Conducting Non-COVID-19 Clinical Trials during the Pandemic: Can Today's Learning Impact Framework Efficiency?

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Abstract

The COVID-19 pandemic has severely disrupted non-coronavirus clinical trials. In the case of life-threatening diseases, such as cancer, this is particularly dangerous, as treatment cannot simply be stopped. In the EU, guidelines for the management of ongoing studies were issued; however, national coordination is still lacking. This article aims to raise awareness on the struggle of managing ongoing clinical trials in the EU during the pandemic. The goals are to bring attention, from a legal and regulatory point of view to the difficulties faced by those involved in clinical research, and to critically position the current hurdles against the backdrop of the existing legal and ethical framework. We investigated the EU guidance and the national approaches of all EU/EEA Member States, and critically discussed selected issues. We argue that the crisis may be an opportunity to foresee meaningful changes in the EU clinical trials framework post-COVID-19.

Keywords

clinical trials —COVID-19 — data protection — legal and ethical framework for clinical research —patients' rights

1 Introduction

The world is combatting a pandemic.[1] The response to the threat differs per country,[2] although calls for a global approach were voiced.[3] After originating in China in December 2019, a total step-away from the normal followed in the rest of the world in March 2020: lockdowns, empty streets, working from home (for those whose work allows it), online education, and a never-ending stream of news under one single title, COVID-19. In Europe, confinement measures started to ease as of April,[4] however the pandemic is far from being over and many are warning about an

[1] World Health Organization, 'Coronavirus disease (COVID-19) outbreak - WHO announces COVID-19 outbreak a pandemic', http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic, 12 March 2020, retrieved 10 May 2020. See also Michael Safi, '100 days that changed the world', *The Guardian,* 8 April 2020, https://www.theguardian.com/world/ng-interactive/2020/apr/08/coronavirus-100-days-that-changed-the-world, retrieved 20 June 2020.

[2] Ryan Heath, 'A global guide to combating the coronavirus', *Politico*, 27 March 2020, https://www.politico.com/news/2020/03/27/coronavirus-global-guide-152375, retrieved 24 August 2020.

[3] United Nations, 'A global approach is the only way to fight COVID-19', 25 March 2020, https://www.unicef.org/press-releases/global-approach-only-way-fight-covid-19-un-says-it-launches-humanitarian-response, retrieved 24 August 2020.

[4] Adveith Nait, 'Europe's Lockdowns Are Easing after Weeks of Restrictions', *Bloomberg*, 20 April 2020, https://www.bloomberg.com/graphics/2020-europe-eases-lockdowns/, retrieved 9 May 2020.

impending second wave.[5] Sustained high pressure on healthcare systems is expected.[6] There is a rush to perform research in order to find a treatment and vaccine against the novel coronavirus,[7] and to inform the increasingly difficult choices that resource-limited healthcare systems will face.[8] The European Medicines Agency (EMA) expressed support for large international clinical trials to test promising treatments.[9] However, the pandemic heavily affected the conduct of research. Many universities and research institutions had to suspend all ongoing research activities unless proven impossible or urgent.[10] To prioritise COVID-19 studies and alleviate the pressure on the healthcare systems, clinical trials for other indications were halted, postponed, or disrupted.[11] In the UK, for example, studies were allowed to continue only if their suspension would have 'significant detrimental effects' on the ongoing care of participants, e.g., when no other treatment exists.[12] The disruption of clinical trials is particularly dangerous for oncology patients, for whom treatment cannot simply be stopped.[13]

Both the EU[14] and the US[15] issued guidance about the management of clinical trials during the crisis. National competent authorities in the EU followed suit, often providing divergent responses.[16] This article aims to raise awareness about the struggle to continue the conduct of

[5] Sam Jones, Kim Willsher, Daniel Boffey, Kate Connolly, 'Europe braces for second wave of coronavirus', *The Guardian*, 27 July 2020, https://www.theguardian.com/world/2020/jul/27/europe-braces-for-second-wave-of-coronavirus?fbclid=IwAR1wY6KaUDascKm8EVI55PraAx-2ovgVds2IYHwbQwVX9VurjFlkIcytt6A, retrieved 17 August 2020.

