EU-STANDS4PM
standards for in silico models for personalised medicine

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

Legal and ethical review of *in silico* modelling

– compact version –

Deliverable 3.1

Imprint

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Publisher

EU-STANDS4PM administrative office on behalf of the EU-STANDS4PM consortium, March 2020
Forschungszentrum Jülich GmbH, Project Management Jülich, Germany
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1. Introduction

This report is the first deliverable of 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 development of *in silico* models for personalised medicine in the EU requires lawful and ethical data integration. The eventual clinical application of these models will also require the use of information in these automated systems in a fair and transparent manner, which respects patients' rights. This report therefore surveys the legal landscape on health data integration, and the challenges that arise when information is re-used to develop analytical or predictive models, which are then re-applied to a patient population. The aim of the report is more specifically 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 opportunities this regulation provides for harmonization and integration of data for *in silico* modelling. The legal and ethical analyses provided in the report is closely related to the data sources relevant for development of *in silico* models.

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.[1] This covers a variety of *data sources*, such as patient records (both electronic and non-electronic), patient or disease registers, cohort data, data from clinical trials, as well as tissue samples and biobank collections. The applicable legal and ethical framework is rather complex and spans provision of healthcare services, research and clinical trials, patients' rights and data protection regulation. In addition, the legal framework is multi-layered and encompasses international, European (EU and Council of Europe), national, and institutional regulation. Furthermore, the legal sources include both *binding hard law* (treaties or Conventions) and *soft law* recommendations.[2]

The legal and ethical framework reflects common human rights-based legal principles, which have emerged at European and international level in the field of the rights of patients and research subjects. These centre on respect for the dignity and inherent worth of the human beings, and underscore the primacy of the individual, as, for example, stipulated in article 2 of the Council of Europe Biomedicine Convention: *the interests and welfare of the human being shall prevail over the sole interest of society*. Rights to autonomy, privacy, data protection, and confidentiality are also basic human rights principles.[3] The legal principles are closely related to well-known guiding principles within medical ethics and bioethics as autonomy, beneficence, non-maleficence and justice.

The report pays particular attention to the nature and role of consent in data integration and use within *in silico* models.[4] Consent has a role both within the Clinical Trials Regulation, the General Data Protection Regulation, and as a basic patient right authorising the use of private or confidential information in patient care. The report also provides comprehensive analyses and discussion of complex

[1] See section 1.2.
[2] See section 1.3.
[3] See section 1.4.
[4] See section 2.

and crucial data protection issues[5] and identifies important patient rights aspects[6] which should be addressed. These key features of the landscape help identify avenues for harmonisation and integration of Big Data for personalised medicine models.

2. Consent

In section 2, consent is explored as understood under the General Data Protection Regulation (GDPR), Clinical Trials Regulation (CTR) and ethico-legal international norms. Under international law, consent emerged as a fundamental norm both of healthcare and research, but is not absolute. National law can limit the requirement of consent, for example in emergencies. Research guidelines also 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. The focus of this section is on the diverging interpretations of different consent modalities as well as waivers of consent in the European and global regulations, which are particularly relevant issues for data sharing in the context of in-silico modelling for personalised medicine.

The section starts with a brief introduction to the historical development of this fundamental concept in the post-World War II period, focusing on the Nuremberg code, early versions of the WMA Declaration of Helsinki, and the Council of Europe Convention on Human Rights and Biomedicine. These documents almost exclusively concentrate on *specific, informed and written consent* to interventions, while not explicitly addressing personal data processing.

At the end of the 20th century, the situation started to change with the increased usage and sharing of human biological materials and personal data in health research. Provisions on consent and/or derogations from specific consent requirements in the case of research on personal data and biological materials (such as "broad" consent, "dynamic" consent, or "informed opt-out") were introduced in addition to classic *interventional* consent.

The need for a legal basis for secondary use or/and collection of data and biological materials for future research has been acknowledged by the Council of Europe, EU instruments as well as recent versions of international documents such as the Declaration of Helsinki and CIOMS guidelines. These documents have also introduced a more radical derogation from "traditional" consent requirements in the form of waivers to consent in some exceptional cases for research on health data and biological materials. This marked an emerging dichotomy between informed consent as applied to research projects involving intervention on humans vs. interpretation of consent under the data protection law.

The adoption of the GDPR and its subsequent interpretation has separated the roles and meaning of consent to physical intervention and the processing of personal data even further. What is more, GDPR introduced the concept of "compatible use". The "compatible use" regime as interpreted by the European Data Protection Board ('EDPB') allows a remarkable exemption from the consent rule because it explicitly notes that personal health data can be processed "for … scientific or historical research purposes or statistical purposes" without the data subject's consent *subject to the conditions (safeguards) set forth in Article 89*.

