86] The Article 29 Working Party draw attention to the requirement for consent to be given, withheld or withdrawn without detriment. In the case of a clinical trial, where consent to processing is a precondition for entering the trial, this may prevent the consent to processing from being entirely free and granular, as it is not entirely optional and non-detrimental to

[83] European Data Protection Board, 'Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR) (art. 70.1.b)', adopted 23 January 2019, available at: <https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_opinionctrq_a_final_en.pdf> accessed 29 January 2020

[84] European Data Protection Supervisor, 'Guidelines on the processing of personal data in the context of public procurement, grants as well as selection and use of external experts', available at: <https://edps.europa.eu/sites/edp/files/publication/13-06-25_procurement_en.pdf> accessed 29 January 2020.

[85] GDPR, Article 4(11).

[86] Recital 33 GDPR and Victoria Chico, 'The Impact of the General Data Protection Regulation on Health Research', (2018) 128 British Medical Bulletin 1.

decline the use of the information. This would particularly be the case where the experimental treatment offered is one the subject is accepting to treat a serious disease, and without the data processing they could not access the treatment.

A number of conditions need to be met before a consent can be valid under the GDPR (Art. 7). Consent needs to be demonstrable, distinguishable from other matters in a written declaration ('granular'), intelligible and capable of being withdrawn as easily as the giving consent ('revocable'). Processing of patient data for research will usually concern a special category of personal data (if the models are related to health or genetics); thus, if consent is the condition relied on for setting aside the prohibition on processing, that consent will need to be 'explicit consent'.

Reliance on consent gives rise to the right to data portability under Article 20 GDPR, although it remains to be seen whether this right has any significant impact in the context of healthcare or research. Where patient related clinical data is being transmitted to third countries, it is not sufficient for an informed consent for participation in the clinical study to exist. Rather, the informed consent must contain clear wording regarding transfer of study data to third countries or international organizations (as the case may be).[87]

It has been argued that some provisions in the GDPR on consent regarding secondary use could jeopardise data sharing. These provisions could undermine the scientific validity of data reused for research purposes. In particular, the possibility of not consenting to secondary use, or consenting only to restricted use (for a given institution or disorder), and more importantly, the possibility of withdrawing consent for secondary use could increase the risk of bias if many patients exercise this right — especially if the patient's satisfaction during hospitalization, or during a study, affects their decision to withdraw consent for secondary use.[88] However, informed consent under the CTR, and under other instruments, must also be revocable, so this is not unique to the GDPR's requirements.

The key distinction between the two Regulations, therefore, appears to be the extent to which they each accommodate further processing of data on the basis of broad consent.

2.4.3 Broad consent under GDPR & CTR

Article 28 (2) CTR explicitly foresees the possibility for the sponsor to ask clinical trial participants, when they give their consent to participate in the trial, to agree to their data being reused "*outside the clinical trial protocol exclusively for scientific purposes*". This could include the re-use of data for in silico modelling purposes. This broad consent, which can be withdrawn at any time and which is used as a basis for secondary use of the data, therefore applies to clinical trials on medicines. However, the same Article makes clear that scientific research that harnesses data outside the clinical trial protocol must be conducted in accordance with applicable data protection laws, which in practice will encompass the GDPR and the applicable legislation at national level.

The European Data Protection Board has adopted an Opinion (3/2019) on the interplay between the EU Clinical Trials Regulation and the GDPR. The opinion notes that both the GDPR and CTR expressly refer

[87] Minssen, note 8.

[88] Jacques Demotes-Mainard, Catherine Cornu and Aurélie Guérin 'How the new European data protection regulation affects clinical research and recommendations?' (2019) 74 Therapies 31-42.

to each other and hence it follows that both legislations apply simultaneously. As data processing under the Clinical Trial Regulation must comply with the GDPR, we will consider the GDPR requirements for consent, and how these interact with the Clinical Trials Regulation.

The GDPR recognises in Recital 33 that achieving specific and granular consent might be difficult in the context of scientific research. It provides:

> *It is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognised ethical standards for scientific research. Data subjects should have the opportunity to give their consent only to certain areas of research or parts of research projects to the extent allowed by the intended purpose.*

Thus, the GDPR acknowledges that specific consent will not always be possible for the secondary use of information such as CTD and introduces a concept of "*consent to certain areas of scientific research."* This appears to permit reliance on 'broad consent' when processing data on the basis of consent. At first glance, Recital 33 brings the GDPR into alignment with Article 28(2) CTR. By broadening the requirements for consent to scientific research, it appears that prospective consent to use information beyond the protocol could be obtained per the CTR, in a way which would also satisfy the GDPR's requirements for consent.

It is still under discussion as to what "*consent to certain areas of scientific research"* means. The Article 29 Working Party, in their guidance on consent under the GDPR, have however cast doubt on the extent to which Recital 33 'broadens' GDPR consent for scientific research:

> *'Considering the strict conditions stated by Article 9 GDPR regarding the processing of special categories of data, WP29 notes that when special categories of data are processed on the basis of explicit consent, applying the flexible approach of Recital 33 will be subject to a stricter interpretation and requires a high degree of scrutiny.' [89]*

Researchers and modellers should therefore exercise caution in relying on this 'broader' consent for GDPR purposes, particularly when processing genetic or health-related data (which are subject to Article 9). Processing data on the basis of broad, explicit consent will require confidence that this will stand up to a 'high degree of scrutiny' as to whether the consent in question is sufficiently granular and revocable.

There are mitigating steps a controller can take to legitimise reliance on broader consent for scientific research. The Article 29 Working Party suggest, for example, obtaining consent with as much specificity as possible initially, and then returning to re-consent as the research progresses.[90] Platforms such as *Dynamic Consent* may offer a way to facilitate this ongoing dialogue with participants, as the consent evolves with the project and is able to become more specific. This is considered further in section 2.6. Safeguards, including data minimisation and ethical review, may also be useful in helping to reduce any intrusion justified on the basis of broad consent. The relationship between professional ethical standards and the GDPR is still under discussion within the European Data Protection Board,[91] and it is

[89] Article 29 Working Party, 'Guidelines on Consent under Regulation 2016/ 679' WP 259 rev.1, as last revised 10 April 2018, p 28.

[90] Ibid, p. 29

[91] European Data Protection Supervisor, note 78.

possible that the outcome of these discussions may impact upon the that role ethical review can play in legitimising broad consent as a basis for processing.

Anonymisation and the broader, ethical significance of consent are also considered in section 2.6.

It is suggested that broad consent as a GDPR basis for processing will be the exception rather than the rule, and where specific consent is not practicable, reliance on other GDPR bases for processing—and particularly the Article 9 scientific research condition—will usually be preferable. Where consent is not selected as a GDPR basis/condition for processing, this does not mean that informed consent does not, nonetheless, have a role to play. We consider the interaction between informed consent and the GDPR in the next subsection.

2.5 GDPR Consent vs Informed Consent

The European Data Protection Supervisor has recently acknowledged the conceptual and operational differences between GDPR consent and informed consent, with the latter remaining an important safeguard even where a different basis for processing is used.[92] Other guidance has also emphasised the fact that the free, granular and revocable consent required under the GDPR may not always be achievable within research. However, this does not mean that other types of consent are no longer relevant. As the UK's National Health Service Health Research Authority advises:

> *'Consent to participation in research is not the same as consent as the legal basis for processing under data protection legislation. An example is that a person is asked to consent to participate in research but is told that, if they agree to participate, data about them will be processed for a task in the public interest. The legal basis for data processing is not consent.*
>
> *[…]*
>
> *If you use 'task in the public interest', it does not automatically mean that the requirements of the common law duty of confidentiality have been met. The requirements of both data protection legislation and the common law duty of confidentiality must be satisfied.' [93]*

This has been echoed more recently by the European Commission, and by the European Data Protection Board's 'Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR).'[94] The Commission's 'Question & Answer' document recognises a distinction between consent as a requirement for participation in clinical trials, and as a basis for processing data under the GDPR,[95] a distinction which was then endorsed by the EDPB.[96] The Commission has emphasised the circumstances in which it may be inappropriate for a trial sponsor to delete participant data, for example if they have suffered a serious

[92] Ibid

[93] NHS Health Research Authority, 'Legal basis for processing data' <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-detailed-guidance/legal-basis-processing-data/.accessed 29 January 2020

[94] Note 8382.

[95] Note 82, p.5

[96] Note 83 p.5

adverse reaction.[97] The EDPB has in turn confirmed that consent may not be the most appropriate basis for processing clinical trial data under the GDPR.

Thus, much of the advice for research organizations has been to move away from, or at least to carefully reconsider, relying on consent for processing under the GDPR, even if informed consent is still obtained. This reliance on GDPR bases other than consent may feel counter intuitive to researchers schooled in the ethical importance of informed consent in human subject research. Nevertheless, the fact that consent may not be the lawful basis for data processing under the GDPR does not affect the need to comply with other separate legal obligations to gain consent in the process of conducting research. Where a person consents to participate in research they are consenting to a number of things other than the processing of their personal data. This is consent to the risks, implications, inconveniences, objectives and benefits of the clinical trial. The need to obtain this consent is unchanged by the data processing requirements in the GDPR, and the fact that this consent must still be sought to run the trial risks does not indicate that the lawful basis for data processing under the GDPR in the trial should also be consent.[98]

With this in mind, we consider how consent may be obtained and managed, regardless of the GDPR basis for processing.

2.6 Implementation of consent

2.6.1 Dynamic consent and the GDPR

Dynamic consent[99] is one of many ways in which GDPR consent could be implemented. As noted above (2.4.2), the Article 29 Working Party suggest that initially broad consent to research could be particularized over time through re-engagement with data subjects, making it more suitable as a basis for processing. Dynamic consent is one way in which this could be achieved. Unlike specific consent in the traditional sense, which may be recorded once and then relied upon, and limited to its documented form, dynamic consent models provide subjects with a digital platform through which they are able to receive information, and tailor their preferences over time. This information could be updated as a project developing in silico models progresses, for example.

The possible negative implications of GDPR on the development of dynamic consent are discussed by van Veen (2018) in the context of observational research and clinical trials. Van Veen concludes that the purpose of the GDPR is to give data subjects more control over their data. However, patient rights might not be adequately balanced against the need for different forms of consent. In particular, van Veen argues that GDPR might undermine attempts to develop a dynamic consent system. The scenario may arise where a patient provides dynamic consent but then stops responding to notifications (van Veen, 2018)[100] in which case the researchers could be left with the uncertainty of an enduringly broad consent.

[97] Note 82, p.7

[98] Chico, note 86.

[99] Isabelle Budin-Ljøsne, et al., 'Dynamic Consent: a potential solution to some of the challenges of modern biomedical research' (2017) 18(4) BMC Medical Ethics 4.

[100] European Parliamentary Research Service, *How the General Data Protection Regulation changes the rules for scientific research* (European Parliamentary Research Service Scientific Foresight Unit (STOA) PE 634.447 – July 2019). Available at:

The re-engagement model certainly requires a willingness of data subjects to take a role in the governance of their data over time.

Despite these concerns, however, others have suggested that a dynamic consent platform can assist in providing the granularity and revocability the Regulation requires from consent, as well as assisting with the GDPR's transparency and record keeping requirements.[101] These latter obligations are important even where consent is not used as the basis for processing. If a data controller reflects on the implications of consent withdrawal, however, and decides the benefits of a robust consent process still outweigh the risks, dynamic consent can help make consent explicit, revocable and granular to satisfy Articles 6,7 and 9 GDPR.[102] This is also assuming, of course, that the consent is freely given from the subject's perspective, and they will not suffer detriment if they withdraw.

2.6.2 Participant Attitudes towards Consent

Although the legal requirements for a valid consent are an important consideration, the role consent plays in securing and maintaining public confidence in data-driven research should also be taken into account. This reflects the ethical significance of consent as a means of respecting the autonomy of data subjects in a way which may go beyond the minimum requirements of the law. Guidance should not only seek to ensure compliance with the law, but also promote reflection as to how consent can help maintain trust and integrity in further uses of data.

The results of a thematic synthesis, for example, have indicated a general, but conditional, support for health data sharing. One of the conditions for support for data sharing was control and consent, although the authors note that no clear consensus (across or within) the studies regarding what this control implied or necessitated.[103] The study yielded no clear indication as to the level of control data subjects wish to exercise over their data, and indeed this desired level of control may vary depending on how much trust subjects have in those using their data.[104] Nevertheless, as a general principle, other studies[105] have helped to confirm that research participants value consent within data sharing: as a mechanism for respecting their autonomy,[106] or even simply as an act of courtesy during a research project.[107] Nicola Howe et al found that some clinical trial participants express a preference for re-

<https://www.europarl.europa.eu/thinktank/en/document.html?reference=EPRS_STU(2019)634447> accessed 29 January 2020

[101] Megan Prictor, Harriet Teare and Jessica Bell 'Consent for processing under the General Data Protection Regulation: Could 'Dynamic Consent' be a useful tool for researchers?' (2019) 3 Journal of Data Protection and Privacy 93-112.

[102] Ibid.

[103] Mhairi Aitken, et al, 'Public responses to the sharing and linkage of health data for research purposes: a systematic review and thematic synthesis of qualitative studies' (2016) 17(1) BMC Medical Ethics 73.

[104] Ibid

[105] As cited in Miranda Mourby, Heather Gowans, Stergios Aidinlis and Hannah Smith, 'Governance of academic research data under the GDPR—lessons from the UK' (2019) 9(3) International Data Privacy Law 192–206.

[106] Amy L McGuire, et al., 'DNA Data Sharing: Research Participants' Perspectives' (2008) 10 Genetics in Medicine 46.

