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How Covid-19 unveils the blurred borderlines between research and clinical practice monitoring: the use case of data protection and consent

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ABSTRACT: In the EU, the race to find Covid-19 treatment solutions has been going hand in hand with the acceleration of authorisation procedures for medicines and medical devices, and regulatory actions to monitor promising off-label and compassionate uses. This arguably contributes to the ongoing blurring of the borderlines between research and clinical practice monitoring. This article aims to map the ethical and legal implications of this trend for data protection and informed consent in pre-marketing and post-marketing studies on medicines and medical devices in the context of the Covid-19 public health emergency.

KEYWORDS: Clinical trial regulation; Covid-19; Data protection; Informed consent; Pharmaceutical and medical device regulation

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1. Introduction

Due to its high transmissibility and its pathological symptomatology, Covid-19 has had a deep impact on health and economic systems all over the world[1]. Since the outbreak of the pandemic, finding ways to prevent or treat such disease has become a top priority for governments and the industry alike. This has prompted regulators to implement measures to speed up approval processes for Covid-19 medicines and medical devices[2], and the EU is certainly no exception[3]. This emergency regulatory approach allows for the development of innovative products (especially vaccines) at an unprecedented pace. Simultaneously, it contributes to the ongoing blurring of the borderlines between research and clinical practice monitoring, moving research (and its uncertainties) from pre-marketing clinical trials to post-marketing settings, with an increasing role for post-marketing (especially observational) studies in real-world data collection.

This article aims to map ethical and legal implications of this trend for data protection and informed consent in studies regarding anti-Covid-19 medicines with special albeit not exclusive reference to pre-marketing and medical devices. To this end, this article follows the following structure. First, it preliminarily outlines the EU regulatory framework governing research on medicines and medical devices, particularly clinical trials, post-marketing studies and observational studies. Against this backdrop, it describes the EU and national emergency regulatory responses to Covid-19 to foster research on medicines and medical devices. Furthermore, it identifies the main challenges to data protection and free and informed consent in the context of the Covid-19 pandemic. Finally, the conclusions sum up the results of our analysis and identify avenues of further research in the context of the Covid-19 public health emergency.

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[1] In general, see M. Nicola *et al.*, *The socio-economic implications of the coronavirus pandemic (COVID-19): A review*, in *International Journal of Surgery*, 78, 2020, 185-193. As for the impact of Covid-19 on healthcare systems, see Z. Wang, K. Tang, *Combating COVID-19: health equity matters*, in *Nat Med*, 26, 2020, 458, doi: 10.1038/s41591-020-0823-6; D.M. Mann, J. Chen, R. Chunara, P.A. Testa, O. Nov, *COVID-19 transforms health care through telemedicine: Evidence from the field*, in *Journal of the American Medical Informatics Association*, 27(7), 2020, 1132–1135, doi. 10.1093/jamia/ocaa072; B. Armocida *et al.*, *The Italian health system and the COVID-19 challenge*, in *Lancet*, 5(5), 2020, E253. As for the economic impact of Covid-19, see W. McKibbin, R. Fernando, *The economic impact of COVID-19*, in R. Baldwin, B. Weder (eds.), *Economics in the Time of COVID-19*, London, 2020, 45-51, available at: https://www.incae.edu/sites/default/files/covid-19.pdf#page=52 (last visited 14/4/2021).

[2] In general, see N. Lurie *et al.*, *Developing Covid-19 Vaccines at Pandemic Speed*, in *N Engl J Med*, 382, 2020, 1969-1973, doi: 10.1056/NEJMp2005630. For more details on the US response, see C. Cassidy, D. Dever, L. Stanbery *et al.*, *FDA efficiency for approval process of COVID-19 therapeutics*, in *Infect Agents Cancer*, 15, 2020, 73, doi: 10.1186/s13027-020-00338-z; A.S. Kesselheim *et al.*, *An Overview of Vaccine Development, Approval, And Regulation, With Implications For COVID-19*, in *Health Affairs*, 40(1), 2021, 25-32, doi: 10.1377/hlthaff.2020.01620.

[3] M. Cavaleri *et al.*, *The European Medicines Agency's EU conditional marketing authorisations for COVID-19 vaccines*, in *Lancet*, 397(10272), 2021, 355-357; A.G. Fraser, P. Szymański, E. Macintyre, M. Landray, *Regulating drugs, medical devices, and diagnostic tests in the European Union: early lessons from the COVID-19 pandemic?*, in *European heart journal*, 41/23, 2020, 2140-2144; H.G.T. Defendi, L. da Silva Madeira, S. Borschiver, *Analysis of the COVID-19 Vaccine Development Process: an Exploratory Study of Accelerating Factors and Innovative Environments*, in *J Pharm Innov*, 2021, doi: 10.1007/s12247-021-09535-8.

2. The EU regulatory framework for research on medicines and medical devices

In the EU, before marketing a medicinal product, a manufacturer must gather safety and effectiveness data in a series of experimental phases (Annex I, Directive 2001/83/EC). Regulators, at the request of the applicant, assess on such data the benefit-risk ratio of the product and, if this ratio is positive, release a marketing authorisation (MA) (Articles 6 *et seq*., Directive 2001/83/EC). After MA, companies and regulators are required to monitor the effects of the approved medicines in the real world (so-called pharmacovigilance; Article 101 *et seq*., Directive 2001/83/EC), e.g., through post-marketing studies (PASs). A similar logic applies to medical devices (MDs), although a proper MA procedure does not apply. This paragraph summarises the EU rules applicable to pre-marketing and post-marketing research concerning medicines and medical devices, setting the ground for the subsequent analysis.

2.1. Clinical trials

In the EU, Directive 2001/20/CE (Clinical Trial Directive, CTD) defines CTs as any investigation into the effects of an investigational medicine (Art. 2(a) CTD). The CTD requires sponsors to obtain an authorization from the Member State where the CT will be conducted (Art. 9(2) CTD). It also subjects CTs to Good Clinical Practice (GCP) (Arts. 1(4) CTD), reflecting basic ethical principles as informed consent, proportionality between expected risks and benefits, and independent ethical review, in line with the Nuremberg Code, the Helsinki Declaration, and the Oviedo Convention on Human Rights and Biomedicine.