[5] See section 3.
[6] See section 4.

Recourse to *broad consent* can be seen as a means enabling secondary use and data sharing in the research context. Therefore, it is important to explore to what extent the GDPR & CTR accommodate further processing of data on the basis of broad consent. Article 28 (2) of CTR explicitly foresees the possibility for the sponsor to ask clinical trial participants, when they give 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. The GDPR in Recital 33 also recognises the option of broad consent, noting that achieving specific and granular consent might be difficult in the context of scientific research. It is added, however, that such a broad consent should only be limited to "certain areas of research or parts of research projects to the extent allowed by the intended purpose". It is still under discussion as to what "consent to certain areas of scientific research" actually means. However, it has already been claimed that such wording can hardly serve as a basis for processing personal data in the context of biobanks and other repositories for future unspecified research.

Dynamic consent can also be seen as a potential means of data sharing within the framework of the GDPR under the legal basis of *explicit consent*. As explained by the Article 29 Working Party, initially broad consent to research could be particularised over time through re-engagement with data subjects, making it more suitable as a basis for processing.

We emphasise the role consent plays in securing and maintaining public confidence in data-driven research. In this respect, it is important to keep data from public surveys in mind which suggest that the majority of participants prefer a thorough initial consent process with agreed terms as opposed to "inferred consent", or inferred opt-in, where researchers neglect to ask for explicit consent to share. This preference for thorough consent should be taken seriously if positive public attitudes towards data sharing are to be maintained, particularly as waiving of consent, "compatible use" and legal basis other than consent become more prevalent justifications for data sharing and secondary use of data.

To conclude, consent has developed from a justification for physical interventions to include a legal action giving permission to 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 chosen in when processing data for research purposes (see below). However, the consent of the data subject is still a fundamental requirement for entry into a clinical trial, and a principle that participants value in research studies as a sign of respect for their wishes, irrespective of how data is processed under the GDPR. Finally, consent is a necessary condition for legitimating the intervention from which the data may be derived.

3. The General Data Protection Regulation

This section illustrates why a federated approach to data integration may be more practicable under the GDPR, due to subsisting national discrepancies. We query whether EU-level anonymization guidance could be updated to recognise the impracticality of deleting or aggregating clinical trial or medical records. We argue that a separate basis for processing is required when personal data are re-used for modelling, and advocate for transparency through soliciting consent to re-use wherever possible, and notification of potential for re-use as a minimum.

3.1 A Harmonised Data Protection Law?

The General Data Protection Regulation has been in force in EU member states since 25 May 2018. Although it applies across the EU and EEA, each country has passed its own implementing legislation, meaning that there are still discrepancies at national level. This means that it remains more challenging to integrate data via a centralised model, as opposed to providing access through data federation (for example).

Joint data controllers need to agree, in an open and transparent way, how they will work together to comply with the GDPR. But if personal data is brought together from different countries, and jointly controlled by organisations from numerous different jurisdictions, this creates a difficult proposition where each data controller has to abide by a different law and guidance. For example:

Basis for processing: In the UK, for example, data controllers are generally discouraged from relying on consent as a basis for processing data for scientific research. In some EU states (e.g. Germany & Lithuania), reliance on consent for research processing is possible or even encouraged.

Anonymization: Under German federal data protection law, researchers are discouraged from anonymising data if this would prevent data subjects from exercising their rights. In the UK, anonymization of research data is encouraged wherever possible.

Exemptions: EU states have passed different derogations from data subject rights for scientific research.

It would be difficult for parties jointly controlling pooled, centrally located data from across the EU to treat all this information the same way. The Article 29 Working Party's description of a 'country of origin' approach—in which data is not controlled jointly, but with information controlled by the national organisation which collected it—to data control in such situations still appears to be the most practical way of integrating data across the EU, despite the GDPR.

New guidance from the European Data Protection Supervisor, coupled with the Q&A on clinical trials and the GDPR between the European Commission and the European Data Protection Board, may help to achieve more of a pan-EU consensus over time. At the time of writing, however, subsisting differences in data protection law through national implementation of the GDPR mean that a federated or 'country of origin' approach remains in most cases a more promising option for data integration for *in silico* modelling.

3.2 Anonymization of Clinical Data

It was noted that the Article 29 Working Party's 2014 guidance on Anonymization Techniques has remained influential, particularly in its emphasis on deletion and aggregation of original data as part of the anonymization process. The European Medicines Agency (for example), has incorporated their advice in their own guidance on anonymising clinical trial data.