[107] Gill Haddow et al., '"Nothing Is Really Safe": A Focus Group Study on the Processes of Anonymizing and Sharing of Health Data for Research Purposes' (2011) 17 Journal of Evaluation in Clinical Practice 1140; Michael Robling, 'Public Attitudes towards the Use of Primary Care Patient Record Data in Medical Research without Consent: A Qualitative Study' (2004) 30 Journal of Medical Ethics 104.

consenting before sharing, and at the very least the majority of participants preferred a thorough initial consent process with agreed terms as opposed to "inferred consent", or inferred opt-in where researchers neglected to ask for explicit consent to share. [108]

In summary, even if consent may not always be the most appropriate basis for processing under the GDPR, there will often still be a role for some form of consent, and there is some evidence this is what data subjects want. This may be particularly true where genetic data are used.[109] These preferences help to substantiate the continuing relevance of informed consent as a bioethical norm, beyond the formal authorities. If even only a partial revocation of consent can be offered, for example, this is better for engendering trust, respecting autonomy and for data minimisation than to disregard consent entirely on the grounds that a different GDPR basis for processing is used.

Active communication at time of consent regarding likely future data uses and types of researchers or archives with which data may be shared should be included as standard on consent form.[110] Engaging participants in research that uses their own data by keeping them informed of the types of studies using their data, and the resultant outcomes (e.g. via newsletters) could enforce researcher accountability.

2.6.3 Consent vs Anonymisation

Ultimately, though, active communication with data subjects is only possible for as long as data are still capable of linkage back to them, and as a legal requirement data should only be kept in an identifiable form for as long as this serves a purpose. Article 11(1) of the GDPR is clear that:

> '*If the purposes for which a controller processes personal data do not or do no longer require the identification of a data subject by the controller, the controller shall not be obliged to maintain, acquire or process additional information in order to identify the data subject for the sole purpose of complying with this Regulation.*'

Therefore, once a point is reached at which it serves no scientific or statistical purpose for data to be kept in a form in which it is capable of linkage to a natural person, it should be anonymised. The Article 29 Working Party confirm that anonymisation is the preferred solution as soon as the scientific research can be achieved without processing personal data.[111] Even if anonymisation takes the data outside the consent and control of the former data subject, the GDPR is clear that personal information should not be retained purely to allow its subjects to have control over it. This would have the paradoxical effect of unnecessarily interfering with privacy in order to seek to enhance it. This represents a limit on the legal utility of consent: data should not be kept in an identifiable form simply to keep it within the parameters of consent.

However, the balance between data subject rights and data minimization is potentially subject to interpretation, and indeed national deviation. While in the UK, for example, individuals are deemed to

[108] Howe, note 33

[109] Pauline McCormack, et al, ''You should at least ask.' The expectations, hopes and fears of rare disease patients on large-scale data and biomaterial sharing for genomics research' (2016) 24 Eur J Hum Genet 1403–1408 (2016).

[110] Note 33

[111] Article 29 Working Party, note 89, p. 29

have no rights in anonymized data, in Germany this has been pre-empted by the Federal Data Protection Act 2017, which provides that:

> *'special categories of personal data as referred to in Article 9 (1) of Regulation (EU) 2016/679 processed for scientific or historical research purposes or statistical purposes shall be rendered anonymous as soon as the research or statistical purpose allows, unless this conflicts with legitimate interests of the data subject.'* [112]

The continuation of data subject rights, and in particular the ability to revoke consent to data processing, may be seen as a 'legitimate interest' justifying the retention of research data in a personal, albeit pseudonymised form for longer periods. In this context, therefore, the balance between consent and anonymisation might be struck differently, despite the guidance from the Article 29 Working Party. Similarly, in circumstances where clinically significant results may be identified, anonymisation will not be appropriate if this prevents re-contacting individuals (see more in section 4.1). It is therefore important to strive for consistency in anonymisation practices, to support consistency in re-contacting patients or participants.[113]

Although anonymisation will eliminate the possibility of communicating with data subjects, and other direct channels of accountability, the terms of the original consent could still be of ethical relevance when anonymised data are used. If people's health information is the original source of any valuable anonymised data, there is at least an ethical argument for also giving people a degree of control over how it is used,[114] even if this falls short of individual consent, for example by surveying their preferences prior to anonymisation.[115]

There is precedent for this compromise between consent and anonymisation with personalised medicine modelling. For example, in the US context, I. Glenn Cohen and colleagues recommend that model developers be allowed to use patient data that have already been collected without explicit consent, as long as these researchers cannot identify the individuals in question.[116] This is the equivalent to using anonymised data without consent, which no longer fall within the scope of the GDPR. However, they also note that as re-identification following data breaches remain possible, and thus recommend that collectors of predictive analytics data notify patients that the data gathered from them in the course of regular healthcare may be used in deidentified form in predictive analytics models. This falls short of actual consent, but is a way of reconciling the GDPR's push towards anonymisation where possible, and managing ongoing risks of re-identification and ethical duties to data subjects.

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[112] Federal Data Protection Act of 30 June 2017 (Federal Law Gazette I p. 2097), section 27 (3)

[113] Yvonne Bombard and Chloe Mighton, 'Recontacting clinical genetics patients with reclassified results: equity and policy challenges' (2019) 27 European Journal of Human Genetics 505.

[114] Thomas Gallagher, Kudakwashe Dube, and Scott McLachlan, 'Ethical Issues in Secondary Use of Personal Health Information' IEEE Future Directions (2018). Available at: <https://cmte.ieee.org/futuredirections/tech-policy-ethics/may2018/ethical-issues-in-secondary-use-of-personal-health-information/> accessed 29 January 2020

[115] Nisha Shah, et al, 'Sharing data for future research—engaging participants' views about data governance beyond the original project: a DIRECT Study' (2019) 21 Genetics in Medicine 1131–1138.

[116] I. Glenn Cohen, et al., note 3.

2.7 Conclusion on consent

We have shown that consent can be a deceptively simple concept which masks a matrix of overlapping law, guidance and bioethical convention. It is therefore unsurprising that there is rich academic literature contesting the appropriate nature and role of consent, even before the GDPR came into force.[117] Even if the scientific information which must be imparted were straightforward, the legal significance and status of the consent is subtly unique to each project, and must be communicated with care.

As we have shown, consent has developed from being a justification of physical interventions to be a legal concept discussed in the processing of data for research purposes. While exceptions from consent to a physical intervention are very rare, it is much more common for alternative bases to be used in the place of informational consent. There are many reasons why consent may not be an appropriate basis for processing under the GDPR, but from the discussion above we would highlight the following:

- If the controller is a public authority, they may need to consider whether their relationship with the data subject creates an imbalance of power which would undermine a claim that their consent was freely given, in particular with regard to Recital 43 GDPR. This will have obvious implications to providers of public healthcare.
- Whether, in any event, there is an imbalance of power which could undermine the free assent of the data subject.
- Whether the data subject would suffer any detriment were they to refuse. For example, where it is necessary for the person's data to be processed in order to participate in a clinical trial, and if they do not participate in the trial they will not have access to e.g. cancer treatment.
- If there are any secondary data subjects whose information would not be covered by one individual's consent. For example, in the context of genetic data the privacy implications for biological relatives should also be considered.[118]
- Whether it is truly possible for data to be deleted if consent is revoked, including by third parties to whom the information will have been made available, or whether it is required to be retained, or becomes inseparable from other data as a result of analyses on original data, or is made available on an open access basis.

However, the question as to whether consent is an appropriate basis for processing personal data under the GDPR does not exhaust consideration of its role in research or healthcare. Even if it is determined not to be appropriate to rely on consent under Articles 6 & 9 GDPR, the consent of the data subject may be important for other reasons. It may be a requirement of entry into a clinical trial, or simply something participants value in research studies as a sign of respect for their wishes, irrespective of how data is processed under the GDPR. Consent also has, naturally, an important role to play in legitimating the intervention from which the data may be derived, or even an intervention which is based on data

[117] Jane L. Hutton and Richard E. Ashcroft, 'Some popular versions of uninformed consent' (2000) 8 Health Care Analysis 1; Susan E. Wallace and Bartha M. Knoppers, 'Harmonised consent in international research consortia: an impossible dream?' (2011) 7 Genomics, Society and Policy 35; Bart W. Shermer, Bart Custers and Simone van der Hof, 'The crisis of consent: how stronger legal protection may lead to weaker consent in data protection' (2014) 16 Ethics and Information Technology 2; Linus Johnsson and Stefan Eriksson, 'Autonomy is a Right, Not a Feat: How Theoretical Misconceptions Have Muddled The Debate on Dynamic Consent to Biobank Research' (2016) 30 bioethics 7.

[118] Mark Taylor, *Genetic Data and the Law: A Critical Perspective on Privacy Protection*, (CUP 2012).

processing, such as when in silico models are used to 'personalise' treatment recommendations. This is considered further in section 4, along with the right to information which accompanies such consent.

Just as the GDPR is not the only significant aspect of the regulation of consent, however, consent is not the only aspect of the GDPR which has implications for data integration and re-use for modelling purposes. The next section explores other aspects of the GDPR which must be navigated for secondary uses of personal data in the EU: scope, anonymisation, the presumption of compatibility and transparency.

3. The General Data Protection Regulation

3.1 Introduction

The General Data Protection Regulation[119] has been in force in EU member states since 25 May 2018, following a two-year implementation period, as well as in EEA member states from July 2018. In theory, the use of personal data within EU member states was expected to have been brought into conformity with the GDPR by the end of this implementation period.[120] However, the reality has been more complicated, with many member states passing their implementing legislation only shortly before the GDPR came into force, or in some cases after the implementation date,[121] or not at all.[122]

Consequently, even though the final text of the GDPR was passed and published in 2016, and data processors had full knowledge of the deadline for compliance, the direct effect of the Regulation has not been straightforward in practice. Although the Regulation applied directly to data controllers from 25 May 2018, this was subject to the following caveats:

[119] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ 2016 L 119/1 (hereafter cited as GDPR).

[120] GDPR, Recital 171.

[121] See for example, European Commission, 'GDPR Implementation: Updated State of play in the Member States (11/04/2019)' available at: <https://ec.europa.eu/transparency/regexpert/index.cfm?do=groupDetail.groupMeetingDoc&docid=30306> accessed 29 January 2020

[122] European Commission, 'General Data Protection Regulation shows results, but work needs to continue' available at:

<https://ec.europa.eu/commission/presscorner/detail/en/IP_19_4449> (accessed 29 January 2020) although at the time of writing Greece and Portugal have now passed implementing legislation, and Slovenia appears to be the only outlier.

(1) Where old national legislation was still in effect, this may have created overlapping or contradictory requirements, although in the majority of Member States this should now be resolved.[123]

(2) Member state legislative delay would also mean delay in any national derogations to the GDPR—including derogations from data subject rights for research and statistical purposes124, as well as derogations for archival purposes.[125]

(3) Key Article 29 Working Party guidance, such as that governing transparency and consent under the GDPR, was not published until 2018.

(4) National data protection authority guidance on the GDPR was also delayed, and in some cases is still in development.[126]

(5) Judicial guidance on the new provisions is also limited, as the Court of Justice of the European Union ('CJEU') is still adjudicating cases which were issued before the GDPR came into force, although in a recent judgment the Court has begun to consider the GDPR as well as the Directive it replaced so the precedent retains utility under the Regulation.[127]

In sum, even though much has been done to adapt practices and legislation in conformity with the GDPR, this has been a slow process in light of significant uncertainty as to:

> the correct interpretation of any novel features of the GDPR;

> the interplay of national derogations and interpretations of the Regulation, which could still lead to inconsistencies across Member States.

It is naturally beyond the scope of this report to resolve the remaining uncertainties around the GDPR, but our contribution is rather to highlight and explore these issues, and make practical suggestions as to how they can be addressed for data integration and in silico modelling.

3.2 Scope of the GDPR

The GDPR applies to the processing of personal data within its territorial and material scope. Processing personal data within the EU is subject to the Regulation (and any other national legislation of the Member State in question). The GDPR will also apply to processors outside the EU to the extent that they process the personal data of individuals in the EU in order to offer them goods or services, or monitor their behaviour.[128]

Therefore, the GDPR will apply to data processing carried out in the EU, or on behalf of a controller based in the EU, or to offer services or monitor the behaviour of people in the EU. Even where this does

[123] Ibid.

[124] GDPR, Article 89(2).

[125] GDPR, Article 89(3).

[126] For example, the UK's Information Commissioner's Office is still updating its guidance on personal data and anonymisation to reflect GDPR provisions, and directs readers to their old guidance on anonymisation in the meantime. Available at: < https://ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/what-is-personal-data/what-is-personal-data/>.accessed 29 January 2020

[127] Case C-507/17 *Google LLC v. Commission nationale de l'informatique et des libertés (CNIL*),

[2020] E.M.L.R. 1 para 41.

[128] GDPR, Article 3.2

not apply, if data are transferred out of the EU (to a third country or international organisation[129]) this transfer will have to be authorised on one of the grounds set out in Chapter V GDPR (which is explored further in the final subsection).

The material scope of the GDPR is superficially straightforward, covering the processing of personal data by automated means (wholly or partly), excluding activities of a purely personal/ household nature, or activities out of the scope of Union law. Two uncertainties arise as regards material scope, however:

(1) If, as some have argued,[130] the GDPR does not apply to medical records, as the delivery of health care is outside EU competence, then the GDPR might apply at some stages of the development of in silico models (if this were to be regarded as scientific or statistical research, rather than the delivery of healthcare), but not to the healthcare contexts in which the modelling data were originally obtained.

(2) There is potential contention as to when data should be regarded as personal, particularly as regards whether individuals are identifiable from the information.