[6] European Commission, 'COVID-19: European Commission recommendations on health systems resilience', 30 March 2020.

[7] See e.g. *Bloomberg*, 'Coronavirus Vaccine Trials Advance in Race for Covid-19 Protection', , https://www.bloomberg.com/features/2020-coronavirus-drug-vaccine-status/, 16 April 2020, last updated 13 August 2020, retrieved 24 August 2020. See also COVID-19 TrialsTracker, run by researchers at the University of Oxford, http://covid19.trialstracker.net/.

[8] COVID-19 Clinical Research Coalition, 'Comment: Global coalition to accelerate COVID-19 clinical research in resource-limited settings', *The Lancet* (2) (2020) 219–221.

[9] European Medicines Agency (EMA), 'Update on treatments and vaccines against COVID-19 under development', https://www.ema.europa.eu/en/news/update-treatments-vaccines-against-covid-19-under-development, 30 March 2020, retrieved 17 August 2020.

[10] See e.g. the measures that were implemented by KU Leuven, with similar policies enacted internationally: KU Leuven, 'Frequently Asked Question: Research', https://www.kuleuven.be/coronavirus/english/FAQ, retrieved 3 April 2020. KU Leuven started to gradually restart research on human subjects as of 8 June 2020, see 'Frequently Asked Questions: Research on Human Subjects', https://www.kuleuven.be/coronavirus/english/FAQ#R-human-subjects-start, retrieved 5 July 2020.

[11] See e.g. Jacqui Thornton, 'Clinical trials suspended in UK to prioritize Covid-19 studies and free up staff', *The BMJ* 368 (2020); Heidi Ledford, 'Coronavirus shuts down trials of drugs for multiple other diseases', *Nature News*, 25 March 2020, https://www.nature.com/articles/d41586-020-00889-6, retrieved 3 April 2020; Adam Feuerstein, 'As Covid-19 spreads, disruptions to clinical trial and drug development accelerate', *Stat Plus*, 23 March 2020, https://www.statnews.com/2020/03/23/as-covid-19-spreads-disruptions-to-clinical-trial-and-drug-development-accelerate/, retrieved 3 April 2020.

[12] Thornton, *ibid*.

[13] Editorial, 'COVID-19: global consequences for oncology', *The Lancet* (21) (2020) 467. The authors discuss treatment of cancer patients in general. In particular, they argue that cancer therapy could be delayed in the cases of oncology patients who develop COVID-19, so as to prioritise treatment of the novel coronavirus. However, they stress that such decisions should be made on a case-by-case basis.

[14] European Medicines Agency (EMA), Good Clinical Practice Inspectors Working Group (GCP IWG), Clinical Trials Facilitation and Coordination Group (CTFG), Clinical Trials Expert Group (CTEG), European Commission, 'Guidance on the management of clinical trials during the COVID - 19 (Coronavirus) pandemic. Version 1', 20 March 2020. The EU guidance was updated twice, and further updates are likely, see Version 2 (27 March 2020) and Version 3 (28 April 2020). In the scope of this article, the focus will be on Version 3. In addition, on 25 March 2020, EMA issued 'Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials' (25 March 2020), which were put for public consultation until 25 April 2020. The final version was published on 26 June 2020, available at: https://www.ema.europa.eu/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en-0.pdf.

[15] US Food and Drug Administration (FDA), 'Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards' (2020).

[16] For an overview of publications for clinical trials in relation to COVID-19, see the document repository set up by the European Forum for Good Clinical Practice, https://efgcp-events.eu/Clinical-Trials-COVID19-Repository.php.

clinical trials in the EU during the pandemic. The goals are to bring attention from a legal and regulatory point of view, to the difficulties faced during the pandemic by those involved in clinical research, and to critically position the current hurdles against the backdrop of the existing legal framework. This contribution is based on the expanded knowledge of the European Organisation for Research and Treatment of Cancer (EORTC),[17] an academic sponsor of clinical trials with international regulatory and policy expertise.