The CTD's failure to facilitate multinational CTs led to the adoption of the CTR. Intended to replace the CTD and domestic implementations, the CTR entered into force on 16 June 2014 but will apply six months after the EU Clinical Trials Information System will have achieved full functionality (Arts. 82(3) and 99 CTR).[4] The CTR clarifies that, while clinical studies include any investigation into the effects of a medicinal product, CTs are clinical studies where «*the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects*» (Art. 2(2) CTR). Also, the CTR centralises the approval of multinational CTs via the EU portal mentioned above.

Therefore, EU law adopts a "segregationist" approach to the medical research-practice divide, under which the two are mutually exclusive[5]. While interventions aimed at increasing scientific knowledge

[4] According to EMA, the launch of the portal is planned for December 2021 (https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation, last visited 14/4/2021) .

[5] This approach is also reflected in the US Belmont Report, an international reference document on the distinction between research and practice (T.L. BEAUCHAMP, Y. SAGHAI, *The historical foundations of the research-practice distinction in bioethics*, in *Theor. Med. Bioeth*, 33(1), 2012, 45-56). For more details on the related debate, see T. BEAUCHAMP, *Why our conceptions of research and practice may not serve the best interest of patients and subjects*, in *J Int Med*, 269, 2011, 383–7; M.F. VERWEIJ, *Commentary: The distinction between research*

constitute medical research, interventions with mere therapeutic aims are clinical practice falling outside CT legislation. This is regardless of whether the intervention is standard or non-standard. This may result in the under-protection of patients receiving non-standard treatments[6]. In any case the possible informative asymmetry shall be covered through the informed consent procedure, that find application also for non-interventional studies.

2.2. Post-authorisation studies

While CTs are typically conducted in preparation for a MA application, they can also be conducted as PASs, after a MA is granted[7]. PASs include Post-authorization Safety Studies (PASSs) and Post-Authorisation Efficacy Studies (PAESs). PASSs aim to gather additional information on the safety and benefit-risk profile of a medicine (Art. 1(15), Directive 2001/83/EC). PASSs can either be CTs or NISs, voluntary or imposed. Imposed PASSs include studies that are a specific obligation for a MA granted based on fewer data than normally required or if new data emerges challenging the initial MA assessment.

Likewise, PAESs cover both CTs and NISs, and may be imposed if (a) a MA has been released based on data less complete than usually required, as in the case of Conditional Marketing Authorisation (CMA) (Art. 14(7) of Regulation (EC) No 726/2004), or (b) efficacy concerns can be resolved only after MA or previous efficacy evaluations should be revised in light of real-world data (Delegated Regulation (EU) No 357/2014). PASs should be registered in the EU PAS Register, where EMA publishes protocols, abstracts and final study reports (Commission Implementing Regulation (EU) No 520/2012).

Finally, it is worth noting that the incoming CTR introduces the notion of low-intervention CTs, i.e., CTs on the use of already authorized medicines (Art. 2(c) CTR). As such, they are poised to enrich the toolbox of PASs. Low-intervention CTs are subject to less stringent requirements. In particular, informed consent may be obtained by «*simplified means*» (Art. 30(3)(c) CTR). This means that informed consent is considered to be given if information about the CT is given to the potential subject and this latter does not object to participation (Art. 30(2) CTR). Also, the CT sponsor determines the «*extent and nature of the monitoring*» considering «*all characteristics of the clinical trial, including* […] *whether the clinical trial is a low-intervention clinical trial*» (Art. 48 CTR). Since low-intervention CTs concern already approved medicines, this latter provision may be interpreted as enabling sponsors to implement weaker forms of monitoring. However, if the CT involves an off-label use for which published evidence is unavailable, the usual requirements apply (Art. 2(c) CTR).

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and practice – a response to T. Beauchamp, in *Journal of Internal Medicine*, 269, 2011, 388-391, doi: 10.1111/j.1365-2796.2011.02350_2.x.

[6] This risk has been highlighted in the literature cited in the previous note and N.E. KASS *et al*., *The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight*, in *The Hastings Center Report*, 43(1), 2013, S4-S15; G. HELGESSON, *Can and should the research–therapy distinction be maintained? Reflections in the light of innovative last-resort treatment*, in *Research Ethics*, 15(2), 2019, 1-14. doi: 10.1177/1747016119835461.

[7] F. TUBACH, *Role of the Post-Marketing Authorisation Studies in Drug Risk Surveillance: Specifications and Methodologies*, in *Therapie*, 66(4), 2011, 355–362; T.J. GIEZEN, A.K. MANTEL-TEEUWISSE, S.M.J.M. STRAUS *et al*., *Evaluation of Post-Authorization Safety Studies in the First Cohort of EU Risk Management Plans at Time of Regulatory Approval*, in *Drug Safety* 32(12), 2009, 1175-1187.

Therefore, low-intervention CTs may overall contribute to further blurring the boundaries between research and practice, lowering the level of regulatory requirements in certain research contexts. This will likely have an impact in the context of conditional and accelerated authorisation procedures, where PASs are increasingly performed to complement and enrich products' data profiles.

2.3. Observational studies

As anticipated, the data supporting the MA of a medicine may also be complemented by the observation of its real-world effects. To this end, non-interventional studies (NISs) are performed. NISs do not interfere with the course of clinical practice and observe data collected from the real world (e.g., from patient registries)[8]. This is why NISs are also called observational studies. This is reflected in their CTD definition: «*the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice, and the prescription of the medicine is separated from the decision to enrol the patient in the investigation. [NISs] do not apply additional diagnostic or monitoring procedures to patients and use epidemiological methods for the analysis of collected data*» (Art. 2(c) CTD). Conversely, the CTR defines NISs as any «*clinical study other than a* [CT]». EMA GVP Module VIII clarifies that NISs «*also include those involving primary data collection (e.g., prospective observational studies and registries in which the data collected derive from routine clinical care)*». However, NISs are left to the Member States, where regulations vary wildly[9]. This complicates multinational observational research[10], despite its increasing importance in real-world data collection in making informed decisions on a medicine's regulatory statues and healthcare strategies[11].

2.4. Medical device clinical evaluation

A similar logic applies to MDs. Regulation (EU) No 2017/745 (Medical Device Regulation, MDR) will become applicable on 26 May 2021 and replace Directive 93/42/EEC (Medical Device Directive, MDD)[12]. The MDR sets out distinct conformity assessment (CA) procedures for different MD classes, based on their risk level. Unlike the MDD, the MDR requires a Clinical Evaluation Report for all MD classes. Manufacturers can obtain a CE marking with clinical investigations (CIs, under Chapter VI and

[8] J.F. ALIDJANOV, K.G. NABER, A. PILATZ *et al.*, *Evaluation of the draft guidelines proposed by EMA and FDA for the clinical diagnosis of acute uncomplicated cystitis in women*, in *World J Urol*, 38, 2020, 63-72.