In terms of the first issue, it is definitely not a problem in Member States (such as the United Kingdom) which have extended the scope of the GDPR to apply to processing outside the scope of EU law.[131] Guidance provided jointly by the European Data Protection Board and the European Data Protection Supervisor seems to assume that the GDPR will apply to patient data within Member States, but this is not made explicit.[132]

It is the authors' experience that the GDPR is considered to apply to medical records in their Member States. However, the question as to whether healthcare could be determined to be outside the scope of EU law remains a potential ambiguity. Consequently, we would recommend that where data are collected with the intention of re-use for research and statistical purposes, a plan for GDPR compliance should be put in place even if the Regulation does not apply in a healthcare context within the Member State in question. Where the data have already been collected, it will have to be considered how the further use can be brought in line with the GDPR, but bringing the data in line with the transparency requirements of the Regulation is likely to be a key step in this.

The second issue, the scope of personal data, is one which pre-dates the GDPR. Indeed, it is an issue on which all current case law as to the scope of personal data has been adjudicated on the previous Directive, even if the updates to the GDPR are subtle, mostly centring on the category of data which have undergone pseudonymisation. As the scope of 'relation' (i.e. whether information 'relates to' an

[129] GDPR Article 4(26) an organisation and its supplemental bodies governed by public international law, or any other body set up by agreement between two or more countries. On its face, this definition would also include EU bodies, but there is no evidence that it has been interpreted in this way and that the European Commission needs to assess its own adequacy! Union bodies are governed by the GDPR-equivalent provisions of Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC (Text with EEA relevance.)

[130] Jasper A. Bovenberg and Mara Almeida, 'Patients v. Myriad or the GDPR Access Right v. the EU Database Right' (2019) 27 Eur J Hum Genet 211–215.

[131] Data Protection Act 2018, s.21

[132] EDPB & EDPS, 'EDPB-EDPS Joint Opinion 1/2019 on the processing of patients' data and the role of the European Commission within the eHealth Digital Service Infrastructure (eHDSI)' available at <https://edps.europa.eu/sites/edp/files/publication/19-07-15_edpb_edps_joint_opinion_ehealth_en.pdf> accessed 27 November 2019.

individual) has been drawn broadly in case law,[133] the key uncertainty is the question as to when an individual is deemed identifiable, and from whose perspective this question should be answered?

This question can ultimately be expressed as: should data be non-identifiable for *everyone* to be considered anonymous, or only for those with lawful access? Or, more practically: do you need to delete or aggregate the original information in order to share data anonymously? This question is considered further in the next section.

3.3 Anonymisation & Synthetic Data

The scope of personal data, and the corresponding standards for anonymisation, is a complex issue. Those sharing or receiving data to develop in silico models need to know whether it is possible to share these data anonymously. The GDPR states that data should not be kept in an identifiable state purely for the purposes of complying with the Regulation[134]—in other words, data should be anonymous unless there is some practical purpose in their being identifiable.[135] However, if anonymisation requires deletion or aggregation of the original data, this will not be possible where the information is derived from patient medical records, for example. Clarity as to anonymisation standards is therefore essential.

As a point of law, there is a lack of clarity as to how the scope of personal data should be interpreted. The CJEU judgment in *Patrick Breyer v Bundesrepublik Deutschland*[136] decided under the Directive acknowledges two competing schools of thought. The 'objective' approach, under which data are personal if they are identifiable by *any* person, and the 'relative' approach in which a different assessment could be made for each potential data controller. Under this latter 'relative' approach, only if the organisation in question, or anyone they could reasonably approach, could identify individuals from the data should they be considered to be processing personal data. While it has been argued that the CJEU has favoured a relative approach in their judgment,[137] the opposite interpretation has also been drawn from the same judgment,[138] so this is not a question free of contention.

Some uncertainty also stems from the status of the Article 29 Working Party's 2014 guidance on anonymisation techniques, which clearly requires an objective standard. While other Article 29 Working Party guidance has been formally endorsed by the succeeding European Data Protection Board,[139] the anonymisation guidance has not, and as such it is less clear whether it continues to be a reliable benchmark. Nevertheless, its position on anonymity has been highly influential, particularly the stipulation:

[133] Case C-434/16, *Peter Nowak v Data Protection Commissioner*, [2018] 1 W.L.R. 3505

[134] GDPR, Article 11 (1).

[135] This point is further reinforced by Article 5(1)(e) which states that data should not be maintained in an identifiable form for any longer than is necessary.

[136] Case C-582/14, (ECJ, 19 October 2016)

[137] Miranda Mourby, et al., 'Are 'pseudonymised' data always personal data? Implications of the GDPR for administrative data research in the UK' (2018) 34 Computer Law & Security Review 2.

[138] Nadezhda Purtova, 'The law of everything. Broad concept of personal data and future of EU data protection law' (2018) 10 Law, Innovation and Technology 40.

[139] The European Data Protection Board, Endorsement 1/2018. Available at: https://edpb.europa.eu/sites/edpb/files/files/news/endorsement_of_wp29_documents_en_0.pdf

> ''… *"the means likely reasonably to be used to determine whether a person is identifiable" are those to be used "by the controller or by any other person". Thus, it is critical to understand that* ***when a data controller does not delete the original (identifiable) data at event-level****, and the data controller hands over part of this dataset (for example after removal or masking of identifiable data), the resulting dataset is still personal data. Only if the data controller would aggregate the data to a level where the individual events are no longer identifiable, the resulting dataset can be qualified as anonymous*.'[140] (Emphasis added)

The A29WP's insistence on deletion or aggregation of original data has been criticised for its impracticability.[141] Nonetheless, it has influenced the European Medicines Agency's guidance on the standard by which clinical data should be anonymised:

> 'Pseudonymisation reduces the linkability of a dataset with the original identity of a data subject but when used alone will not result in an anonymous dataset, therefore data protection rules still apply. It is, therefore, important to clarify that pseudonymisation is not an anonymisation method but a useful security measure. Consequently, additional measures should be considered in order to render the dataset anonymised**, including removing and generalising attributes or deleting the original data or at least bringing them to a highly aggregated level.'** [142] (Emphasis added)

As the European Commission has emphasised in the context of consent, there are many circumstances in which it would be inappropriate to delete data from clinical trials,[143] such as serious adverse reactions, and the same would be true of deletion for anonymisation. It therefore appears unlikely, following this guidance, that data collected in healthcare or clinical trial contexts could be anonymised for further use.

In summary, the scope of personal data is an uncertain and contentious question, meaning a cautious approach may be justified in practice. Unless and until the European Data Protection Board, or the CJEU, issues new guidance on the scope of personal data under the GDPR, it may be best to assume that guidance requiring an objective standard of anonymisation still holds. Therefore, where data have been obtained from a context in which deletion of original records is not possible (such as healthcare or a clinical trial) it is safest to assume they cannot be anonymised for further use. However, as there is scope for alternative interpretations, this is an issue on which it would be beneficial to watch for developments, and bear in mind implications of any future guidance.

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[140] Article 29 Data Protection Working Party, Opinion 05/2014 on Anonymisation Techniques, Adopted on 10 April 2014 (0829/14/ENWP216), page 9.

[141] Khaled El Emam and Cecilia Alvarez, 'A critical appraisal of the Article 29 Working Party Opinion 05/2014 on data anonymization techniques' (2015) 5(1) International Data Privacy Law 73–87.

[142] European Medicines Agency, 'External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use,' (2018) version 1.4 <https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data_en-3.pdf> accessed 26 July 2019, p.41

[143] European Commission Directorate-General for Health and Food Safety, 'Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation, page 7, available at: <https://ec.europa.eu/health/sites/health/files/files/documents/qa_clinicaltrials_gdpr_en.pdf> accessed 29 January 2020

Furthermore, it is worth considering that in future anonymisation may lie not so much in the suppression or deletion of data attributes as in the creation of new, synthetic data. If executed successfully, these data would have the same qualities as the information from which they were derived, and reveal the same statistical relationships, but should not relate (or be capable of relation) to any natural living person, as the individuals in the set should be fictitious and lack a real-world direct equivalent. At a policy level, it has been recommended that the UK's health service should offer synthetic datasets, which they can share with private sector organisations for research and product or service development at the early stages of the innovation process.[144] Subject to the estimated utility of synthetic data for health-related in silico models, this is a recommendation which could be adopted more widely. It has been suggested that creation of synthetic datasets is a key way of widening access to data whilst preserving privacy,[145] and so it is worth considering whether creation of a permanent, synthetic dataset for modellers to use on an open access basis could be a final stage in the data integration process.

As anonymisation may otherwise have a limited role to play in data integration for in silico modelling, the process of pseudonymisation is all the more important. This is explored in the next subsection.

3.4 Pseudonymisation & Data Minimisation

Pseudonymisaiton is defined in the GDPR as:

> '*the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person*' [146]

Pseudonymisaton does not change the fact that the data are personal, and within the scope of the GDPR, although if the data controller in question can demonstrate that they are not in a position to identify a data subject they may not have to comply with data subject rights.[147] Otherwise, all the other principles and provisions of the GDPR will apply. Pseudonymisation is possible within an organisation, where there are controls to keep the identifiers away from the data, but is also possible where the information is split across two or more organisations, such as when an extract of a dataset is shared with a third party.

There are a number of reasons why pseudonymisation is a key aspect of compliance with the GDPR, but in the context of in silico model development it is especially important as it is an example of the type of safeguard required for data to be processed under the scientific research and statistical purposes condition.[148] These safeguards, of which pseudonymisation is the sole named and emphasised example, are also prerequisites for the research exemptions in the GDPR, which allow data to be retained for

[144] Eleonora Harwich and Rose Lasko-Skinner, Reform, 'Making NHS data work for everyone' (2018) available at: <https://reform.uk/sites/default/files/2018-12/Making%20NHS%20data%20work%20for%20everyone%20WEB_1.pdf> accessed 29 January 2020

[145] Rittika Shamsuddin et al., 'Virtual Patient Model: An Approach for Generating Synthetic Healthcare Time Series Data', 2018 IEEE International Conference on Healthcare Informatics (ICHI), 2018, 208–18. Available at: < <https://ieeexplore.ieee.org/document/8419364> accessed 29 January 2020

[146] GDPR, Article 4.5.

[147] GDPR, Recital 29.

[148] GDPR, Article 9.2.j

longer periods,[149] to be re-used as a compatible purpose,[150] and permits an exemption to the transparency requirements where data are obtained from a third party if this would involve disproportionate effort.[151] The research exemptions also permit derogation from the right to erasure and notification,[152] with more exemptions from data subject rights available at Member State level through national level.[153]

In sum, there is considerable flexibility afforded to data processing for scientific research or statistical purposes under the GDPR, and in the case of special category data such as health information this may be the only appropriate condition for processing where explicit consent is not an option. The safeguards required of such processing are therefore very important, and pseudonymisation as a means of ensuring data minimisation is a prime example as the measure specifically mentioned in Article 89(1) GDPR.

Pseudonymisation is by no means the only way in which data minimisation can be achieved, however, and it is important that model developers also respect the requirement to use only the minimum data—only the necessary number of attributes, for example, and a sample size no larger than is necessary to develop, test and validate the model. Synthetic data could also be used, but as long as these data are not capable of attribution back to the real individuals from whom the data were derived, they would not be pseudonymised data and would fall outside the scope of the GDPR.

The advantage of a pseudonymisation model is that the data remain identifiable for the original data provider, who can maintain a relationship with the data subjects, ensure appropriate transparency is in place and be the main point of contact for individuals seeking to exercise their data subject rights. In such a situation, it is possible that the data provider and recipient may be joint data controllers, with their respective responsibilities for GDPR compliance apportioned in accordance with their ability to identify and contact data subjects. The next subsection provides more information on data controllers, joint or otherwise.

3.5 Data Control & Bases for Processing

The distinction between sole and joint data control is a key issue for data integration. When data are shared for modelling purposes, it will be important to identify which organisation(s) is taking decisions about the data in question, and in turn taking responsibility and liability for that further processing.

The Article 29 Working Party outlines what could be deemed a default position within integrated data:

> *'Another possible structure is the "origin-based approach", which arises when each controller is responsible for the data it introduces in the system. This is the case of some EU-wide*

[149] GDPR, Article 5.1.e

[150] GDPR, Article 5.1.b

[151] GDPR, Article 14.5.b

[152] GDPR, Articles 17 and 19

[153] The UK has made full use of the national derogations for research, meaning that almost all data subject rights can be deviated from in the context of research if their application would render impossible or seriously impair the research or statistical purposes.

databases, where control - and thus the obligation to act on requests for access and rectification - is attributed on the basis of the national origin of personal data.'[154]

This 'origin-based' approach may not apply under all data sharing models, however; for example, the DIabetes REsearCh on patient stratification ('DIRECT') consortium, an Innovative Medicines Initiative, public-private consortium of organisations in EEA countries to support a personalised medicine for type II diabetes.

The project collected data from a number of EU Member States. Participants visited clinical study centres, donated samples which were genetically sequenced and provided phenotypic data through blood and urine tests. Pseudonymised data, identified by study number but omitting direct identifiers, were uploaded by the study centres to a private server operated by the Technical University of Denmark, based in Copenhagen. Participants gave a broad consent for their data to be used for research into diabetes and related conditions. Access to these data was then approved by a 3-tiered data access committee, drawn from a number of consortium members.[155]

The Data Access Committee represents an alternative to the origin-based approach. Under this model, whatever the origin of the data, the majority of members of the consortium have the capacity to determine the manner and purposes of processing. This points towards a more even distribution of data control than the "origin-based approach" would allow.

The organizations represented on such a committee would therefore be acting as data controllers, as they are determining the manner and purposes of processing. This potentially creates difficulties where these organisations are subject to their own national laws. The simultaneous application of the national law of each data controller causes inconsistencies.[156] In such cases. The clashing requirements of different GDPR implementations (e.g. different recommended bases for processing or research exemptions) could become difficult to navigate.