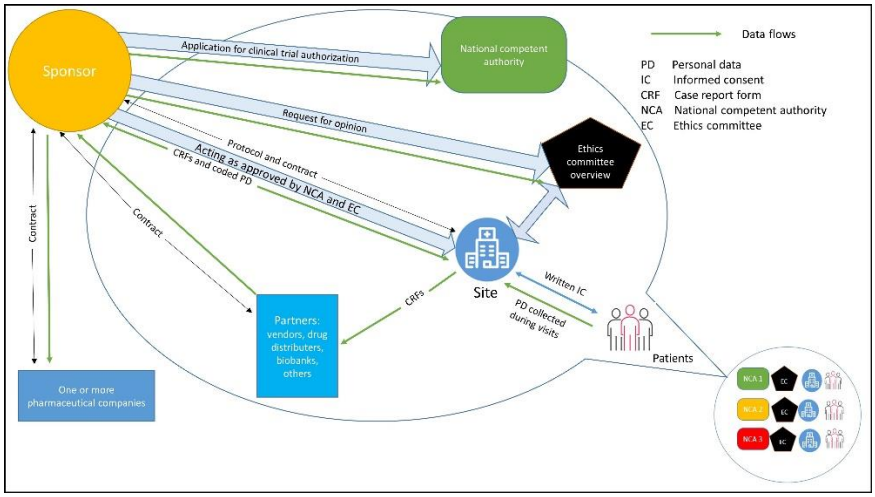

Figure 1 Pan-European (academic) clinical trial[18]

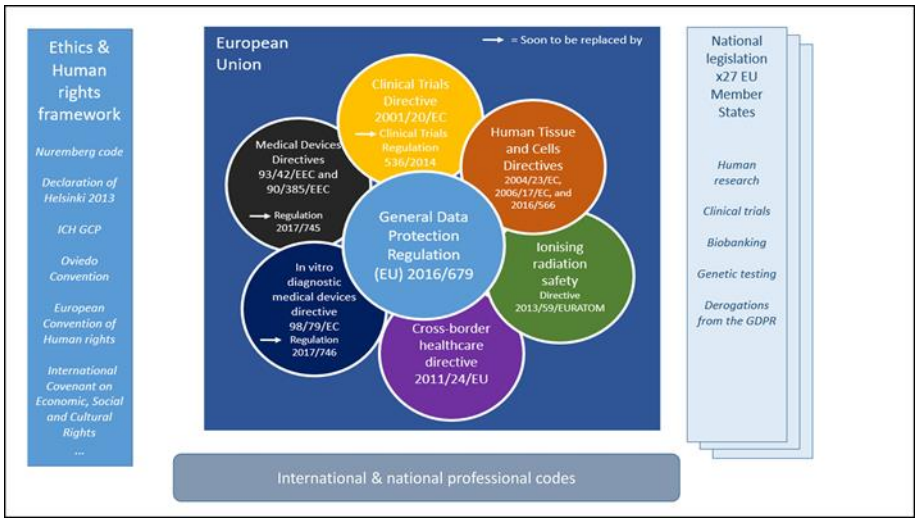

Figure 2 EU clinical research framework[19]

[17] EORTC is a pan-European non-profit clinical cancer research organisation. It develops, conducts, coordinates and stimulates high-quality translational and clinical trial research to improve the survival and quality of life of cancer patients. See more at https://www.eortc.org/.

[18] Fig. 2 builds on 'Data flows in clinical trials', in Kristof Van Quathem, 'Controlling personal data – the case of clinical trials', *P&I* (2009) 74-79. In case the trial is commercial, the pharmaceutical company will be the sponsor.

[19] The figure is a modified version of Fig. 1 in Anastassia Negrouk et al., 'Clinical Trials, Data Protection and Patient Empowerment in the Era of the New EU Regulations', *Public Health Genomics* 18(6) (2015) 386–395.