[9] I. RAMIREZ, *Navigating the maze of requirements for obtaining approval of non-interventional studies (NIS) in the European Union*, in *Ger Med Sci.*, 13, 2015, Doc21, doi: 10.3205/000225.

[10] Observational studies naturally interact with pharmacovigilance and data protection law. For more details on such aspects, see, respectively, S.E. GÜLMEZ, *The new pharmacovigilance legislation and impact on observational studies*, in *Marmara Pharmaceutical Journal*, 17, 2013, 61-64, doi: 10.12991/201317374; G.H.P. METNITZ *et al.*, *The General Data Protection Regulation and its effect on epidemiological and observational research*, in *The Lancet Respiratory Medicine*, 8(1), 2020, 23-24.

[11] F. CLAUDOT *et al.*, *Ethics and observational studies in medical research: various rules in a common framework*, in *International Journal of Epidemiology*, 38,(4), 2009, 1104–1108, doi: 10.1093/ije/dyp164.

[12] Regulation (EU) 2020/561 of the European Parliament and of the Council of 23 April 2020 amending Regulation (EU) 2017/745 on medical devices, as regards the dates of application of certain of its provisions.

Annex X MDR). CIs are subject to several European Commission implementing measures[13] and the standards ISO 14155-1:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice). This framework is similar to GCP, which subjects CIs to scientific principles on clinical data collection and human experimentation ethical standards. CIs may be randomized clinical trials or a different study types, if their validity is duly proved to NCAs. Alternatively, manufacturers can claim equivalence with another product (Art. 61(3)(a) MDR); yet the MDR requires more equivalence evidence than the MDD (§ 3(e), Annex XIV MDR). Thus, not only high-risk but also medium-risk MDs will likely require CIs. Finally, the MDR requires Post-Market Surveillance (PMS) and Post-Market Clinical Follow Up (PMCF) (Chapter VII and Annex IX MDR). In particular, PMCF studies aim to confirm the safety and performance data acquired in the pre-approval phase. They can be structured like pre-approval studies (Art 74 MDR).

3. Regulatory responses to the Covid-19 epidemic in the EU

In the face of the Covid-19 pandemic, the EU scientific community and pharmaceutical/MD industry have been striving to develop medicines, vaccines, and medical devices to prevent and treat Covid-19. This paragraph offers an overview of the regulatory responses implemented by the EU and national competent authorities (NCAs) to support these endeavours[14].

This overview suggests that the race to find Covid-19 treatment solutions in the EU is based on two main regulatory pillars: (i) accelerated authorisation procedures; (ii) recommendations concerning off-label uses of medicines approved for other indications and (iii) compassionate uses of investigational products. All three pillars have implication on both informed consent to trial/treatment and on personal data processing.

Such an impact is also related to the strategy chosen by regulators to promote forms of clinical practice monitoring. Indeed, given the EU "segregation" between research and practice (see above, paragraph 2.1), patients receiving non-standard therapies may theoretically be exposed to substantially experimental uncertainties outside the protections required for experimentations on humans. In other terms, accelerated procedures blur the borderlines between medical research and practice, and may result in the scientific uncertainties inherent in the lack of comprehensive data being transferred from pre-approval trials to clinical practice. This situation likely induced regulators to compensate the less complete data required to approve Covid-19 produces with strengthened clinical practice monitoring. It is worth noticing as well that many jurisdictions have introduced[15] or

[13] See https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_guidance_meddevs.pdf (last visited 14/4/2021). For further details on the role of such guidance under the incoming MDR, see B. WILKINSON, R. VAN BOXTEL, *The Medical Device Regulation of the European Union Intensifies Focus on Clinical Benefits of Devices*, in *Ther Innov Regul Sci*, 54, 2020, 613-617, doi: 10.1007/s43441-019-00094-2.

[14] See below paragraphs 3.1 to 3.4.

[15] For instance, France has limited the civil liability of physicians prescribing medicines off-label against Covid-19 (Arts. L.3131-3 e L.3131-20, *Code de la Santé Publique*, following *loi* 290/2020). Similar proposals are discussed in Italy (G. COMANDÉ, *La responsabilità sanitaria al tempo del Coronavirus...e dopo*, in *Danno e responsabilità*, 2020, 297). In the USA, several states introduced forms of criminal and civil liability immunity for healthcare institutions and providers (R.L. KLITZMAN, *Legal Immunity for Physicians During the COVID-19 Pandemic: Needs to Address Legal and Ethical Challenges*, in *Chest*, 158(4), 2020, 1343-1345, doi:

are evaluating the option to introduce liability shields for medical doctors and healthcare facilities during the pandemic, eventually weakening patients' toolbox in case of harm.

3.1. Acceleration of authorisation procedures

The European Medicines Agency (EMA) has strived to accelerate the development of anti-Covid-19 products. To promote evidence generation, EMA provided recommendations on clinical trials (CTs)[16] and observational studies of real-world data during the pandemic[17]. EMA also set up research networks to conduct observational post-authorisation safety studies (PASS)[18].

EMA has also combined Rolling Review (RR) and Conditional Marketing Authorisation (CMA) to accelerate the approval of several anti-Covid-19 vaccines[19]. With RR, EMA evaluates data as they emerge in the development process (usually, applicants submit all data in the marketing authorisation application)[20]. Conversely, CMA is an authorisation for medicines addressing unmet medical needs in emergencies declared by WHO or EU (Regulation (EC) No 507/2006). It is granted based on less comprehensive data than usually required if the benefit of the medicine's immediate availability outweighs the risk associated with incomplete data. CMA holders must subsequently collect additional data to confirm that the benefit-risk ratio is positive. Since this acceleration of approval procedures may result in experimental uncertainties being transferred to clinical practice, EMA set up a pharmacovigilance plan[21] for Covid-19 vaccines strengthening ordinary pharmacovigilance activities, e.g., requiring MAHs (Market Authorization Holders) to outline the post-authorisation safety follow-up in the Risk Management Plans[22] and submit EMA monthly summary safety reports besides regular periodic safety update reports[23].

10.1016/j.chest.2020.06.007). At the federal level, the Public Readiness and Emergency Preparedness Act also offers extensive liability immunity during public health emergencies (N. AL-AZRI, *Health Care Workers' Legal Liability and Immunity During the COVID-19 Pandemic*, in *Disaster Medicine and Public Health Preparedness*, 2020, 1-2, doi:10.1017/dmp.2020.449).