[154] Article 29 Working Party, 'Opinion 1/2010 on the concepts of "controller" and "processor"', WP 169, p.21, available at:< https://ec.europa.eu/justice/article-29/documentation/opinion-recommendation/files/2010/wp169_en.pdf> accessed 29 January 2020

[155] Harriet Teare, et al., 'The governance structure for data access in the DIRECT consortium: an innovative medicines initiative (IMI) project' (2018) 14 Life Sciences, Society and Policy 20.

[156] Most national data protection laws apply to the activities of controllers established in their territory (such as making decisions about access to data) regardless as to whether the processing itself takes place within the country, see e.g. Data Protection Act s.207. This could lead to multiple applications of national laws in an international joint data control scenario.

The following table gives an illustration of the kinds of national discrepancies in the implementation of the GDPR at national level:

Country	Basis/ Condition for Research Processing
United Kingdom	Researchers are encouraged **not** to rely on consent as a basis for processing data in health and social care research.[157] Special category data may be processed under Article 9(1)(j) as long as substantial damage or distress is not caused to the subjects, and no decisions/ measures are made affecting them.[158]
Denmark	The Article 6(1)(e) public interest basis is used for research,[159] but scientific and statistical studies require '*significant importance to society'* to process special category data under Article 9(1)(j)[160]
Germany (Federal level)	Special category data **may** be used without consent under Article 9(1)(j), but only '*if such processing is necessary for these purposes and the interests of the controller in processing* ***substantially outweigh*** *those of the data subject in not processing the data'*[161] (emphasis added)
Lithuania	Informed consent is one of the bases for processing data for research purposes. Special category data **may** be used for research purposes without consent under Article 9(1)(j) in accordance with Article 89(1).

In terms of processing special category (e.g. health-related or genetic) data for research and statistical studies under Article 9(1)(j), this table illustrates how the UK has set the lowest bar in requiring only that the safeguards of no distress or resulting decisions about subjects arise out of the processing. Denmark requires significant importance to society, and Germany the substantial outweighing of the subjects' interests. It is easy to envisage how this could pose difficulty in terms of data integration: data processed without consent under Article 9(1)(j) in the UK may not meet the statutory balancing act of interests required in Germany, for example. The European Data Protection Supervisor has recently set standards for the application of Article 9(j) GDPR to scientific research:[162] widespread adoption of these standards could help to lessen the risk of national variation creating obstacles to data integration. However, the EDPS also refer to some enduring ambiguity as to what constitutes 'scientific research'[163] (despite the broad approach apparently taken by the GDPR) which represents a persisting element of uncertainty.

National variation in data protection standards is perhaps a longstanding issue,[164] but it is evidently one that survives the implementation of the GDPR. As data integration almost inevitably involves data

[157] NHS Health Research Authority, 'Consent in Research' 19 April 2018, < https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/what-law-says/consent-research/> accessed 27 November 2019.

[158] Data Protection Act 2018, s.19

[159] CESSDA, note 21

[160] Data Protection Act No. 502 of 23 May 2018, s.10(1)

[161] Federal Data Protection Act: Act to Adapt Data Protection Law to Regulation (EU) 2016/679 and to Implement Directive (EU) 2016/680, s.27(1)

[162] European Data Protection Supervisor, note 78, p. 12

[163] Ibid, p.23.

[164] See Susan E. Wallace and Bartha M. Knoppers, note 117

sharing in one form or another, consideration as to whether a recipient, an intermediary or an approver obtains or shares data controller responsibility is an important part of any standards. Joint data control should be unambiguously identified, with guidance given as to how such joint controllers can make transparent arrangements for their respective responsibilities under the GDPR.[165] In circumstances of international data control, the additional complexity of simultaneous application of different versions of the GDPR needs to be considered—a level of complexity which may in fact justify reversion to the origin-based approach, where each contributing country controls the portion of the data it contributed.

3.6 Data Controllers vs Processors

An additional important distinction is whether the relationship created by a transfer of data is controller-controller, or whether it is genuinely a controller-processor relationship. The terms of a controller-processor relationship must be set out in a binding written contract, with certain instructions included in the contract.[166] However, it is important to note that a transfer under a controller-processor agreement will only be appropriate in the limited circumstances where a processor is providing a service to the controller, and will only process the data in accordance with written outcome. In such circumstances, the processor should not have any interest in the outcome of the processing beyond the delivery of services they are expected to provide. In other words, they should not be processing the data for their own purposes, or even be helping to determine the purposes for which, or manner in which, the data are used.

An illustration of the importance of correctly characterising the relationship surrounding a data transfer in the context of in silico modelling for healthcare is the five-year partnership between Google's DeepMind Health company and the Royal Free NHS Trust in the UK. DeepMind health transferred the identifiable patient records of 1.6 million individuals (a number which the supervisory authority found to be disproportionate to the stated aim, thus breaching the data minimisation principle[167]). Although this transfer was executed on the basis of a controller-processor relationship whereby Google DeepMind was simply providing a service to develop software to identify risk of acute kidney injury, academic scrutiny of the terms of the collaboration suggest this was not reflective of DeepMind's role in actively shaping the programme of development.[168]

Where the development of in silico models involves actors outside the healthcare sector, in particular commercial organisations, it is important that the relationship between the data providers and the model developers is accurately characterised. This is necessary for GDPR compliance, as it will determine the appropriate type of contract, but it is also important for the sake of transparency with data subjects, particularly patients, that the parties are frank and open about the nature of their relationship, and the benefits they will respectively receive from the processing of the data. If the commercial sector is to profit from the use of patient data— to develop proprietary models, for example— there is evidence

[165] GDPR, Article 26

[166] GDPR, Article 28

[167] Letter from Elizabeth Denham DBE to Sir David Sloman, 3 July 2017, available at: <https://ico.org.uk/media/action-weve-taken/undertakings/2014353/undertaking-cover-letter-revised-04072017-to-first-person.pdf> accessed 29 January 2020

[168] Julia Powles and Hal Hodson, 'Google DeepMind and healthcare in an age of algorithms' (2017) 7(4) Health and Technology 351–367.

that the public would expect an equitable distribution of the benefits, such as affordable health service access to the models.[169] This may be more of an ethical consideration than a strictly legal one, but it is nonetheless an important factor to maintain public trust in data sharing for in silico modelling.

3.7 Presumption of Compatibility

The question as to whether the 'presumption of compatibility' eliminates the need for consent, or indeed any other legal basis, in research is considered in section 2.4.4. This is a question which is worth considering in its own right, however, and in particular whether focusing purely on the 'legal basis' aspect of the first principle presents too narrow a view of its requirements, and neglects the broader requirements of lawfulness and transparency.

Although the EDPB has refused to rule out compatibility as a substitute for a legal basis, it has not gone so far as to endorse the approach either, or explore all the potential implications of the question. As no-one seems to contend that it is possible to process special category data without an Article 9 condition in place, it is difficult to see how requiring an Article 6 basis (often an easier criterion to satisfy) represents an additional burden on data controllers.

Furthermore, it must be remembered that even if research and statistical purposes are automatically considered to be compatible purposes, this only satisfies the second data protection principle and *one aspect* of the first. Article 5(1)(a) GDPR requires that personal data be:

> *Processed lawfully, fairly and in a transparent manner in relation to the data subject ('lawfulness, fairness and transparency')*

While the 'lawfulness' element relates partly to the lawful basis requirement in Article 6, it would also relate to the duty to comply with other laws, such as the duty to respect reasonable expectations of privacy and confidentiality. Similarly, the rest of the principle includes fairness and transparency, which would also connect to what subjects would reasonably expect in the use of their data (explored in the next section). Consequently, even if the EDPB is correct and the presumption of compatibility could override the need for a lawful basis, the use of the data must still be transparent, and correspond with what data subjects have been led to expect would happen to their information. The requirement to be fair and transparent with data subjects still applies in research and statistical use, if even such purposes are otherwise deemed 'compatible,' so if the research use was vastly different from the processing subjects would reasonably expect, there would still be a question mark as to whether the processing was lawful.

3.8 Transparency

As noted above, the GDPR requires concise and easily accessible information[170] be provided to data subjects about how their data will be used and (if applicable) shared, and the rights they have in relation to their personal data. This information should be provided when the information is collected from the

[169] Victoria Chico, Amanda Hunn and Mark Taylor, 'Public views on sharing anonymised patient-level data where there is a mixed public and private benefit' (2019, Health Research Authority & University of Sheffield School of Law) available at < https://www.hra.nhs.uk/about-us/news-updates/sharing-anonymised-patient-level-data-where-there-mixed-public-and-private-benefit-new-report/> accessed 29 January 2020

[170] GDPR, Article 12.

data subject,[171] or when obtained from a third party.[172] People should also be informed if they will be subject to significant decisions based solely on automated processing (of which, more in Section 6). There is, however, an exception when information are obtained from a third party, and it would be impossible or involve disproportionate effort to contact the data subjects, particularly in the case of further uses for research.[173] This is a key exception for data recipients, particularly where for data minimisation purposes they have not been provided with sufficient information to contact the subjects (as outlined above, additional information should not be shared or retained purely for the purposes of compliance with the Regulation[174]).

However, the original data collector will retain an ongoing duty of transparency under Article 13 GDPR, and should update the data subject if their information will be used for a purpose other than that for which it was originally obtained.[175] They will have a duty to inform subjects who were not already aware that their information would be used for statistical modelling purposes, therefore, even if the model developer (if a different entity) does not necessarily have to contact subjects. This is logical, as if the new recipient had to contact people as well, this would require all data to be shared with contact information, and involve a much greater interference with data subject privacy (essentially rendering pseudonymisation impossible as the recipient would need to receive direct identifiers).

Even if it is possible for in silico models to be developed using anonymised or synthetic data, if such data are derived from personal data the subjects of these data should still be informed. Although the ultimate anonymous or synthetic data would be outside the scope of the GDPR, the processing of personal data to develop anonymous/synthetic information would still be ultimately for a research/statistical purpose, thus triggering the notification requirements. It has also been recommended in a US context that patients should be notified that their healthcare data may be used in deidentified form in predictive analytics models, although in this case because of the persistent (if small) risk of reidentification.[176]

In summary, it is important that a balance be struck between data minimisation and the retention of sufficient information to contact data subjects for transparency purposes. In the case of health-related in silico models, it is fortunate that the initial collectors of information are likely to be bodies who will be required to retain records, such as healthcare providers or clinical trial sponsors. As such, these bodies are likely to have a key responsibility for ensuring transparency in the further processing of data for in silico modelling.

3.9 Publicly Available Data

The suitability of consent as a basis for processing data under the GDPR has been explored in a dedicated section of this report. As outlined in that section, GDPR consent can only be relied upon where the consent is revocable.[177] This is clearly not the case where data have been made publicly available by the

[171] GDPR, Article 13.

[172] GDPR, Article 14.

[173] GDPR, Article 14(5).

[174] GDPR, Article 11.

[175] GDPR, Article 13(3).

[176] I. Glenn Cohen, et al., note 3.

[177] GDPR, Article 7.

data subject, who would be unable to contact all users of their information to ask them to delete it. Neither would there be the data minimisation safeguards necessary for the data to be processed on the basis of scientific research, archival or statistical purposes.[178] The only remaining option is likely to be that any special category (health-related or genetic) information has been manifestly made public by the data subject.[179]

An example of this sort of open data, which may be an additional source of data for in silico modelling, are open access genetic registries. The 'openSNP' websites, for example, offers users of 23andMe, deCODEme or FamilyTreeDNA the opportunity to upload their data on a completely open basis, subject to a very explicit disclaimer about the potential, uncertain consequences for themselves and their genetic relatives.[180] While clearly informal in tone, the degree of candour in the openSNP disclaimer is instructive in its effectiveness in alerting data subjects to the uncertain implications of their decision to share their data.

The idea of 'manifest' publicity is not necessarily straightforward. The GDPR appears to rely on the idea of an indisputably public sphere, but this may be more complex in practice as many privacy scholars have contended that was is considered 'public' is more contextual than absolute. Helen Nissenbaum in particular has argued that privacy is as much a matter of contextual integrity as it is a single, simple division between public and private spaces.[181] Just because someone has posted their information on social media, for example, does not mean that they would reasonably expect such information to be used by their doctor, for example, to follow their lifestyle or check for health-related information. A grey area emerges in the case of research or other public authorities who may use publicly available data (but for which the intended audience/ context was primarily social) for the fulfilment of their functions. The European Medicines Agency, for example, is considering the use of social media data for pharmacovigilance without a clear indication as to what notice, or potential for opt-outs, they would offer citizens in such circumstances. The Big Data taskforce report commits to supporting the development of guidance on the ethical and legal implications of using social media data,[182] but as yet the degree of notification social media users would receive is unclear.

The legal test for rights of privacy and confidentiality are both connected to the test of reasonable expectations, having regard to 'all the circumstances.' These circumstances, I would suggest, encompass the facts of the case, and the particular information the data subject was given, but also the broader societal norms which Nissenbaum highlights as governing data use, as the context which gives meaning to these specific details. Furthermore, some have argued that compliance with these rights, where private information is used, is not only contingent upon accordance with reasonable expectations, but

[178] GDPR, Article 9(2)(j).

[179] GDPR, Article 9(2)(e).

[180] openSNP disclaimer, <https://opensnp.org/disclaimer> accessed 29 January 2020, example: '*Medical and genetic data can be used to discriminate against people. Due to medical or genetic information, an employer may not give you a job, an insurance company may request higher payments, and who knows what any evil™ government will do with your data? Although some countries have laws against genetic discrimination, these laws certainly will not cover all possible discrimination scenarios and could change in the future. Again: these are side effects and risks which also can apply to your kinship if you chose to upload this information*.'