2 The EU Clinical Trials Framework

For this piece, it is relevant to provide a bird-eye view of the EU clinical research framework. Clinical trials are strictly regulated and subject to mandatory ethical oversight. By nature, they involve the collaboration of many different actors and the establishment of complex data flows (see Fig. 1). Currently, the conduct of clinical trials is governed by the EU Clinical Trial Directive (EC) 2001/20/EC (hereafter CTD) and by national legislation put in place to implement it. The Clinical Trials Regulation (EU) 536/2014 (hereafter CTR) is set to replace the CTD. Still, it will only come into application once the Clinical Trials Information System (CTIS) becomes fully functional, expected to happen in 2022.[20] In addition to the CTD, however, a large number of other legal and ethical instruments have to be complied with (see Fig. 2), and not all of them were designed with the goal to coordinate research per se. Although several reforms were enacted in recent years,[21] criticism regarding a continued lack of consideration for the complexities of modern research persists.[22] In general, the lack of harmonisation continues to be firmly placed among the biggest hurdles for scientific studies.[23] Additionally, the challenges introduced by the EU General Data Protection Regulation 2016/679 (hereafter GDPR) occupy a prominent part of the academic and institutional debates.[24] The European Data Protection Board (EDPB) and the European Commission have already started to address some of the most pertinent questions. Opinion 3/2019 (EDPB) and the Questions and Answers on the interplay between the CTR and the GDPR, issued by the European Commission, provide some clarity on key issues such as, *inter alia*, the distinction between informed consent for participation in research as an ethical requirement and informed consent as one of the legal bases for the processing of personal data,

[20] The timing depends on confirmation of full functionality of CTIS through an independent audit that is scheduled to commence in December 2020. CTR will become applicable six months after the European Commission publishes notice of this confirmation. For more information, see EMA, *Clinical Trial Regulation: Clinical Trials Information System development*, https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation#clinical-trials-information-system-development-section , retrieved 16 April 2020.

[21] See e.g. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, set to apply in May 2022 and Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, set originally to apply in May 2020. In light of the COVID-19 outbreak, the European Commission issued a proposal for postponement of the date of application of the Medical Devices Regulation to May 2021. At the time of writing of this article, the proposal is not yet adopted by the Parliament and Council. See European Commission, 'Proposal for a Regulation of the European Parliament and of the Council amending Regulation (EU) 2017/745 on medical devices as regards the dates of application of certain of its provisions', 3 April 2020, https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1585911322778&uri=COM:2020:144:FIN, retrieved 20 August 2020.

[22] Anastassia Negrouk, Denis Lacombe and Françoise Meunier, 'Diverging EU health regulations: The urgent need for coordination and convergence', *Journal of Cancer Policy* (17) (2018) 24–29.

[23] Snezana Djurisic et al., 'Barriers to the conduct of randomized clinical trials within all disease areas', *Trials* (18) (2017) 1–10.

[24] See e.g., Evert Ben van Veen, 'Observational health research in Europe: Understanding the General Data Protection Regulation and underlying debate', *European Journal of Cancer* (104) (2018) 70–80; Anastassia Negrouk and Denis Lacombe, 'Does GDPR harm or benefit research participants? An EORTC point of view', *The Lancet Oncology* (19) (2018) 1278–1280; Jacques Demotes-Mainard et al., 'How the new European data protection regulation affects clinical research and recommendations?', *Therapie* (74) (2019) 31–42; Marcelo Ienca et al. 'How the General Data Protection Regulation changes the rules for scientific research. Study for the European Parliament Panel for the Future of Science and Technology (STOA)', July 2019, available at: http://www.europarl.europa.eu/thinktank/en/document.html?reference=EPRS_STU(2019)634447; Tim Minssen, Neethu Rajam, Marcel Bogers, 'Clinical trial data transparency and GDPR compliance: Implications for data sharing and open innovation', *Science and Public Policy* (2020) scaa014 1–11.