We highlight that the 2014 guidance preceded the judgement in *Patrick Breyer v Bundesrepublik Deutschland*[7], and subsequent guidance may need to take into account this intervening case. In particular, it is currently advised that original data (such as clinical trial documentation or medical

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

records) would need to be deleted or aggregated for subsequently shared information to be considered anonymous. It was queried whether this is always strictly necessary for context-specific anonymity, or whether the relationship between the sharer and recipient could be managed in such a way (e.g. through contract prohibiting re-identification) as to remove the necessity of deleting the original data.

As it stands, however, it is acknowledged that the 2014 guidance from the Article 29 Working Party is still authoritative and has not been formally disavowed or corrected. As such, it will not usually be possible to anonymise medical or clinical trial data, as deletion or aggregation of the records is not a realistic option these contexts. We therefore work on the assumption that most information collected from clinical trial or medical environments will be incapable of anonymization by current standards, and will therefore be subject to the GDPR when used for *in silico* modelling for personalised medicine.

Pseudonymisation, and other methods of data minimisation, remain important when sharing data lawfully, even if they remain within scope of the GDPR.

3.3 Re-using Data for Research & Statistical Purposes

We note the disagreement between the European Commission and the European Data Protection Board as to whether personal data from clinical trials need a new basis for processing when re-used for research.

The controversy centres in part on interpretations of Recital 50 GDPR, which suggests that no separate basis is needed when data are re-used for research. This could be seen to relate to the first principle of the GDPR (lawfulness) or the second (compatible purposes). We cautiously suggest that it would be bold to rely on Recital 50 GDPR to the extent of re-using people's identifiable information without notice, and contrary to their reasonable expectations of privacy.

As such, we recommend that data controllers identify a basis and condition for re-using health-related data under Articles 6 & 9 GDPR, even when this re-use is for research or statistical purposes. We respectfully suggest that the mere existence of Article 9(j) GDPR—the condition on which special categories of personal data can be processed for research & statistical purposes—indicates that a separate basis is required for this processing.

3.4 Transparency

We highlighted the importance of transparency under the GDPR, which applies regardless of whether data are processed on the basis of consent. Even where the basis for processing is public interest and scientific research, the data subject should still be informed at the point when their data are collected that their information will be used in this way.

In practice, it may be convenient to achieve GDPR transparency by obtaining consent for data re-use for *in silico* modelling. Even if this consent is not relied upon as a basis for processing—as it may be insufficiently granular, or stem from a power imbalance— obtaining consent for *in silico* modelling could be a way to ensure GDPR transparency, comply with confidentiality and privacy rights, as well as complying with ethical obligations to uphold the dignity and autonomy of data subjects.

We suggest that data subjects should be notified when their information is collected, even if collection takes place in a context most would regard as public. For example, people posting personal information

on social media may in a sense be making these details public, but they might still have a reasonable expectation that this information would not be used for public health surveillance or pharmacovigilance.

Noting in particular the action taken by the Polish Supervisory Authority in response to mass data scraping without notification,[8] we acknowledge that new sources of data for modelling may be tempting, but the apparently public nature of the data should not be taken for granted, and privacy rights under Article 8 European Convention on Human Rights, as well as the GDPR transparency principle, point towards notification of data scraping wherever possible.

4. Patients' Rights

Section Four maps international and European legal and ethical regulations on the right to information and self-determination, and equal access to healthcare, while providing an assessment of the challenges for harmonization and integration of data for *in silico* modelling. We analyse the content and scope of these rights as recognised under international conventions and non-binding recommendations.

4.1 The Right to Information

Following the Council of Europe Biomedicine Convention, patients have a *right to know* what information is collected on their health and the possibility of future use of their data. This right is not absolute and can be limited, for example, to protect the patient or the rights of others. The Biomedicine Convention is legally binding on states that have ratified the Convention. How ratifying states implement the Convention varies, however. Therefore, it is always necessary to consult domestic law.

The GDPR, which also safeguards a right to information when data is collected, has direct effect in all EU Member States. Patients also have a right to an explanation of significant decisions based *solely* on automated processing under GDPR. Again, national differences may apply. For example, in some Member States, the right to information may be limited if it would render impossible or seriously impair research.

The legal and ethical position regarding *secondary findings* is an important aspect of the right to information, with implications for *in silico* modelling. Yet, the question of when and whether to inform patients of secondary findings is unresolved at international level. For example, the Biomedicine Convention recognises a right to know and a right not to know, although neither is absolute and can be limited in order to avoid "*a serious risk for the health of others*". In some countries, national law provides more clarity, although in others, these issues are not explicitly regulated by law.