[181] Helen Nissenbaum, 'Privacy as Contextual Integrity' (2004) 79 Washington Law Review 119-157.

[182] Heads of Medicines Agency and European Medicines Agency, <https://www.ema.europa.eu/en/documents/minutes/hma/ema-joint-task-force-big-data-summary-report_en.pdf> accessed 29 January 2020

also on reasonable notice and the option to opt out.[183] However, it is highly unlikely that the option to opt out is being offered to everyone whose open-access data is used in research.

Article 14 of the GDPR has some role to play in this context, stating as it does that transparent information should be provided to the data subject when personal data are not collected from them directly, but via a third party (in this case a public platform). Reasonable expectations play a role in the application of Article 14, as the Article 29 Working Party advises:

> '*the requirements of fairness and accountability under the GDPR require data controllers to always consider the reasonable expectations of data subjects, the effect that the processing may have on them and their ability to exercise their rights in relation to that processing, when deciding at what point to provide the Article 14 information*.'[184]

There is therefore, potentially, a helpful alignment between the circumstances in which data are deemed to be private, and the test for judging the time-frame in which they can expect the notification (and thus opportunity for objection) that enables respect for their right to privacy under Article 8 European Convention on Human Rights (ECHR), as well as compliance with the GDPR. However, Article 14 notification is not guaranteed in the context of scientific research, as a controller may opt out of this where such notification would require a 'disproportionate effort' and Article 89 safeguards are in place.[185] This could potentially present a difficulty where private information is used, but the Article 14 research exemption is relied upon, as a GDPR exemption is ineffective against a claim of infringement of privacy, which is a distinct cause of action.[186] This would justify some caution in relying on the research exemption to Article 14 where private information is used, particularly by a public authority. Consideration should be given to the necessary notice required to satisfy Article 8 ECHR, as well as the GDPR.

The UK National Data Guardian for Health and Social Care[187] has pledged to look further into the navigation of reasonable expectations as a basis for disclosure for direct care, but has also expressed an interest in progressing the concept as an important aspect to shape the boundaries of information sharing.[188] In the context of precision medicine modelling, investigations of reasonable expectations should go beyond direct care, as the expectations of subjects will be relevant to the use of their information to develop in silico models.

3.10 International Transfers

Although the focus in this report is on EU standards, we acknowledge that there may be instances where it is desirable to share personal data from the EU with an organisation in a third country for modelling purposes. This is not a major focus of this report, but it is worth noting that where the European

[183] Mark J Taylor and James Wilson, 'Reasonable Expectations of Privacy and Disclosure of Health Data' (2019) 27(3) Medical Law Review 432-460.

[184] Article 29 Working Party, 'Guidelines on transparency under Regulation 2016/679' WP 260, p. 15.

[185] Article 14 (5)(b). The disproportionate effort would at least have to 'seriously impair' the research, or render it impossible, for this exemption to apply.

[186] Miranda Mourby, et al, note 105.

[187] A role which was afforded statutory recognition under Data Protection Act 2018.

[188] National Data Guardian, *National Data Guardian for Health and Social Care: a consultation about priorities*, 18 February 2019.

Commission has not decided that a third country offers a sufficient level of protection,[189] Article 46 GDPR offers a discrete set of options for lawful transfer, which may well be a standard contractual clause in practice. Article 49 GDPR makes it clear that derogations, such as consent, should only be used as a basis for transfer '*in the absence of*' a safeguard such as a standard contractual clause, so it is clear that such safeguards are preferable to any such exception.

As Standard Contractual Clauses have to be adopted in their entirety within contracts, they can justifiably be criticized as inflexible means of authorizing a transfer. However, they remain a strong option for personal data transfers between organisations, unless and until a code of conduct for health data is approved under Article 40 GDPR.[190]

3.11 Conclusion

In conclusion, even after eighteen months of the GDPR's application throughout the EU, uncertainties such as the scope of personal data will subsist until guidance from the Court of Justice of the European Union, European Data Protection Board and national supervisory authorities is forthcoming.[191] The CJEU's recent move to begin considering cases referred under the preceding Directive under the GDPR as well is a promising move, and hopefully more GDPR guidance will be forthcoming. In the interim, however, we can only highlight uncertainty, and suggest practical measures to address it—such as relying on stricter standards of anonymisation by default, even if this renders patient record data incapable of anonymisation for further use. Cultivation of synthetic data, and pseudonymisation across organisations, are other ways of re-using data with minimised privacy impact.

Despite the GDPR's stated aim of facilitating the free movement of personal data within the Union, in reality this movement cannot be seamless as there are national variations, particularly as regards research and statistical modelling. Key potential discrepancies for our current purposes are:

(1) Some Member States may not apply the GDPR in a healthcare context, which could create difficulties if personal data are then re-used for research and have to be brought into GDPR compliance;
(2) The circumstances in which special category data can be processed for research under Article 9(1)(j) vary between Member States;
(3) National derogations from data subject rights for scientific research & statistical purposes may differ between Member States. For example, one may pass research exemptions from the rights to subject access, rectification, erasure and/ or objection, and another does not.

These discrepancies are potential impediments to complete data integration. If an integrated dataset is jointly controlled by a number of organisations established in different member states, the relevant data could therefore be simultaneously subject to the various versions of the GDPR which apply in each respective organisation's territory. This could lead to situations in which, for example, a research

[189] GDPR, Article 45.

[190] Mark Phillips, 'International data-sharing norms: from the OECD to the General Data Protection Regulation (GDPR)' (2018) 137(8) Human Genetics 575–582.

[191] In the case of the European Data Protection Board, it appears that updated guidance on anonymisation is unlikely in the foreseeable future, see Lilly Taranto and Paula Garcia, 'Medical Research Council Advises on How to Anonymise Information for Research Purposes' available at: <https://www.hldataprotection.com/2019/10/articles/international-eu-privacy/medical-research-council-advises-on-how-to-anonymise-information-for-research-purposes/> accessed 27 November 2019.

exemption from a data subject right exists for one controller but not for another, undermining the concept that the manner of data processing can be truly determined jointly.

In cases of international data integration, therefore, the Article 29 Working Party's original recommendation of an origin-based approach may still be the best approach under the GDPR, as the Regulation has direct, but not identical, effect in different Member States. Alternatively, the data could be transferred to the control of a new, single controller, but if this meant any change in basis for processing, or applicable data subject rights, with the change in applicable law data subjects will have to be made aware of this.

Transparency has been identified as a key aspect of both GDPR compliance and management of reasonable expectations of privacy, the latter being highly contextual. The original organisation which collects the personal data is likely to retain an ongoing duty of transparency as to the re-use of data, which means that further users do not necessarily need additional information about data subjects in order to contact them. Collection of data from the data subject could also include data made public by the data subject, and so novel sources of health-related information—such as social media—should not be used casually without appropriate notification. Transparency and the right to information will be considered beyond the context of the GDPR within the next section.

4. Patients' rights: legal, ethical and policy considerations of in silico modelling

In this section, international and European treaties, case law and recommendations concerning rights to information, confidentiality and equal access to healthcare are identified. A legal analysis of the scope of patients' rights is carried out to assess how the development and application of in silico models may impact such rights. Legal and ethical issues surrounding children and persons with cognitive impairments are also discussed, as special legal protections apply. The binding and non-binding standards discussed in this section are phrased broadly and subject to national implementation. It is not feasible to comprehensively assess each Member State's implementation but examples from national laws are included, where appropriate. Non-binding guidelines from professional bodies are also discussed, as although not legally binding, professionals may be required to follow them.

4.1 Informed Consent and the Right to Information

As introduced in section 2.2 informed consent is an important legal principle in patients' rights regulation. Whereas consent is discussed in section 2, we will explore the right to information in this section.

In silico models may have implications for the right to information at the time of consent/ re-consent, during data processing (for example, where models generate (secondary) findings) and in their application (if in silico modelling is used to determine treatment decisions - to what extent do patients have a right of explanation). Council of Europe conventions and recommendations protect information as a right that encompasses *patient access* to health information, information on *secondary use* of patient data for research, and access to results and findings concerning health generated from research. The GDPR ensures information standards and introduces a limited right to explanation. The scope of the

right to information varies however, as exemplified by the ongoing discussion concerning rights and obligations for secondary findings.

The Biomedicine Convention asserts that patients have a right to know what information is collected on their health and the possibility of future use of their data.[192] Soft law standards recommend that patients should be informed if their records or samples may be re-used for research.[193] Prior to consenting to the storage of biological materials for future research, persons should be given "comprehensible information", including on the nature of any envisaged research use, the conditions applicable to storage and other relevant conditions, such as re-contact and feedback.[194] All information should be given in a manner appropriate to the patient's capacity for understanding.[195] Thus, when data is being gathered, patients should be informed that their information may later be used in the development of in silico models, for example. The rights of patients to receive information is however not absolute; it can be limited in exceptional cases, *inter alia*, to protect the patient[196] and the rights of others.[197] Further, the extent to which the right to information is feasible in the context of big data, where a greater volume of data is collected that ever before, may be questioned. For example, in some cases, it is difficult even for the developer to explain how an algorithm generated a decision.[198]

Elements of the right to information are operationalised by the General Data Protection Regulation, provided the data have not been anonymised. As a starting point, information must be provided when data is collected from the data subject[199], or from a third party[200] (see the 'transparency' section 3.8, above). This information should cover how the data will be used, including if there is any automated processing which *solely* supports legal or otherwise significant effects. Controllers should also inform subjects about their rights under the GDPR, and provide contact details in case they wish to enforce them. The transparency requirements are thus a gateway to subjects' understanding that their personal information is being used, and what rights of control they have over it. As noted earlier, this is a sufficiently important gateway to all other GDPR rights that the Polish supervisory authority has imposed a fine for failing to contact subjects of public information, even though millions of individuals were concerned.[201] This case has cast doubt as to when it constitutes a 'disproportionate effort' to contact individuals, although it has been suggested that it constitutes a 'radical' interpretation of Article 14 GDPR.[202]

[192] Biomedicine Convention, Articles 10.1, 10.2.

[193] CIOMS, Commentary on Guideline 4.

[194] Recommendation CM/Rec (2016)6, note 69, article 10.1.

[195] Patient Rights Declaration, paragraphs 2.4, 2.5.

[196] Biomedicine Convention, Article 10.3; Genetic Testing Protocol, Article 16.

[197] Biomedicine Convention, Article 26.

[198] I Glenn Cohen, Harry S Graver, Cops, Docs and Code: A Dialogue between Big Data in Health Care and Predictive Policing (2017) 51 University of California, Davis 437, at 439.

[199] GDPR, Article 13

[200] GDPR, Article 14

[201] Note 15.

[202] Natasha Lomas, 'Covert data-scraping on watch as EU DPA lays down 'radical' GDPR red line' 30 March 2019 <https://techcrunch.com/2019/03/30/covert-data-scraping-on-watch-as-eu-dpa-lays-down-radical-gdpr-red-line/?guccounter=1&guce_referrer_us=aHR0cHM6Ly9pYXBwLm9yZy9uZXdzL2EvcG9sYW5kcy1kcGEtaXNzdWVzLWZpcnN0LWdkcHItZmluZS8&guce_referrer_cs=soTyKV8Zyp_u5K1JoQrbsQ> accessed 29 January 2020

Assuming the data subject has received this initial information, and is therefore aware of who controls their data and how to contact them, they are entitled to request more information about the use of their personal data under Article 15 GDPR. While many Member States have passed research and statistical exemptions from Article 15,[203] these exemptions should only prevent the provision of information if compliance with this right would render impossible or seriously impair research.[204] This severely restricts the scope of the exception, and makes compliance with the right of access (and information) a default, even in the context of research. This includes a further right to an explanation of significant decisions based solely on automated processing under Article 15(1)(h), which mirrors Articles 13 and 14 in requiring '*meaningful information about the logic involved*' in the processing, as well as its potential consequences for the subject

This is one of many reasons why in silico models in personalised medicine will have to be *explainable*. This is potentially of less relevance at the research stage, as models still in development should not be used to make decisions about people before they have been tested and validated. Once implemented, however, it is essential that no decisions about patients are made 'solely' on the basis of these models, unless this has been authorised under Member State law (or, very exceptionally, the patient has explicitly consented to this form of automated decision-making).[205] If the patient *does* consent to this automated decision-making, they will then be entitled to receive information about the logic of the decision-making under Articles 13, 14 or 15, and to contest the decision or obtain human intervention.[206]

The fact that the 'right to an explanation' of automated processing only arises if decisions are based '*solely*' on automated processing severely limits the scope of the right.[207] It is perhaps better understood as a safeguard, rather than a general right, engaged only in the exceptional circumstances where people *are* subjected to decisions based solely automated processing.[208] However, the default need for human intervention means that the logic of the model must at least be explainable to the clinician using (but not solely relying upon) it. Doctors should be able to override the recommendation of a model, on the basis of factors it has not taken into account,[209] but to do so they must understand what factors the model has weighed in the first place. Therefore, even if the patient does not have a direct right to an explanation, if the decision is not based 'solely' on the algorithm, the intervening clinician will retain their medical duty to make them aware of material risks and benefits in obtaining consent to treatment,[210] which may in turn require explanation of the model where it is relied upon (in part) for their advice.

[203] For example, the UK, Denmark and Germany.

[204] Per the wording of the derogation in GDPR, Article 89(2).

[205] GDPR, Article 22(2).

[206] GDPR, Article 22(3).

[207] Sandra Wachter, Brent Mittelstadt and Luciano Floridi, 'Why a Right to Explanation of Automated Decision-Making Does Not Exist in the General Data Protection Regulation' (2017) 7 International Data Privacy Law 2.