and the distinction between primary and secondary use of clinical trial data.[25] However, a high degree of uncertainty still abides, as many questions remain unresolved.[26]

3 Management of Clinical Trials during the COVID-19 Pandemic

As shown above, the clinical trials framework is complex to navigate, and weaknesses may become more visible when put to test by the pandemic. Many implications for ongoing clinical trials are expected.[27] Sponsors are required to conduct a risk assessment of (1) COVID-19 potentially affecting trial participants directly, and (2) COVID-19 related measures affecting the trial conduct.[28] All available guidance puts patient safety first, stating that it must always prevail above preserving the quality of the trial data,[29] in line with Good Clinical Practice (GCP).[30] In its Points to consider on implications of COVID-19 on methodological aspects of ongoing clinical trials, EMA supports the continuance of ongoing clinical trials by stating that 'it is an ethical mandate to proceed with a trial that has been started so that the efforts taken by study participants and physicians can benefit drug development and inform patient care'.[31] This statement is further nuanced by the recommendation to sponsors to integrate all available knowledge from the ethical, the medical, and the methodological perspective into decision making about the future conduct of a trial while carefully considering advice from regulatory and healthcare authorities responsible for study participant and employee safety.[32]

In the interest of completion, it should be noted that at EMA's focus[33] are registration clinical trials[34] performed by the pharmaceutical industry, i.e., trials designed to fulfil regulatory requirements (e.g., to demonstrate that a new medicine has a positive risk/ benefit balance). Commercial clinical trials account for more than 70% of all studies conducted in Europe.[35] However, it is important that so-called applied research - also described as treatment optimisation[36] - is considered as well. Applied research can be defined as 'optimizing the way treatments are utilized in real-world conditions through the conduct of studies',[37] set up to answer research questions such as how to combine new with existing treatments, how well the

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[25] EDPB, 'Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR)'; European Commission. DG Health and Food Safety, 'Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation (2019)'.

[26] European Data Protection Supervisor (EDPS), 'A Preliminary Opinion on data protection and scientific research', 6 January 2020. In its opinion, EDPS called for intensifying the dialogue between data protection authorities and ethical review boards, EU codes of conduct for scientific research and a closer alignment between the EU research framework and data protection standards.

[27] EMA Points to consider, p. 2, *supra* note 14.

[28] *Ibid*. p. 3.

[29] EU guidance (Version 3), p. 7; EMA Points to consider, *ibid*., p. 2,; all national guidelines.

[30] Principle 2.3, International Conference on Harmonisation of Good Clinical Practice (ICH GCP) E6 R2.

[31] EMA Points to consider, p. 2, *supra* note 14.

[32] *Ibid*., p. 2.

[33] European Medicines Agency, 'Clinical trials in human medicines', https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials-human-medicines, retrieved 24 August 2020.

[34] Denis Lacombe et al., 'Late translational research: putting forward a new model for developing new anti-cancer treatments that addresses the needs of patients and society', *Molecular Oncology* 13(3) (2019) 558–566 (2019).

[35] European Medicines Agency, 'EudraCT Public Web Report for July 2020', 1 August 2020, https://eudract.ema.europa.eu/docs/statistics/EudraCT_Statistics_2020/EudraCT_Public_Report_Stats_March_2020.pdf, retrieved 17 August 2020.

[36] Emmanuelle Kempf et al., '"Mind the gap" between the development of therapeutic innovations and the clinical practice in oncology: A proposal of the European Organisation for Research and Treatment of Cancer (EORTC) to optimise cancer clinical research', *European Journal of Cancer* (86) (2017) 143–149; Denis Lacombe et al., 'Establishing treatment optimisation as part of personalised medicine development', *European Journal of Cancer* (113) (2019) 96–97.

[37] Robbe Saesen et al., 'Views of European Drug Development Stakeholders on Treatment Optimization and Its Potential for Use in Decision-Making', *Frontiers in Pharmacology* (11) (2020) 1–18.

new intervention performs compared to alternative treatments, etc.[38] Such patient-centred questions are currently addressed only during the post-market approval stage in a non-systematic and voluntary way by academic researchers and not-for-profit research organisations,[39] such as the EORTC.