We therefore present the recommendations of The European Society on Human Genetics (ESHG) and American College of Medical Genetics and Genomics (ACMG). ESHG recommends that the healthcare professional report findings in the case of "serious health problems" in either the person being tested or close relatives, where treatment or prevention is possible. In contrast, the ACMG provides a "minimum list" of incidental findings that clinicians should report. Patients may however, opt out. This position has not been adopted in a European context. Therefore, should *in silico* modelling be adopted

[8] President of the Personal Data Protection Office, Decision ZSPR.421.3.2018, 15 March 2019, available at: accessed 27 November 2019

in the clinic, procedures regarding secondary findings are likely to be regulated at local level and thereby underlie variations.

Under European law, in genetics, there is no established general legal *duty to re-contact* 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. However, ethical or local communication policies may apply. We again underline the importance of transparency with patients regarding expectations.

Research subjects also have a right to information, although access to findings is generally considered more modest than the patient's right. The Additional Protocol concerning Biomedical Research binds ratifying states to make the conclusions of research available to participants, as well as findings "of relevance to the current or future health or quality of life of research participants". The ASHG strongly recommends that researchers attempt to re-contact participants if a reinterpretation of genetic research findings is related to the phenotype under study or is reasonably expected to affect a research participant's medical management. Again, national law may stipulate specific protections and obligations, which can have implications for *in silico* modelling and harmonisation.

4.2 Confidentiality

The right of patients and research subjects to confidentiality is protected under international law, including the European Convention on Human Rights. However, confidentiality may be limited where provided by law or with patient consent. In some countries, for example, patients' relatives can be informed of pertinent genetic findings, even where the patient refuses to consent. In some instances, healthcare professionals may be obligated to inform under their professional duty of care. Any such duty is likely to be limited to findings that may lead to serious and foreseeable harm to an identifiable relative. Researchers, on the other hand, do not have a duty to inform relatives of findings. Again, transparency underlines that healthcare professionals and researchers explain the content and limits of confidentiality.

4.3 The Right to Health & Prohibition of Discrimination

Discrimination in access to healthcare on grounds of, *inter alia*, race, sex, physical or mental disability and health status is prohibited by the International Covenant on Economic Social and Cultural Rights (ICESCR). Genetic discrimination is also prohibited in states that have ratified the Council of Europe Genetic Testing Protocol. Furthermore, states should take steps towards providing *equitable* access to healthcare, per the Biomedicine Convention.

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. Following the ICESCR, all persons should thereby be able to benefit from and take part in scientific research, without discrimination, although this right is not absolute.

Researchers and healthcare professionals should consider and evaluate risks of discrimination and stigmatisation associated with the development and application of *in silico* models.

4.4 Vulnerable Groups

International conventions enshrine special rules on participation of persons with disabilities and children in research.

Several protective provisions apply, whereby research should 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. 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. Where a person is not capable of giving consent, another can typically provide substituted consent, although the individual's participation must be solicited.

The classic human rights approach to persons without capacity to consent has thereby been protective. In the case of children, this remains, although decisions should be made with their *best interests* as a primary concern. Children should also be enabled to participate in decisions regarding their health. For example, several recommendations seek to limit genetic testing on children. 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". The European Society of Human Genetics similarly recommends that testing of persons without capacity to consent should be for their direct benefit. The American Society of Human Genetics (ASHG) acknowledges that testing for adult-onset conditions should be deferred; although 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. Again, variations will apply at domestic and local level.

The Convention on the Rights of Persons with Disabilities instead enshrines equal rights for persons with disabilities and seeks to move from protection to participation. The Convention suggests thereby that substituted decision making should not be permitted.

It is necessary to be mindful of the limitations to including persons without capacity in research. At the same time, discrimination and inequity should be avoided. The best interests principle (minors) and equality principle (persons with disabilities) underscore the need to include all groups of society in the benefits of *in silico* modelling, while respecting individuals' inherent dignity.

Section Four notes three overarching challenges. The first is the volume of recommendations, which often intersect and sometimes differ. Legally binding treaties are usually subject to domestic implementation and broadly phrased. While this allows for diversity in legal approaches, it also results in a fragmented legal space, which can be challenging to navigate and thereby impede harmonisation and integration. A second challenge is that many of the recommendations are outdated and may be unsuitable for big data driven healthcare and treatment. Finally, varying legal and ethical standards continue to apply to treatment and research, although it can be argued that this distinction is increasingly blurred.

5. Acknowledgements

EU-STANDS4PM is funded by the European Union Horizon2020 framework programme of the European Commission Directorate-General for Research and Innovation under Grant Agreement # 825843.

The current review corresponds to Deliverable 3.1 " EU-wide mapping report on legal and ethical considerations regarding data protection, clinical trials regulation and patient rights for predictive silico models in personalized medicine" of Work Package 3 "Legal ethics, policy and certification for data-driven *in silico* models in personalized medicine".


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