[208] This may take place, exceptionally, where necessary for a contract with the data subject, where authorised by Member State law, or where the data subject explicitly consent to the automated decision-making, GDPR, Article 22(2). However, if special categories of data are used, explicit consent or substantial public interest (as laid down by member state law) is required under Article 22(4), lessening the scope of the contractual basis. This should not include any decisions about children.

[209] I. Glenn Cohen, et al., note 3.

[210] For example, *Montgomery v Lanarkshire Health Board* [2015] UKSC 11.

4.1.1 Secondary Findings and Patients

In silico models have the potential to generate secondary findings that were not foreseen in the consent process.[211] Yet, the question of when and whether to inform patients of secondary findings is unresolved at international level. Council of Europe treaties recognise both a patient right to know and right not to know.[212] Neither right is absolute; the right not to know can be breached where compliance would constitute "a serious risk for the health of others".[213] Regional genetics bodies have issued differing recommendations, highlighting the lack of unanimity.

The European Society on Human Genetics (ESHG) recommends that if an incidental finding suggests "serious health problems" in either the person being genetically tested or close relatives, where treatment or prevention is possible, the healthcare professional should report the findings.[214] In the case of children, guidelines should be established to "balance the autonomy and interests of the child and the parental rights and needs (not) to receive information that may be in the interest of their (future) family".[215]

The American College of Medical Genetics and Genomics (ACMG) instead prescribes a "minimum list" of incidental findings that clinicians should report if identified, regardless of patient preference.[216] The following are prioritised: disorders for which preventative measures and or treatments are available and disorders which might be asymptomatic for long periods. However, this list is subject to criticism; it has been suggested that the list of genes is a only starting point for when recontact should take place.[217]

The ACMG relied upon clinicians and laboratory personnel's "fiduciary duty to prevent harm", which it was considered overrides autonomy.[218] In a subsequent statement however, the ACMG amended its guidance to recommend that individuals have the opportunity to opt out of information on secondary findings. Parents can also opt out of secondary findings.[219] The American Society of Human Genetics (ASHG) recommends that parents should be able to decline secondary findings, unless there is strong evidence that the finding has "urgent and serious implications" for the child's health or welfare, and

[211] Secondary findings are those that go beyond the scope of the original investigation. They are also known as unexpected or incidental findings.

[212] Article 10.2 of the Biomedicine Convention. Genetic Testing Protocol, Article 16. Recommendation CM/Rec (2019) 2 of the Committee of Ministers to member states on the protection of health related data (adopted by the Committee of Ministers on 27 March 2019), appendix to recommendation at 7.6.

[213] Ibid, para 11.7.

[214] 'Whole-genome sequencing in health care: Recommendations of the European Society of Human Genetics' (2013) 21 European Journal of Human Genetics 580–584, 583.

[215] Ibid, 583.

[216] RC Green, et al. 'ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing' (2013) 15(7) Genet Med 565–574. The recommendations do not apply to preconception or prenatal sequencing, new-born sequencing or sequencing of healthy children and adults (at 569).

[217] GP Jarvik, et al., 'Return of genomic results to research participants: the floor, the ceiling, and the choices in between' (2014) 94 Am J Hum Gene 818-26, 823.

[218] Ibid, 568

[219] ACMG Board of Directors, 'ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing' (2015) 17(1) Genetics in medicine 68-9.

effective action can be taken to mitigate the impact.[220] There is no European consensus on when secondary findings must be reported. Therefore, should in silico models be implemented in patient care, clinicians will need to consult domestic regulations. Where this question goes unanswered by domestic law, the clinician must balance the right to know with the right not to know.

4.1.2 Duty to re-contact

In 2019, the ESHG issued recommendations, finding that there is no established general legal duty to recontact patients should new health information come to light, such as new treatments or a reclassification of a variant in any international agreements or legal precedent. A decision to re-contact should be based on the best interests of the patient/ family and on previous agreements with the patient.[221] However, autonomy, beneficence and nonmaleficence are also pertinent.[222] The right not to know, adverse psychological consequences and privacy speak against unsolicited contact.[223] If the patient is deceased, it may also be morally advisable to warn family, should new information of relevance to their health be discovered.[224] An individualised approach to deciding when to return results has also been suggested, for example, reproductive information may be relevant for some patients but not others.[225] However, practical limitations must also be recognised, such as resource and time limitations, and lack of infrastructure.[226]

4.1.3 Secondary Findings and Research Subjects

In the research context, laws and policies on return of incidental findings vary, which can hamper international collaboration.[227] Research subjects also have a right to information, although some view this as more limited – given that the primary pursuit of research is scientific discovery – not treatment.[228]

According to the Additional Protocol concerning Biomedical Research, the *conclusions* of the research shall be made available to participants in reasonable time, on request.[229] Furthermore,

> *If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them. That shall be done within a*

[220] Jeffrey R. Botkin, et al., 'Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents' (2015) 97(2) The American Journal of Human Genetics' 6–21, 9.

[221] European Society of Human Genetics , 'Recontacting patients in clinical genetics services: recommendations of the European Society of Human Genetics' (2019) 27 European Journal of Human Genetics 169–182, 179.

[222] Ellen Otten, et al., 'Is there a duty to recontact in light of new genetic technologies? A systematic review of the literature' (2015) 17 Genetics in Medicine 668–678, 671.

[223] Noor A. A. Giesbertz, et al., 'A duty to recontact in genetics: context matters' (2019) 20 Nature Reviews Genetics 371–372.

[224] Ibid; Corette Ploem, et al., 'A Duty to Recontact in the Context of Genetics: Futuristic or Realistic?' (2018) 25(5) European Journal of Health Law 537-553.

[225] Colin Mitchell, et al, 'Exploring the potential duty of care in clinical genomics under UK law' (2017) 17 Medical Law International 3.

[226] Otten, note 223.

[227] Adrian Thorogood, Gratien Dalpe and Bartha Knoppers,. 'Return of individual genomic research results: are laws and policies keeping step?' (2019) 27 European Journal of Human Genetics 535–546.

[228] GP Jarvik, et al., note 218, 820.

[229] Additional Protocol concerning Biomedical Research, Article 28.2.

> *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.*[230]

While ratifying states are subject to the above provisions, non-binding standards, like CIOMS, advise a broader interpretation - that research participations be informed of 'any finding that relates to their particular health status' and that subjects have a right to access their data on demand.[231] This provision if understood broadly could prove unfeasible and extremely burdensome. In all cases, in light of the principle of transparency, clear policies should be in place on feedback concerning findings relevant to the health of research participants.[232]

In terms of *genetic research* findings, the ASHG strongly recommends that researchers attempt to re-contact participants if the reinterpretation is related to the phenotype under study or is reasonably expected to affect a research participant's medical management. If reinterpretation is not expected to affect management, ASHG advises re-contact for correction of the classification of the variant previously reported.[233] Any responsibility to re-contact is limited to the duration of research funding.[234] The ASHG has held that the obligation to re-contact research participants is stronger where research is ongoing and active, informed consent set an expectation for re-contact, the new interpretation has a high degree of certainty, the reinterpretation would be relevant to the condition under study or likely to change medical management.[235] Researchers do not have a responsibility to hunt genetic data or literature for changes in variant interpretation.[236]

In order to preserve autonomy, it has also been suggested that participants should have the option to refuse research genomic results, unless the study aims are related to the return of the data.[237] Parents should also have the right to refuse results unless they have "high health significance to the minor in childhood".[238] Jarvik et al differentiate between "known" incidental findings and findings where the variant is unknown to the family. In the latter case, the argument for informing is stronger and offers greater familial benefit.[239]

In conclusion, the international framework for patients' rights enshrines strong information rights, suggesting that patients should be informed about uses of their health data and subsequent findings, unless they explicitly decline. Furthermore, if models yield secondary findings, these should be transmitted if they have health implications, provided the patient has not expressed a desire not to know. Even in such a case, the patients' wishes may be overridden to advert serious harm to the individual or others. For research participants, their rights are more limited given the differing

[230] Ibid, Article 27.

[231] CIOMS, Guideline 5.

[232] Recommendation CM/Rec(2016)6, Article 17.1.

[233] 'ASHG Position Statement: The Responsibility to Recontact Research Participants after Reinterpretation of Genetic and Genomic Research Results' (2019) 104 The American Journal of Human Genetics 578–595, 584.

[234] Ibid, 585.

[235] Ibid, 583.

[236] Ibid, 585; also Jarvik GP, note 218, 823.

[237] Jarvik, ibid.

[238] Ibid.

[239] Ibid, 821.

obligations owed. However, there is a growing emphasis on re-contact, where there are serious health implications. Yet, it may be difficult to fully actualise the right to information where in silico modelling are developed on the basis of large data sets that are difficult to trace or anonymised. Finally, as the rights and recommendations are broadly phrased, their scope will be subject to domestic law. For example, Spanish law stipulates that researchers must overrule participants´ right not know to avoid serious harm to the participant or his relatives.[240]

The requirement to respect confidentiality is considered in the next section.

4.2 Confidentiality

The right to respect for private life is enshrined in numerous international treaties. This right furthermore includes a right to protection of personal data.[241] The European Court of Human Rights has held that "personal data protection plays a primordial role" in the exercise of the right to respect for private life protected by Article 8 ECHR.[242] While a state has a certain margin of appreciation in determining how to protect personal data, where a particularly important aspect of an individual's life is at issue, the margin is narrower.[243] Domestic law should enshrine safeguards and ensure that data are relevant, not excessive in relation to the purposes for which they are stored and preserved in a form that permits identification for no longer than required by the purpose.[244]

Confidentiality is a central aspect of private life in healthcare and research. It requires that personal and health information be protected from unjustified disclosure to third parties, such as companies or relatives. For example, the Council of Europe has drawn particular attention to insurance, holding that health related personal data should only be used for insurance purposes where, inter alia, the relevance of the data has been justified, the quality and validity of the data are in accordance with generally accepted scientific and clinical standards, processing is proportionate in relation to the nature and importance of the risk.[245] This means that, separate from GDPR, patients and research subjects may be owed a duty of confidentiality.

However, there are several limitations to confidentiality. Confidential information may therefore, for example, be disclosed where provided for by law, or where the patient consents.[246] The CIOMS guidelines recommend that prospective subjects be informed of the limits of investigators to ensure strict confidentiality.[247] Also of issue is where the data is stored – genomic data, for example, may be

[240] Thorogood, et al, note 228, 540.

[241] Biomedicine Convention, Article 10.1, 10.2; Additional Protocol concerning Biomedical Research, Article 25.2.See also, EUCFR, article 7; European Patient Rights Declaration, paragraph 1.4.

[242] European Court of Human Rights, Aycaguer v. France, (Application no. 8806/12), para 38.

[243] Ibid, para 37.

[244] Ibid, para 38.

[245] Recommendation CM/Rec(2016)8 of the Committee of Ministers to the member States on the processing of personal health-related data for insurance purposes, including data resulting from genetic tests (Adopted by the Committee of Ministers on 26 October 2016 at the 1269 meeting of the Ministers' Deputies), Article 5.

[246] Patient Rights Declaration, paragraph 4.2.

[247] CIOMS, Guideline 18.

included in electronic patient records when patient genomes are sequenced in connection with treatment, yet data held in medical records is easier for researchers to access than tissue samples.[248]

Another pertinent issue in relation to confidentiality is the rights of genetic relations, i.e. whether patient confidentiality can be set aside to inform relations contrary to the patient's wishes. Available recommendations vary but agree that it is for the national legislature to decide the boundaries of confidentiality. The Genetic Testing Protocol places the emphasis on the patient, stating that if results can be relevant to the health of other family members, the *patient* shall be informed.[249] The explanatory report advises that national law should provide appropriate provisions to ensure that family members can receive information which may be crucial for their future health, while at the same time respecting principles of confidentiality and privacy. If the tested person does not agree to contact family members, establishing a mediating or decision-making body could be considered.[250]

The Committee of Ministers has recommended that unexpected findings only be communicated if of "direct clinical importance to the person or the family". Communication to family members should only be authorised by national law if the person tested refuses expressly to inform even though the individual's life is in danger.[251] Despite the principle of professional secrecy, consideration should be given to informing family members about matters relevant to their health or that of their future children.[252]

Therefore, recommendations suggest that confidentiality should only be set aside where it can prevent serious harm or death. This is extended in Italian law, for example, which allows for disclosure to prevent health of family members "from being jeopardised".[253] Healthcare professionals may also be under legal obligations to assist persons whose lives are in danger, which could speak in favour of breaching confidentiality to save the lives of relatives.[254]

The scope of the clinician's duty of care towards relatives is currently being adjudicated in the UK. The UK Court of Appeal found in 2017 that it was 'arguable' that clinicians had a duty of care to return a finding of a Huntington's gene to their patient's daughter, based on her Article 8 right to a family life (given the implications this could have for her children).[255] At the time of writing, the case has been returned to trial,[256] and whether a duty of care is found on the part of medical professionals could also

[248] Jennifer Kulynych and Henry T Greely 'Clinical genomics, big data and electronic medical records: reconciling patient rights with research when privacy and science collide' (2017) Journal of Law and Bioscience 94-132.

[249] Genetic Testing Protocol, Article 18. As does Recommendation CM/Rec(2010)11 of the Committee of Ministers to member states on the impact of genetics on the organisation of health care services and training of health professionals, para IV.2.

[250] Explanatory report to the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes, CETS no. 203, Strasbourg, 27.XII.2008, paragraphs 139-141.

[251] Council of Europe, Committee of Ministers, Recommendation No. R (92) 3 on Genetic Testing and Screening for Health Care Purposes (Feb. 10, 1992), Principle 11.

[252] Ibid, Principle 9.

[253] Thorogood, et al, note 227

[254] Section 253 of the Danish Penal Code.