[16] EMA, *Guidance on the management of clinical trials during the Covid-19 (Coronavirus) pandemic*, Bruxelles, 4 February 2021, https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf (last visited 14/4/2021).

[17] A. POTTEGÅRD, X. KURZ, N. MOORE, C.F. CHRISTIANSEN, O. KLUNGEL, *Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic*, in *Pharmacoepidemiol Drug Saf*., 29, 2020, 825-831.

[18] EMA, *Pharmacovigilance Plan of the EU Regulatory Network for Covid-19*, EMA/333964/2020, 3-4. EMA also encouraged researchers to register observational studies in the EU electronic register of post-authorisation studies (EU PAS Register) and share protocols and reports (https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-vaccines-covid-19-post-authorisation, last visited 14/4/2021).

[19] *Pzifer*, *Moderna*, and *Astrazeneca*. See M. CAVALERI, H. ENZMANN, S. STRAUS, E. COOKE, *The European Medicines Agency's EU conditional marketing authorisations for COVID-19 vaccines*, in *Lancet*, 397/10272, 2021, 355-357.

[20] https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-developers-companies/covid-19-guidance-assessment-marketing-authorisation (last visited 14/4/2021).

[21] EMA, *Pharmacovigilance Plan of the EU Regulatory Network for Covid-19*, cit.

[22] EMA, *Pharmacovigilance Plan of the EU Regulatory Network for Covid-19*, cit., 3.

[23] Id.

However, there is no explicit obligation to inform patients about the conditional nature of the product's authorisation, also for the purposes of informed consent acquisition. This is a significant weakness of the emergency system, in which patients exposed to additional uncertainties should be made fully aware of this and give a specific consent.

3.2.. Off-label and compassionate uses

In lack of approved alternatives, physicians have been trying to treat Covid-19 patients with medicines approved for other conditions since the beginning of the Covid-19 outbreak [24]. While such 'off-label' prescriptions[25] offer promising therapeutic opportunities, they may practically expose patients to experimental risks since they have not been thoroughly studied and validated[26]. This grey area between clinical research and practice has caught the attention of EMA, which has released several recommendations[27].

Compassionate use programs (CUPs)[28] are another area blurring clinical research and practice in which EMA has provided guidance. Under Article 83, Regulation (EC) 726/2004, Member States set up CUPs to grant access to experimental medicines to patients unable to join RTCs and suffering from severe diseases that cannot be treated with authorised medicines[29]. EMA provided recommendations to favour a common approach in the EU and has released recommendations concerning potential Covid-19 treatments[30]. Finally, it is worth noting that the EMA's recommendations on off-label and compassionate use do not include specific information and consent provisions explicitly requiring to disclose the unauthorised nature of the prescription to patients.

3.3. Personal protective equipment and medical devices

The Covid-19 epidemic made the demand for personal protective equipment (PPE) and (MDs) skyrocket, including face masks, disinfectants, and ventilators. Therefore, the European Commission

[24] A. Shojaei, P. Salari, *COVID-19 and off label use of drugs: an ethical viewpoint*, in *DARU J Pharm Sci*, 28, 2020, 789-793; J.D. Alpern, E. Gertner, *Off-Label Therapies for COVID-19—Are We All In This Together?*, in *Clin. Pharmacol. Ther.*, 108, 2020, 182-184, doi: 10.1002/cpt.1862.

[25] In general, see European Commission, *Study on off-label use of medicinal products in the European Union*, Bruxelles, 2017, 7. On the civil liability implications of off-label prescribing, see A. Parziale, *Responsabilità civile da usi off-label di farmaci nell'UE: una prospettiva precauzionale*, in *Opinio Juris in Comparatione*, I(1), 2020, 11-29;; M. Di Paolo, B. Guidi, L. Nocco, *La prescrizione off-label: dentro o fuori la norma?*, in *Resp. Civ. Prev.*, 2010, 2165; F. Massimino, *La prescrizione dei farmaci «off label»: adempimenti, obblighi e responsabilità del medico*, in *Danno e Resp.*, 2003, 925.

[26] European Commission, *Study on off-label use of medicinal products in the European Union*, cit., cit., 112.

[27] E.g., see EMA, *COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine*, EMA/202483/2020 Rev.; EMA, *EMA gives advice on the use of non-steroidal antiinflammatories for COVID-19*, EMA/136850/2020.

[28] In general, see G. Balasubramanian *et al.*, *An overview of Compassionate Use Programs in the European Union member states*, in *Intractable & Rare Diseases Research*, 5(4), 2016, 244-254, doi: 10.5582/irdr.2016.01054; H. Sou, *EU Compassionate Use Programmes (CUPs)*, in *Pharm Med*, 24, 2010, 223-229.

[29] See below paragraph 3.4.

[30] E.g., see EMA, *EMA provides recommendations on compassionate use of remdesivir for COVID-19*, EMA/152575/2020.

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has recommended the use of all the measures available to expand the supply (Article 1, Commission Recommendation (EU) 2020/403). In particular, Member States should consider authorising derogations from conformity assessment procedures under Articles 11(13), Directive 93/42/EEC and 59, Regulation (EU) 2017/745 (Article 5 of the Recommendation). Also, market surveillance authorities may authorise the marketing of PPE and MDs ensuring an adequate level of health and safety according to the relevant regulations before conformity assessment is finalised, for a limited time and while the necessary procedures are finalised (Article 7 of the Recommendation). This means that, once a market surveillance authority confirms that a MD is compliant, the first batch of products may be marketed, although it does not bear the CE marking. Finally, the European Commission has provided practical guidance on PPE, disinfectants, and 3D-printed MDs[31]. As in the case of CMA, there is, however, no explicit obligation to disclose to patients that a MD has been marketed based on a less comprehensive assessment.