[255] ABC v St George's Healthcare NHS Trust and others [2017] EWCA Civ 336, [2017]

[256] Emma Wray, 'The scope of the Doctor's Duty of Care – ABC Revisited' 18 November 2019 <https://www.hja.net/the-scope-of-the-doctors-duty-of-care-abc-revisited/> accessed 29 January 2020

have implications for both clinicians and researchers.[257] In the absence of a clear statement of principle that this duty of care overrides the duty of confidence, however, it is difficult to demonstrate that a patient's reasonable expectations of privacy and confidentiality have been satisfied unless they consent to the sharing or return of findings. Unless these reasonable expectations of privacy and confidence are respected, there is a risk of unlawful use of data (and thus also a breach of the first principle of the GDPR), as well as a breach of the second principle of the GDPR, as a purpose not reasonably expected may not be a compatible use of data.[258]

In the US, ASHG guidelines on familial disclosure state that health care workers have a positive duty to inform patients about potential genetic risks to their relatives. If patients decline to inform their relatives, disclosure can be permitted where

> *the harm is likely to occur and is serious and foreseeable; where the at risk relative(s) is identifiable; and where the disease is preventable/ treatable or medically accepted standards indicate that early monitoring will reduce the risk.*[259]

Disclosure should not occur where the disease is neither treatable nor preventable.[260] Seriousness is not defined and should be interpreted on a case-by-case basis. The ASHG has also recommended the development of mechanisms for sharing family history and genetic results with family members.[261]

Generally, there is no duty on researchers to inform relatives of health information pertaining to them. For example, the CIOMS guidelines recommend that investigators should not disclose results of diagnostic genetic tests to relatives of subjects without the subjects' consent. The Committee of Ministers Recommendation on research on biological materials of human origin recognises that research may entail risks for the subject's family, which should be minimised and not be "disproportionate to the potential benefit of the research activities".[262] The recommendation considers the following as risks: misinterpretation of information, psychological distress, stigmatisation and use of unvalidated research.[263]

A further question is whether confidentiality continues to apply after death. The GDPR, for example, does not apply to personal data belonging to the dead, unless specified by member state law.[264] In contrast, according to the Patient's Declaration, confidentiality should apply after death, although confidentiality may be overruled subject to the exceptions listed above.[265] Removing biological material from a corpse is however, unlikely to fall within the provisions of Article 8 ECHR. In *Mortensen v.*

[257] Colin Mitchell, Corrette Ploem, Victoria Chico et al, 'Exploring the potential duty of care in clinical genomics under UK law' (2017) 17 Medical Law International 3

[258] GDPR, Recital 50

[259] The American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure, 'ASHG Statement: Professional Disclosure of Familial Genetic Information' (1998) 62 Am. J. Hum. Genet 474–483, 474.

[260] Ibid, 474.

[261] Botkin, note 221 , 16.

[262] Recommendation CM/Rec (2016)6, note 69, Article 4.2.

[263] Committee on Bioethics (DH-BIO) b. Recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin – Explanatory Memorandum, 1256 Meeting, 11 May 2016 4 Human rights, paragraph 22.

[264] Recital 27, GDPR. See further: https://www.twobirds.com/en/in-focus/general-data-protection-regulation/gdpr-tracker/deceased-persons accessed 29 January 2020

[265] Patient Rights Declaration, paragraph 4.1.

Denmark, the European Court of Human Rights refused to hold that the deceased's rights under Article 8 had been violated where he was already dead at the time of the alleged violation.[266] However, the Court has been willing to find that the removal of the deceased's organs without a relative's assent (where the relative was provided with a right to express their wishes by law) could result in a violation of relative's rights under Article 8.[267] Therefore, the rights of the dead in terms of data use and reuse will depend on national law.

The above discussion emphasises that while patients and research subjects are owed a duty of confidentiality, it can be set aside where the patient consents, or where provided for by law. In exceptional circumstances, dependent on national law, confidentiality can be breached in the interests of the patient or family. Such exceptions can have implications for patient autonomy, as well as willingness to take part in or consent to healthcare data being reused for research. We therefore recommend that any limitation son confidentiality be made clear to individuals at the outset, in line with the principle of transparency.

4.3 Right to Health & Discrimination/ Equity

In silico personalised medicine can have implications for equity and non-discrimination, should applications only be suitable for certain patient groups or lead to worse health outcomes for vulnerable groups, such as ethnic minorities, women and children. Big data may entrench discrimination due to limited available datasets on minorities who may, for example, leave less of a digital footprint.[268] Models may furthermore underestimate risks among underrepresented groups.[269] For example, in the US, an algorithm widely used to identify patients who would benefit from care programmes was found to exhibit racial bias.[270] Furthermore, big data research can have sensitive "biographical, cultural, ethnic and racial" implications for participants.[271] Algorithms can pose risks to equity due to biases in the algorithm or of their designers, including an absence of human checks or inadequate training of analysts. On the other hand, there is the potential to address existing inequalities, for example, use of electronic health records can combat biases already present in public health.[272]

Numerous international treaties proscribe discrimination in healthcare. The International Covenant on Economic Social and Cultural Rights (ICESCR) prohibits discrimination in access to healthcare on grounds of, *inter alia*, race, sex, physical or mental disability and health status.[273] Appropriate healthcare should

[266] *The Estate Of Kresten Filtenborg Mortensen v. Denmark* (Application no. 1338/03).

[267] *Petrova v. Latvia* (Application no. 4605/05)

[268] I Glenn Cohen, et al. Note 199, at 448.

[269] Kelly A McClellan, Denise Avard, Jacques Simard and Bartha M Knoppers, 'Personalised medicine and access to health care: potential for inequitable access?' (2013) 21(2) Eur J Hum Genet. 143–147.

[270] Ziad Obermeyer, et al., 'Dissecting racial bias in an algorithm used to manage the health of populations' (2019) SCIENCE 447-453.

[271] Effy Vayena and Alessandro Blasimme, 'Health Research with Big Data: Time for Systemic Oversight' (2018) 46 The Journal of Law, Medicine & Ethics 119–29, at 124.

[272] Hoffman, Sharona, and Andy Podgurski, 'Big Bad Data: Law, Public Health, and Biomedical Databases' (2013) 41(1)_suppl The Journal of Law, Medicine & Ethics 56–60, 56.

[273] Article 12 ICESCR; General Comment, para 18; See also, Patient Rights Declaration; Article 35, EUCFR.

also be "continuously available and accessible to all *equitably*, without discrimination" and according to resources.[274]

Special focus has been given to genetic discrimination. The Genetic Testing Protocol prohibits discrimination on grounds of genetic heritage and calls on states to take "appropriate measures" to prevent stigmatization based on genetic characteristics".[275] According to the CRPD Committee, protection against 'discrimination on all grounds' includes disability; health status; genetic or other predisposition towards illness.[276] The Committee calls on states to "prevent discriminatory denial of health care or health services" on the basis of disability.[277]

CoE Recommendation CM/Rec (2016)6 states that appropriate measures should be taken to prevent discrimination, and minimize stigmatization of any person, family or group.[278] Access to treatment must thereby be based on transparent criteria.[279] The CESCR Committee places emphasis on vulnerable or marginalised groups:

> *health facilities, goods and services must be accessible to all, especially the most vulnerable or marginalized sections of the population, in law and in fact, without discrimination on any of the prohibited grounds.*[280]

Similarly, the European Social Committee has highlighted that disadvantaged groups' access to health care should not be impeded.[281]

Equity in healthcare is also underscored. The Biomedicine Convention holds that states must take "appropriate measures" towards providing *equitable* access to healthcare.[282] The UNESCO Declaration on the Human Genome similarly states that benefits from advances concerning the human genome should be available to all.[283] The Committee of Ministers further recommends that "all policies need to be assessed and evaluated in terms of their impacts on social cohesion, social exclusion and health."[284] The health system should provide "equality of opportunity for people to enjoy the highest attainable level of health".[285] According to the CESCR Committee:

[274] Patient Rights Declaration, paragraph 5.1.

[275] Genetic Testing Protocol, Article 4. See also, Biomedicine Convention, Article 11.

[276] CRPD Committee, General comment No. 6 (2018) on equality and non-discrimination, para 21.

[277] UN General Assembly, Convention on the Rights of Persons with Disabilities, 13 December 2006, A/RES/61/106, Article 25(f).

[278] Recommendation (2016)6, Article 5.1.

[279] Council of Europe, European Social Charter (Revised), 3 May 1996, ETS 163, Article E.

[280] CRPD Committee, General comment No. 6, para 12(b)(i).

[281] See, for example, *Médecins du Monde - International v. France*, Collective Complaint No. 67/2011.

[282] Biomedicine Convention, Article 3.

[283] Universal Declaration on the Human Genome and Human Rights, Article 12.

[284] Appendix to Council of Europe, Committee of Ministers, Recommendation Rec(2001)12 of the Committee of Ministers to member states on the adaptation of health care services to the demand for health care and health care services of people in marginal situations (Adopted by the Committee of Ministers on 10 October 2001 at the 768th meeting of the Ministers' Deputies) , I.7.

[285] CESCR General Comment No. 14: The Right to the Highest Attainable Standard of Health (Art. 12) Adopted at the Twenty-second Session of the Committee on Economic, Social and Cultural Rights, on 11 August 2000 (Contained in Document E/C.12/2000/4) para 8.

> *investments should not disproportionately favour expensive curative health services which are often accessible only to a small, privileged fraction of the population, rather than primary and preventive health care benefiting a far larger part of the population.* [286]

In terms of research, the Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research emphasises that social risks, such as discrimination and stigmatization, must be taken into account when assessing research risks. Likewise, research should be sensitive to risks of stigmatising or exposing a group to discrimination.[287] Groups or communities must be invited to take part in research in a way that the burdens and benefits of the research will be equitably distributed.[288]

Furthermore, the right to "enjoy the benefits of scientific progress and its applications", as recognised under the ICESCR, has been interpreted to include:

- access to the benefits of science by everyone, without discrimination;
- opportunities for all to contribute to the scientific enterprise and freedom indispensable for scientific research;
- participation of individuals and communities in decision-making; and
- an enabling environment. [289]

All persons should thereby be able to benefit from and take part in scientific research, without discrimination. This right is however, not absolute and may be limited by, in so far as compatible with the nature of the rights in covenant, to promote the 'general welfare in a democratic society' (Art 4 ICESCR).

Participation is a fundamental principle of human rights that can combat discrimination and inequity. Citizens have, for example, the right to participate in the decision-making process affecting healthcare.[290] To facilitate participation, information should be widely disseminated, accessible, timely, easy to understand and relevant.[291] All relevant population groups should participate on an equal basis.[292] The Committee of Ministers therefore recommends that persons with disabilities are "as fully involved as possible in the decision-making process".[293] The Convention on the Rights of the Child

[286] Ibid, para 19

[287] CIOMS, Commentary on Guideline 8.

[288] CIOMS, Guideline 12.

[289] Report of the Special Rapporteur in the field of cultural rights, 'The right to enjoy the benefits of scientific progress and its applications' A/HRC/20/26, 14 May 2012, para 25.

[290] Council of Europe Committee Of Ministers, Recommendation No. R (2000) 5 of the Committee of Ministers to member states on the development of structures for citizen and patient participation in the decision-making process affecting health care (Adopted by the Committee of Ministers on 24 February 2000 at the 699 meeting of the Ministers' Deputies) Appendix to Recommendation No. R (2000) 5, Guidelines, I.1.

[291] Appendix to Recommendation No. R (2000) 5 Guidelines, II.16

[292] Appendix to Recommendation No. R (2000) 5 Guidelines, II.9.

[293] Council of Europe, Committee of Ministers, Recommendation Rec(2006)5 of the Committee of Ministers to member states on the Council of Europe Action Plan to promote the rights and full participation of people with disabilities in society: improving the quality of life of people with disabilities in Europe 2006-2015 (Adopted by the Committee of Ministers on 5 April 2006 at the 961st meeting of the Ministers' Deputies), 3.9.2(i).

recognises the right of the child (who is capable of doing so) to express views freely and for due weight to be given in accordance with the age and maturity of the child.[294]

The European Group on Ethics in Science and New Technologies (EGE) to the European Commission has also noted:

> *The potential for empowerment and enrichment will turn on the degree of voice or agency it accords, access to decision-making and goal setting; or the dividend reaped in terms of education and skills.*[295]

Freedom from discrimination and equity are enshrined in international conventions and recommendations. Therefore, health technologies should avoid discrimination and creating (or increasing) inequities in healthcare. Models should be mindful of the potential to entrench or widen disparities and exclude certain groups. Participation should be pursued as a means by which discrimination and inequity can be addressed. However, operationalising participation is not without challenges.

4.4 Vulnerable Groups

In silico modelling may have special implications for vulnerable groups, in particular, people with cognitive impairments and children. Furthermore, these groups raise distinct legal questions, in terms of consent and data use. In the case of persons with disabilities, international law now emphasise empowerment, in contrast to earlier, protective treaties. International instruments focused on children and persons with disabilities take a similar but distinct approach: for children participation increases as capacity develops, while adults should be supported in continuing to take part in decision-making.[296]

4.4.1 Rights of Persons with Disabilities

There are several protective limitations on participation of persons without legal competence to consent in research. However, these are increasingly challenged by the Convention on Rights of Persons with Disabilities, which prohibits discrimination on grounds of disability.

In contrast, under the Biomedicine convention, scientific research may only involve persons without capacity to consent if several conditions are met, including, the results of the research have the potential to produce "real and direct benefit" to the person's health, and research of comparable effectiveness cannot be carried out on individuals capable of giving consent.[297] Research on persons with mental or behavioural disorders should only be carried out where the research cannot be equally well carried out on persons who can consent and the purpose of the research is to obtain knowledge relevant to the particular health needs of persons with mental or behavioural disorders.[298]

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[294] N General Assembly, Convention on the Rights of the Child, 20 November 1989, United Nations, Treaty Series, vol. 1577, p. 3, Article 12.1.