3.4. National policies

EU Member States have generally acted to accelerate approval procedures for the protocols of CTs, observational studies, and CUPs, while strengthening pharmacovigilance. For instance, Italy has streamlined[32] and centralised the procedures for CTs, observational studies, and CUPs protocols, subjecting them to approval by the scientific committees of the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) and the Ethics Committee of the Lazzaro Spallanzani Institute for Infectious Diseases (Article 40, Law-Decree No. 23/2020, converted into Law No. 40/2020)[33].
Likewise, the French Medicines Agency (*Autorité Nationale de Sécurité du Médicament*, ANSM) has accelerated the assessment of CT authorization applications[34] and CUPs[35], while strengthening pharmacovigilance for anti-Covid-19 off-label uses[36]. No derogations on informed consent procedures are envisaged in France[37]. The Spanish Medicines Agency (*Agencia Española de*

[31] https://ec.europa.eu/growth/content/coronavirus-commission-issues-questions-and-answers-help-increase-production-safe-medical_en (last visited 14/4/2021).
[32] AIFA, *Circolare sulle procedure semplificate per gli studi e i programmi di uso terapeutico compassionevole per l'emergenza da Covid-19*, 22 May 2020.
[33] According to AIFA, the informed consent form is still a mandatory document to be submitted to the Ethics Committee during pandemic CTs. The collection of informed consents could follow alternative paths, like telephone calls, followed by e-mail confirmation or validated electronic systems, but the written template shall be obtained at the very first occasion, see AIFA notice, *Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency*, 7.4.2020 https://www.aifa.gov.it/documents/20142/871583/Comunicato_gestione_studi_clinici_in_emergenza_COVID-19_EN_07.04.2020.pdf/77493ac7-b799-5312-837d-b5f256f63c59 (last visited 14/4/2021)
[34] https://www.ansm.sante.fr/Activites/Essais-cliniques/COVID-19-Essais-cliniques-en-cours/(offset)/0 (last visited 14/4/2021).
[35] *Autorisations Temporaires d'Utilisation*: https://www.ansm.sante.fr/Dossiers/COVID-19/AMM-ATU-essais-cliniques-visas-publicitaires-vos-demarches-durant-la-pandemie/(offset)/7 (last visited 14/4/2021).
[36] ANSM, *Pharmacovigilance et addictovigilance dans le contexte du COVID-19 : une surveillance renforcée*, https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Systemes-de-vigilances-de-l-Agence/COVID-19-Dispositif-renforce-de-Pharmacovigilance-et-d-Addictovigilance/(offset)/0 (last visited 14/4/2021).
[37] Bird & Bird, *Clinical Trials: France. Emergency legislation* https://www.twobirds.com/~/media/pdfs/in-focus/coronavirus/lsh-tracker/clinical-trials_france.pdf?la=en&hash=4C12B58C20B2D1E249B0D87D6CE6D5E53FCA1441 (last visited 5/4/2021).

Medicamentos y Productos Sanitarios, AEMPS) has also streamlined CTs and observational studies[38]. AEMPS provided scientific advice on CTs[39] and recommendations on anti-Covid-19 off-label uses based on CTs and observational studies[40]. AEMPS also facilitated access to potential anti-Covid-19 treatments through CTs or CUPs, while reinforcing pharmacovigilance[41]. Some other Member States have gone even further with NCAs granting national emergency MAs for vaccines not authorised by EMA (e.g., Hungary with the Russian *Sputnik V* and Chinese *Sinopharm* Covid-19 vaccines)[42].

Finally, MDs have been addressed at the national level as well. While Notified Bodies have shared several applicable standards[43], NCAs have issued guidelines for manufacturers. For instance, AIFA clarified how manufacturers can apply for derogations to standard approval procedures[44], and ANSM streamlined the approval of "innovative" MD solutions, e.g., 3D-printed MDs[45].

Generally, neither national emergency legislations and NCAs' recommendations on medicines and MDs seem to include specific information and consent obligations in favour of patients. Among the jurisdictions considered in this paragraph, it is worth noting the remarkable exception of France, where physicians have a specific obligation to disclose to patients the unauthorised regulatory status of a prescription (Arts. L. 5121-12-1, III, *Code de la Santé Publique*). In the case of accelerated MAs, the lack of specific information and consent obligations may result in the under-protection of patients receiving treatments approved with less complete data, *de facto* turning them into subjects for "a continuing trial".

4. Data protection issues

In parallel with informed consent for treatment, the blurring between research and clinical practice monitoring poses several interrelated challenges also to personal data protection. They are related to the research activities connected to the pandemic and might refer either to patients or healthy

[38] AEMPS, *Actuaciones de la AEMPS para agilizar y fomentar los ensayos clínicos y estudios observacionales sobre COVID-19*, MUH, 11/2020.

[39] AEMPS, *Información sobre investigación clínica sobre la COVID19*, 19 November 2020, https://www.aemps.gob.es/laAEMPS/docs/NI_AEMPS-investigacion-clinica.pdf?x98091 (last visited 14/4/2021).

[40] AEMPS, *La AEMPS informa sobre el buen uso de medicamentos relacionados con COVID-19*, MUH, 9/2020.

[41] AEMPS, *Tratamientos disponibles sujetos a condiciones especiales de acceso para el manejo de la infección respiratoria por SARS-CoV-2*, 9 July 2020, https://www.aemps.gob.es/laAEMPS/docs/medicamentos-disponibles-SARS-CoV-2-8-7-2020.pdf?x98091 (last visited 14/4/2021). Informed consent shall be obtained avoiding the risk of contagion, allowing the recording of the patient's willingness orally obtained and preferably before a witness, see AEMPS, *La AEMPS informa sobre el buen uso de medicamentos relacionados con COVID-19*, MUH, 4/2020.

[42] The Czech Republic and Slovakia have also considered authorising the Sputnik V vaccine autonomously (E. HOLT, *Countries split from EU on COVID-19 vaccines*, in *Lancet*, 397(10278), 2021, 958, doi: 10.1016/S0140-6736(21)00620-6).

[43] A.G. FRASER, P. SZYMAŃSKI, E. MACINTYRE, M. LANDRAY, *Regulating drugs, medical devices, and diagnostic tests in the European Union: early lessons from the COVID-19 pandemic?*, cit., 2140-2144.

[44] ITALIAN MINISTRY OF HEALTH, *Richieste di Autorizzazioni in deroga ai sensi dell'art. 11, comma 14 del D.Lgs. n. 46/97 ed Emergenza COVID 19*, 5 May 2020.

[45] ANSM, *Impression 3D pour la fabrication de dispositifs médicaux dans le cadre de la crise du Covid-19*, 2020.

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persons in the process of identifying possible causes and solutions to the covid-19 related diseases[46]. As anticipated, several protocols and projects have been designed to accelerate the detection, diagnosis, and treatment of the disease, as well as to prevent the virus diffusion (mostly restrictions on gathering and movement of individuals). In fact, the need for introducing measures to map the spread of the virus and, at the same time, to adopt effective organizational measures to protect privacy sparked a challenging debate on how to balance the public health and data protection.

Since the very first legislative initiatives on the matter it has been sought a concrete balance between the protection of patients' fundamental rights and the need to accelerate the procedures. Both research for treatment and the control of the spread of the virus have triggered a much-heated debate across the world[47]. At the EU level concerns over personal data processing and the risks to data subjects unfolded in guidelines referring both to research and to contact tracing. In both instances individual and collective right to health (treatment and prevention) have been at the fore for a balancing exercise with other fundamental rights and liberties ranging from the freedom of movement to personal data protection. Key elements on both accounts have been offered by the European Data Protection Board (EDPB).

On April 21st, 2020, the European Data Protection Board adopted the *Guidelines 03/2020 on the processing of data concerning health for the purpose of scientific research in the context of the COVID-19 outbreak*[48], addressing how to comply with the principles stated in the Regulation (EU) No 679/2016 – General Data Protection Regulation (GDPR) in the Covid-19 emergency context.

A driving principle in them is that public health purposes, which require simplified, but effective, procedures, shall not compromise the GDPR principles, so that the value of personal data is preserved while they are re-used for research purposes. A clear guidance is provided by the Recital 46 GDPR, quoting «*humanitarian purposes, including for monitoring epidemics and their spread*» as a possible scenario to pursue «*an interest which is essential for the life of the data subject or that of another natural person*» under «*important grounds of public interest*» giving content to the provision of art. 9.2. *sub* i.

The mentioned EDPB Guidelines identifies the possible sources of health data, including (a) those «*information collected by a health care provider in a patient record*»; (b) those «*that become health data by cross referencing with other data thus revealing the state of health or health risks*» or other information related to a specific context; (c) those provided during "self-check" surveys. It is important to note that this non-exhaustive list envisages the possibility of data integration/fusion from different environments (e.g., medical records, tracing activities, and self-check) acknowledging the possibility and benefits of a data driven approach. Nevertheless, the message is clear: those

[46] EUROPEAN COMMISSION, *Joint European Roadmap towards lifting COVID-19 containment measures*, available at: https://ec.europa.eu/info/sites/info/files/communication_-_a_european_roadmap_to_lifting_coronavirus_containment_measures_0.pdf (last visited 14/4/2021).

[47] See for example, contributions included in VV.AA., *Opinio Juris in Comparatione*, Special Issue 2020, available at: https://www.opiniojurisincomparatione.org/ (last visited 14/04/2021; B. BOUDREAUX *et al.*, *Data privacy during pandemics*, Rand Corporation, 2020; W. NAUDÉ, *Artificial Intelligence Against COVID-19*, IZA, 2021.

[48] EDPB, *Guidelines 03/2020 on the processing of data concerning health for the purpose of scientific research in the context of the COVID-19 outbreak*, 21.4.2020, https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_guidelines_202003_healthdatascientificresearchcovid19_en.pdf (last visited 14/4/2021).

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activities are legitimate and possible under the GDPR's rules without undermining its protective scope. After all, we can add it is its actual scope to lay «*down rules relating to the protection of natural persons with regard to the processing of personal data and rules relating to the free movement of personal data*» (art. 1) at the same time and it is in its DNA to enable a continuous balance of interacting fundamental rights and liberties.

Indeed, building on the very structure of the GDPR, *Guidelines 03/2020* recall the main principles enabling a compliant re-use of personal data and, at the same time, boosting the development of research activities in the context of COVID-19 as well. In particular, the framework identified by article 89 GDPR together with 9.2 *sub* i) and j) GDPR provides the required boundaries to handle sensitive data in the aim of containing the pandemic and for the related research activities[49].

In the scenario of Covid-19, the needed assessments involving the GDPR regulatory system balancing data subjects' rights and data controllers' obligations has unfolded along two main lines and specific aims: (i) to enable systems of tracing, tracking, treating (the so called 3Ts) as the main methodology to combat the virus[50]; and (ii) to ensure that fundamental rights are preserved and protected through the technical and organisational measures in terms of governance of flows and corresponding data retention. It is worth noticing again that the fundamental right to data protection has been sustained (at least by the EDPB) as a driving force to ensure that other fundamental rights and liberties keep their level of protection. In this way, the right to data protection becomes a functional but not subservient fundamental to the protection of individual and collective rights to health; it becomes an essential element to ensure that the right to health can be better deployed (e.g., so that potential infected persons can be warned - saving lives - without exposing them to limitations in access to healthcare services, for example, or to social discrimination).

Similarly, and at the level of research on the other hand, the right to protection of personal data is functional to avoid that the collective interest might, during the pandemic or once the state of emergency has ceased, choose individuals or minorities to be sacrificed directly or indirectly to a majority, altering the difficult balance between the individual right and the collective interest in health. Indeed, a clear example of how personal data have been used to these purposes is the contact tracing App developed in the first months after the world pandemic was declared [51].

Another challenging topic involving Covid-19 containment and data processing concerns the EU health passport and its possible re-use outside airports. While it is clear that the electronic nature of such a vaccination certificate (as what it is, after all) might only raise concerns about its cybersecurity, concerns that could be easily solved with current standard technology, it is also clear

[49] E. VENTRELLA, *Privacy in emergency circumstances: data protection and the COVID-19 pandemic*. *ERA Forum* 21**,** 2020, 379–393, https://doi.org/10.1007/s12027-020-00629-3; M. KĘDZIOR, *The right to data protection and the COVID-19 pandemic: the European approach*. *ERA Forum* 21**,** 2021, 533–543, https://doi.org/10.1007/s12027-020-00644-4

[50] EDPB, *Guidelines 04/2020 on the use of location data and contact tracing tools in the context of the COVID-19 outbreak*, 21.4.2020, https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_guidelines_20200420_contact_tracing_covid_with_annex_en.pdf (last visited 14/4/2021).

[51] G. COMANDÉ, M. MONTI, *App-lichiamo la privacy: considerazioni sulla tutela dei dati personali nello sviluppo delle app di tracciamento*, in M. MALVICINI, T. PORTALURI, A. MARTINENGO, *Le parole della crisi. Le politiche dopo la pandemia. Guida non emergenziale al post-Covid-19*, 2020, Naples, 93 *et seq*.