[295] Opinion No. 29 of the European Group On Ethics in Science and New Technologies, The ethical implications of new health technologies and citizen participation (European Commission, Brussels, 13 October 2015), p. 62.

[296] Dalpe, Gratien, 'A Tale of Two Capacities: Including Children and Decisionally Vulnerable Adults in Biomedical Research' (2019) 10 Frontiers in genetics 1, 4.

[297] Biomedicine Convention, Article 17.1.

[298] CIOMS, guideline 15.

Exceptionally, research may be carried out if these conditions are *not* met, where the research only entails minimal risks and burden, and has the aim of significantly contributing to conferring benefit on the person or persons with the same condition or age category.[299] These conditions are subject to the proviso that the individual does not object.[300] The CIOMS guidelines stipulate that in such cases the risk from research should be no more likely and not greater than the risk attached to routine medical or psychological examination. Slight increases above such risks may be permitted where there is an overriding scientific or medical rationale and where approved by an ethics committee.[301]

The Biomedicine Convention endorses *substituted decision-making*, whereby the known, previously expressed or presumed wishes of the patient should be taken into account.[302] Similarly, the Genetic Testing Protocol holds that 'wishes relating to a genetic test expressed previously by an adult at a time where he or she had capacity to consent shall be taken into account.'[303] Patients must nevertheless be involved in the decision making to the 'fullest extent which capacity allows',[304] while the Biomedicine Convention states that the individual shall 'as far as possible take part'.[305] The UNESCO Declaration on the Human Genome and Human Rights states that where individuals cannot consent, consent should be guided by the persons' *best interests*.[306] Under the GDPR, processing of personal data of persons without capacity to consent can be authorised in necessary to "protect the vital interest of the data subject" or when in the context of scientific research.

Soft law recommendations seek to support autonomy. For example, Recommendation No. R (2019) 2 adds "if a legally incapacitated person is capable of understanding, he/ she should be informed before his/ her data are collected or processed".[307] Similarly, according to the Helsinki Declaration, persons without capacity, who are capable of giving assent, should be asked to do so. Dissent should be respected.[308] If the person gains or regains capacity to consent, reasonable efforts should be made to seek their consent for continued storage and research use of their biological materials.[309]

In contrast, the CRPD Committee calls on states not to permit substitute decision-makers to consent on behalf of persons with disabilities. Instead, health professionals should engage persons with disabilities through *supported decision-making*, and ensure that others do not have undue influence over their decisions.[310] Health decisions should only be taken where free and informed consent has been secured.[311]

[299] Biomedicine Convention, Article 17.2.

[300] Additional Protocol concerning Biomedical Research, Article 15.1.v.

[301] CIOMS, guideline 9.

[302] Patient Rights Declaration, paragraph 3.7. Biomedicine Convention, Article 9.

[303] Genetic Testing Protocol, Article 12.2.

[304] Patient Rights Declaration, paragraphs 3.5.

[305] Biomedicine Convention, Article 6.3.

[306] Universal Declaration on the Human Genome and Human Rights, Article 5(b).

[307] para 11.5.

[308] Helsinki Declaration, 29.

[309] Recommendation, article 12.5.

[310] Committee on the Rights of Persons with Disabilities, General comment No. 1 (2014) Article 12: Equal recognition before the law, para 41.

[311] General comment No. 1 (2014), para 42.

The human rights of persons with disabilities have thereby evolved from a protective to participatory approach. In this manner, patients with cognitive limitations should be supported in participating in treatment and research decisions to ensure compliance with the CRPD.

4.4.2 Rights of Children

In silico modelling may also have special implications for children's rights, including their rights to privacy and to the highest attainable standard of health.[312] Minors can be vulnerable as they often cannot consent to medical treatment or to take part in research and thereby depend on their parents to safeguard their interest. The Convention on the Rights of the Child (CRC) holds that the best interests of the child is a "a primary consideration" in all actions concerning them,[313] and shall prevail over the "interest of general society or scientific advancement".[314]

The age at which children can consent to treatment and research varies among member states. In some countries a set age is specified by law. Under Irish law, a person over the age of 16 years can give consent to surgical, medical or dental treatment and it is not necessary to obtain consent for it from his or her parent(s) or legal guardian(s).[315] In England, however, a child under 16 years can consent to treatment if the child fully understands the consequences of the treatment (mature minor rule).[316] Under Danish law, children can give consent aged 15 years but parents must be informed and involved until age 18.[317] Dutch law employs dual consent, whereby children aged 12-16 can co-consent with their parents.[318]

Regardless of legal competency, international law highlights child participation and assent - "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".[319] In the case of research on children, investigators must ensure that the research could not be carried out equally well with adults, that the assent of the child has been obtained to the extent of the child's capabilities and the child's refusal to take part is respected.[320] When the child reaches adulthood, a new consent should be obtained.[321]

According to the Genetic Testing Protocol, genetic testing on minors must be deferred until they gain capacity, unless the delay would be "detrimental to his or her health or well-being".[322] Generally speaking, screening for *late onset diseases* should be the exception – also when it takes place in the

[312] CRC, Articles 16, 24.

[313] Article 3 CRC. See also, EUCFR, article 24.2.

[314] Committee on the Rights of the Child, General comment No. 15 (2013) on the right of the child to the enjoyment of the highest attainable standard of health (art. 24), (17 April 2013), para 85.

[315] Section 23 of the Non-Fatal Offences against the Person Act 1997

[316] *Gillick v West Norfolk and Wisbeck Health Authority* 1986 3 All ER402.

[317] Sundhedsloven § 17.

[318] Dutch Medical Treatment Contract Act of 1995

[319] Genetic Testing Protocol, Article 12.1. Biomedicine Convention, Article 6.2.

[320] CIOMS, Guideline 14.

[321] CIOMS, guideline 17.

[322] Genetic Testing Protocol, Article 10.

context of scientific research.[323] The Council of Europe recommends that unless neonatal screening has direct health benefit to the child, it should be postponed until the child can decide.[324] Whole genome sequencing of foetuses may also raise rights issues, namely the privacy of the child after birth.[325]

The European Society of Human Genetics recommends that testing of persons without capacity to consent should be for their direct benefit. If the parents' decision is not to the direct benefit of the minor, however, healthcare professionals have 'the responsibility to defend the interests of the minor'. Presymptomatic and predictive testing for adult onset conditions should only be conducted if preventative actions can be initiated before adulthood. Otherwise, testing should be deferred. Carrier testing should be discouraged until the minor is able to consent out of respect for the child´s autonomy. Parents should have the opportunity to decide if they wish to be informed, should carrier status be incidentally discovered.[326] However, it has also been suggested that if a secondary finding is 'serious and treatable', disclosure could override parents´ refusal.[327] On the other end of the spectrum, overtreatment should also be avoided, meaning that findings where the clinical utility is unclear, should not be transmitted.[328]

In 2015, the American Society of Human Genetics (ASHG) recommended encouraging parents to defer testing for adult-onset conditions until adulthood or the child can participate. In high-risk families, testing could be justified to "alleviate substantial psychosocial distress" or facilitate specific life planning decisions, given that the impact on children is uncertain. Genetic testing for adult onset conditions can be justified in the research context because of societal importance and where risks are minimised, and parental consent and children's assent is provided.[329] The ASHG neither recommends nor discourages carrier testing in minors with family history given the lack of empirical evidence on psychosocial impacts. Parental consent and adolescent assent should be provided.[330]

4.4.3 Conclusion on Vulnerable Groups

The rights and interests of vulnerable adults and children must be safeguarded from abuse in treatment and research contexts. Vulnerable groups should not be automatically excluded from treatment or research based on cognitive limitations. Instead, all persons must be given necessary support to aid

[323] Explanatory Report to Convention on 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, ETS no. 164, Oviedo, 4.IV.1997, para 81.

[324] Council of Europe, Committee of Ministers, Recommendation No. R (94) 11 on Screening as a Tool of Preventive Medicine (Oct. 10, 1994), para 2.6.

[325] See also, Kavot Zillén, Jameson Garland and Santa Slokenberga (Commissioned by the Committee on Bioethics for the Council of Europe), *The Rights of Children in Biomedicine: Challenges posed by scientific advances and uncertainties* (11 January 2017), p. 35-6.

[326] 'Genetic testing in asymptomatic minors: recommendations of the European Society of Human

Genetics Recommendations of the European Society of Human Genetics' (2009) 17 European Journal of Human Genetics 720–721, 721.

[327] Gabrielle M Christenhusz, Koenraad Devriendt amd Kris Dierickx, 'To tell or not to tell? A systematic review of ethical reflections on incidental findings arising in genetics contexts' (2013) 21 European Journal of Human Genetics 248–255, 249.

[328] Ibid.

[329] Botkin, et al., note 220, 8.

[330] Ibid, 10.

decision-making. Failure to do so could limit the applicability of models to vulnerable patient groups and impede the development of new treatments for childhood diseases or Alzheimer's and dementia research. Furthermore, it must also be recognised that groups are not homogeneous and instead intersect, for example children may also have disabilities or impairments and thereby fall under both the CRC and CRPD.

4.5 Conclusion on Patients' Rights

We have described and assessed the European framework for protecting patient and research subjects' rights to information, confidentiality, and access to healthcare. However, the scope of these norms depend on national implementation, which can lead to divergences at Member State level. Again, we highlight the need for transparency so that patients and research subjects are informed as to how their data may be used, what results they can expect and under what circumstances confidentiality could be breached. Furthermore, we call for the developers of models to be mindful of the potential for discrimination or inequity due to data gaps. Finally, children and persons with cognitive disabilities should be supported in making informed decisions regarding treatment and research.

5. Conclusions

The goal of this report has been twofold: firstly, to provide a survey of the European data protection and clinical trials regulations, as well as legal and ethical regulation relevant for protection of equal access to health, and right to information and self-determination relevant for harmonization and integration of data in in-silico modelling. Secondly, an assessment of the challenges and opportunities these regulations provide for harmonization and integration of data for in-silico modelling. This work has helped Work Package 3 of EU-STANDS4PM to identify lines of future enquiry for 2020.

In section 2, consent is explored as understood under the GDPR, CTR and ethico-legal international norms. Under international law, consent is a fundamental norm of healthcare and research, but not absolute. National law can limit the requirement of consent, for example in emergencies. Research guidelines recognise that limitations can be placed on consent if specified by law, corresponding to an important public interest and consistent with international human rights law.

Although specific consent is favoured in the Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine, the CTR recognises broad consent to gathering data from clinical trials to be used in future research. Secondary use of biological and dry data should generally only be allowed when re-consent is given. However, in exceptional cases, such as where the person is uncontactable, secondary use of an identifiable material may be permitted.

We underscore that the GDPR understanding of consent differs from that found within the CTR, particularly with regards to the level of specificity required.

Consent will be complicated, however, when we come to consider use cases of in silico models within medical treatment, as the line between information and intervention will blur wherever information is used to support interventions. Where in silico models are used within medical support software, and qualify as medical devices, they may themselves be subject to clinical trials. Even when this is not the case, it is possible that in silico models may be used to supplement, or even 'personalise,' data from

clinical trials (extrapolating to different age groups, for example). There are thus numerous ways in which in silico models may interact with clinical trials' regulation, and these will be highlighted in our use cases.

Aspects of the GDPR with implications for integrating data for modelling purposes have been highlighted in section 3. These have offered a degree of flexibility, owing to exemptions for scientific research and statistical purposes. However, we have also shown in section 4 that in silico models may be used outside of a research context, and in the course of diagnosis or decisions about treatment. This engages a broad spectrum of patients' rights, including a different complexion of rights and obligations under the GDPR once the latitude for research is no longer extended.

We note the uncertainty surrounding whether the presumption of compatibility eliminates the need for another legal basis for research. We conclude that considerable uncertainty remains concerning GDPR. We therefore suggest relying on stricter standards of anonymisation by default, pseudonymisation and other ways of re-using data with minimised privacy impact, such as, for example, cultivation of synthetic data. We highlight however, that varying national implementations of GDPR, for example, in the basis or condition for processing research data poses difficulties for data controllers, and guidance must accommodate these divergences.

Section Four introduces patients' rights under international, Council of Europe and EU law, supplemented by non-binding recommendations. Although this framework provides for a detailed set of rights, it is subject to national implementation and variations. As rights are often framed broadly, there are likely to be distinctions at national level. Patients' rights to know what information is collected on their health and the possibility of future use of their data was explored. Following the GDPR, models should be explainable. A right to explanation arises where individuals are subjected to decisions based solely automated processing. Should a model lead to secondary findings, there is a lack of international consensus on the circumstances under which this should be reported. There is no legal duty to re-contact patients should new health information come to light. The conclusions of research studies should however, be made available to participants.

As with the right to information, confidentiality is not absolute and may be set aside in limited cases. For example, national law may allow for informing relatives of health findings with implications for them, in cases of serious harm. We note the potential for in silico modelling to have implications for non-discrimination and equity. Discrimination is prohibited in a range of international treaties, with focus on genetic discrimination. Equity in treatment and research should be pursued.

Children and people with disabilities have special entitlements under international law.

We have emphasised the legal and ethical impetus to obtain the data of potentially excluded groups within in silico modelling data. For example, the participation of children and adults lacking capacity should be encouraged wherever it may have research value, and supportive decision-making used where possible. This is another dimension to our work on consent, and we will continue in our use-cases to reflect on how consent processes can be not only lawful but also appropriately inclusive.

We will carry these reflections into the next phase of our work, and in particular the development of use cases, and avenues for lawful and ethical data use, which we will put to stakeholders in a workshop. This will ultimately lead to the development of concrete guidance on the integration and use of data for in silico modelling within the lifecycle of personalised medicine.

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