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that it might entail a different level of risks for fundamental rights and liberties if it is used beyond its envisaged purpose of *facilitating* cross border travelling. Here the risk is reuse or a function creep. In the first case, for instance, if data for the issuance of the EU health passport is re-used beyond their original purpose it could undermine trust in it and the whole voluntariness of adhesion to it. Furthermore, if its original purpose is twisted, and, even if by law, it is requested to grant access to reopening activities (e.g. access to gyms is granted only to EU health passport holders) discrimination concerns and conflicts with other constitutional tenets might arise. An example is offered by the fact that vaccination is not offered to all individuals at the same time because of priority criteria. While it could be useful to facilitate the reopening of certain activities by enabling vaccinated individuals to them, it still be problematic under the right to equality.

Also in this case, the balance between simplified procedures and data protection cannot *be considered as a precondition for free movement, and any measures shall be adopted to avoid possible discrimination against those who do not hold a health passport*[52].

More in general, Authors[53] have already remarked how the Italian emergency legislation described the cases in which it is justified to process personal data under Articles 6, 9, 10 of the GDPR, excluding any derogation from the technical and organizational measures to be adopted for its processing: the Italian emergency statute of March 9th, 2020 deals with personal data processing in its Article 14, providing specific legal conditions for authorized data controllers to enable or disable personal data flows in execution of the emergency plan.

In particular and for example, the Italian provisions identify the subjects that are authorized to carry out the processing of personal data belonging to special categories of data and judicial ones, as long as they are «*necessary for the performance of the functions assigned to it in the context of the emergency caused by the spread of COVID*». Thus, procedural facilitations have a clear and narrow personal scope and purpose that do not undermine the aims of the GDPR while extending the traditional scope of art. 9 GDPR. For instance, medical and health care personnel naturally included under art. 9.2. *sub* i include, according to the mentioned Italian statute, the civil protection staff, public and private structures operating in the health sector, entities appointed to ensure the implementation of emergency measures ensuring that facilitations are applied across the board without discriminations but not beyond what is needed. Other categories of personal data flows (like the general data under Article 6 GDPR) or sensitive and judicial data flows processed with public and private entities other than the above-mentioned categories can be enabled only if «*essential for the performance of activities related to the handling of the health emergency in progress*». With reference to this possible extension, the principles of minimisation, proportionality and purpose limitation identified in article 5 GDPR remain fully applicable.

A modular approach can be appreciated when considering the measures aimed at facilitating data flows within the clinical context: only emergency medical personnel is exempted from providing the

[52] R.C.H. Brown, J. Savulescu, B. Williams, *et al.*, *Passport to freedom? Immunity passports for COVID-19*, in *Journal of Medical Ethics*, 46, 2020, 652-659.

[53] G. Comandé, D. Amram, G. Malgieri, *The democracy of emergency at the time of the coronavirus: the virtues of privacy*, in *Opinio Juris in Comparatione*, [S.l.], mar. 2020, available at: http://www.opiniojurisincomparatione.org/opinio/article/view/144/152 (last visited 14/4/2021).

privacy notice or is authorized to formulate a simplified one, as stated in Article 23, paragraph 1, *sub* e GDPR. In any case, as a minimal guarantee, it is required to communicate at least orally these limitations to the data subjects in order to avoid any risk of information asymmetries or the generation of privileged positions[54]. Therefore, transparency and data minimisation principles remain key to maintaining an accountable approach towards personal data flows during the emergency in the clinical context as well.

In contrast, the principle of accountability, as the mechanism to demonstrate any adopted organizational and technical measure, finds some limitations to avoid any negative impact on the speediness of healthcare procedures. To this end, as far as the internal authorizations delegating the processing within the given organization are concerned, the above-listed categories - as long as they are "front line" operators - can be provided orally authorizing to access the data flows. These exceptions introduce temporarily simplified procedures to allow a proper allocation of resources and time towards healthcare activities, without entirely compromising the GDPR system of duties and rights. Their temporary nature clearly requires that once the emergency declaration is called off the regular procedures need to be reinstated and the appointment will need to be done again in writing with clear and detailed instructions.

A year after the described emergency statutory law, it could be interesting to analyse possible mechanisms of monitoring and assessment of the law in action in order to verify whether or not the stated boundaries are still effective to solve the illustrated balance.

5. The role of informed consent

The described structural mechanism of temporary exceptions introduced in Italy, as an example of a more general issue, within the main boundaries of the GDPR principles find application also in the design of clinical trials. Under Article 17 of the recalled emergency statute, research protocols on Covid-19 shall be submitted to the appointed national competent ethical committee. This measure developed a privileged channel for researchers to access standard procedures to design and implement clinical trials[55].

An important part of a clinical protocol concerns patients' information sheet and informed consent. As known, informed consent to participate in a clinical study shall be distinguished from the legal basis for data processing, as clarified by the EDPB[56]. However, both legal provisions deal with the transparency of the procedures to make the participants / data subjects aware of what could happen and how this could impact their life. Human dignity is preserved if the initial information asymmetry is covered by a transparent information that allows the individuals to understand, to maintain the control on her data / performed activity and to make their decision on participating to the procedure / trial.

[54] *Ibid.*

[55] Art. 40, D.L. 8 aprile 2020, n. 23 on "*Disposizioni urgenti materia di sperimentazione dei medicinali per l'emergenza epidemiologica da COVID*".

[56] EDPB, *Guidelines 05/2020 on consent under Regulation 2016/679*, available at: https://edpb.europa.eu/sites/edpb/files/files/file1/edpb_guidelines_202005_consent_en.pdf (last visited 14/4/2021).

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The informed consent template is composed of three main forms: the information sheet, including all information related to the study (sponsor, funding program, purposes, tasks / activities required and corresponding benefits / risks, contacts to withdraw / ask for information, insurance details, the incidental findings policy etc), the privacy information notice according to articles 13 and 14 GDPR (including the information on data controller, DPO, type of data processed, means, purposes and legal basis, data retention policy, and rights that the data subject may exercise), and the informed consent templates where the research subject may consent to all / any activities of the study. The three documents shall be provided to the participants who is able to freely give their consent without any pressure and fully understanding that no disadvantages are envisaged if they decide not to take part to the trial.

In the context of pandemic research, the Italian ISS Bioethics Working Group provided some remarks[57] considering the peculiar situation of vulnerability of Covid-19 patients. In fact, if the observational studies are not performed in a clinical centre, informed consent can be digitally collected in order to comply with the movement restrictions. In these cases, particular attention shall be paid to the fulfilment of the recruitment conditions and to possible (also transient) incapacity.

One, possibly positive, consequence on consent for both CT and its related personal data processing activities is the acceleration of the already ongoing process of virtualisation for CTs. Indeed, the rush towards forms of *eConsent* (e.g., *Bring Your Own Device -BYOD*[58]) or any other form of progressive virtualization of CTs[59] has been boosted by the need to close existing CTs or to establish quickly new ones.

For Covid-19 patients in clinical centres, the EMA distinguished three scenarios[60]. The first one concerns the oral consent, that is allowed, in presence of witness who can sign in place of the patient, if it is difficult to obtain a written one because of her specific conditions (e.g, isolation). The second one relies with the deferred consent when patient's conditions are critical, and it is possible to collect it at a later time[61]. In this case a written justification shall be provided by the clinicians to justify the choice. The third one recalls the case, where the renewal of consent is required, for example if there are some amendments to the protocol. According to this approach alternative procedure can be implemented to collect the informed consent only if properly justified by the pandemic situation itself. For instance, consent of Covid-19 patients who are incapacitated (e.g.,

[57] ISS, *COVID-19 Bioethics Working Group, Research ethics during the COVID-19 pandemic: observational and, in particular, epidemiological studies*, May 2020, available at: https://www.iss.it/documents/5430402/0/Rapporto+ISS+COVID-19+n.+47+EN.pdf/ef384c21-d41a-65f2-6e66-f7aace63c664?t=1602261818760 (last visited 14/4/2021).

[58] https://www-01.ibm.com/common/ssi/cgi-bin/ssialias?infotype=AN&subtype=CA&htmlfid=897/ENUS220-409&appname=USN.

[59] E.*g. Electronic Patient Reported Outcomes Measures (ePROs) ; Electronic Patient Reported Experiences Measures (ePREMs); Electronic Clinical Outcomes Assessment (eCOA); or Synthetic Control Arm.*

[60] EMA, *Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic. version 3*, 28 April 2020, Brussels, 2020.

[61] R. VAN DER GRAAF, MA. HOOGERWERF & M.C. DE VRIES. *The ethics of deferred consent in times of pandemics*. *Nat Med*, 26, 2020, 1328–1330, https://doi.org/10.1038/s41591-020-0999-9.

isolation) may be given orally by the trial participant (as in the case of Article 2 *sub* j of Directive 2001/20/EC) in the presence of an impartial witness[62].

Exemptions are instead envisaged only if stated by the law. This is the case where it is not possible to acquire the data subject's informed consent even from third parties, for data processing «*exclusively in connection with clinical trials and the compassionate use of medicinal products for human use with a view to the treatment and prevention of COVID-19*»[63].

Both for personal data processing and informed consent for research purposes, the general ethical legal framework allows for some derogations to promote the fights against the pandemic. These temporary and limited derogations are in any case framed in a solid architecture to protect fundamental rights. A clear example of them is the reach of art. 49.1. *sub* a and d GDPR, enabling «a transfer or a set of transfers of personal data to a third country or an international organisation» allowing for derogations but only on a temporary basis. Thus, the general architecture of the GDPR allows temporary derogations (e.g., to share trial data for vaccines) and not for longer-term post-emergency projects for which the normal rules would apply again.

6. Conclusions and further research

Before the Covid-19 epidemic broke out, the EU pharmaceutical / MD regulation was already experiencing a gradual blurring between medical research and practice, with the movements for early access[64] and 'learning' healthcare systems[65], along with the increasing scientific and regulatory importance of real-world data gathered from clinical practice monitoring[66]. This is challenging the conventional distinctions underpinning the regulatory framework, which has rigidly segregated research and therapy since (at least) the seminal Belmont Report[67]. Mostly focusing on accelerated approval, the regulatory responses to the Covid-19 pandemic have significantly accelerated this trend. A similar trend has interested the virtualization of trials and the process to acquire consent to the trial and to the related data processing. This may theoretically result in experimental uncertainties being transferred to the real-world treatments. This prompted pharmaceutical (and medical device) regulators to compensate for the lack of data comprehensiveness at the time of

[62] See above para 3.4. for the national implementations.

[63] ITALIAN DATA PROTECTION AUTHORITY, *Coronavirus and data protection*, available at: https://www.garanteprivacy.it/temi/coronavirus/faq (last visited 14/4/2021).

[64] S. PATIL, *Early access programs: Benefits, challenges, and key considerations for successful implementation*, in *Perspectives in Clinical Research*, 7(1), 2016, 4-8, doi:10.4103/2229-3485.173779.

[65] A. BUDRIONIS, J.G. BELLIKA, *The Learning Healthcare System: Where are we now? A systematic review*, in *Journal of Biomedical Informatics*, 64, 2016, 87-92, doi: 10.1016/j.jbi.2016.09.018.

[66] A. CAVE, X. KURZ, P. ARLETT, *Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe*, in *Clin. Pharmacol. Ther.*, 106, 2019, 36-39, doi: 10.1002/cpt.1426.

[67] N.E. KASS *et al.*, *The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight,* in *The Hastings Center Report*, 43(1), 2013, S4-S15, doi: 10.1002/hast.133; F.G. MILLER, *Revisiting the Belmont Report: The ethical significance of the distinction between clinical research and medical care*, in *Newsletter on Medicine and Philosophy*, 5(2), 2006, 10–14. The Belmont Report itself was, however, aware of the limitations of such a rigid divide. This is made clear by its recommendations concerning 'innovative' clinical practice, for which some kind of oversight was advised (https://www.hhs.gov/ohrp/regulations-and-policy/belmontreport/index.html, last access 14/4/2021).

approval with the strengthening of post-marketing monitoring, where observational research plays an increasing role. Although these processes need to be welcomed, we argued that these trends have deep implications for the data protection and for an effective informed consent of patients. Indeed, both data protection and informed consent regulation offer ways to reconcile simplified procedures and protection of patients' fundamental rights.

Once acknowledged that the pandemic has only accelerated processes already set in motions by the expansive use of big data in medical and epidemiological research and by the need to virtualize several moments of CTs it appears clear the need to further investigate how to reap all the benefits of the evolutions we mentioned without diluting the safeguards envisaged by the regulation and the general principles to protect human dignity and patients' autonomy without impairing the accelerating pace of scientific research.

From the above analysis emerged how the unfolding of flexible approaches, relaxing pragmatically some rules but accompanying them with safeguards (e.g., temporary nature of derogation, reinforcement of protective measures by way of PASs and PAESs, safeguards against function creeps) in the context of the pandemic is the track on which CTs and their interplay with personal data protection law will unfold in the close future. This magmatic and fast evolving scenario certainly deserves further research and a more comparative analysis for which we should not wait the end of the world pandemic.