3.1 *Patient Safety and Integrity: What Are We Contemplating?*

Oncology patients are among the high-risk groups for COVID-19, due to their underlying illness and because cancer therapies often suppress the immune system.[40] Whereas the decision to suspend studies with healthy volunteers may seem clear-cut, as it will prevent the risk of coronavirus infection, more complex ethical considerations permeate decision-making in cancer clinical trials. To illustrate, it is unethical to stop treatment if trial participants are benefitting from it.[41] The EU guidance stresses that if a trial is halted, even temporarily, this may compromise the well-being and best interests of patients.[42] Furthermore, a temporary halt may eventually lead to study termination. This poses an ethical dilemma also with respect to patients for whom trial continuation is not relevant anymore, e.g., participants who were part of the study before the pandemic. Among the main reasons that most patients agree to participate is the wish to help medical research and future patients with the same condition.[43] The expected benefit for society is the justification for the risks that patients face. Hence, a premature/unjustified trial termination would ruin the chance for participants' reward.[44]

Having the patients' safety and well-being front and centre, several possibilities regarding what to do in practice emerge. When unable to leave their homes due to confinement measures, the patient's physical visits to the hospitals may be converted into phone or video calls. If the patient is prevented from reaching the investigational site, laboratory tests and imaging could be performed at a local laboratory, located closer to the patient's home. In the case of drug trials, the Investigational Medicinal Product (IMP)[45] may be distributed directly to the patient, if self-administering is possible. The EU guidance provides a list of measures that could be considered for ongoing trials during the pandemic.[46] Fig. 3 illustrates how some of these changes would affect normal study conduct.

3.2 *How to Address Continuity during Disruption?*

To implement the examples listed above, the clinical trial sponsor must strictly observe the legal and ethical rules for research, and employ a risk-based approach[47] to ensure continuity. The study protocol is the document that should be adhered to in order to secure compliance with the

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[38] Kempf et al., *supra* note 36; Denis Lacombe et al., 'Precision Medicine: From "Omics" to Economics towards Data-Driven Healthcare - Time for European Transformation', *Biomedicine Hub* (2) (2017) 1–10; Denis Lacombe et al., 'Moving forward from drug-centred to patient-centred research: A white paper initiated by EORTC and developed together with the BioMed Alliance members', *European Respiratory Journal* (53) (2019) 1–6; Saesen et al., *supra* note 37.

[39] *Supra* note 36; s*upra* note 37.

[40] Editorial, *supra* note 13.

[41] This could be seen as a violation of the biomedical ethics principles of beneficence and non-maleficence.

[42] EU guidance (Version 3), p. 6, *supra* note 14.

[43] M. Lièvre et al., 'Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility', *BMJ* (322) (2001) 603–605.

[44] *Ibid*., p. 604.

[45] Article 2(d) of the CTD.

[46] Changes may include: conversion of physical visits into phone or video visits, postponement or complete cancellation of visits, interruption or slowing down of recruitment of new trial participants, extension of the duration of the trial, postponement of trials or of activation of sites, closing of sites, transfer of patients to investigational sites away from risk zones, or closer to their home (if unavoidable), initiation of new trial sites (if no other solutions exists for the participant), temporary halt at some or all trial sites, local laboratory to perform critical laboratory tests, in case the patient cannot reach the site. See EU guidance (Version 3), p. 4-5, *supra* note 14.

[47] EMA Points to consider, *supra* note 14, p. 2.

rules and regulations.[48] Any changes made to it – such as delivering the IMP directly to the patient - would constitute protocol deviations,[49] or would require prior approval by the relevant regulatory bodies or ethics committees. All changes should be balanced and proportionate, and the legitimate interest of trial sites in avoiding time and staffing burden during the pandemic should be taken into account. Besides, measures should be documented with a justification how they will ensure patient safety, data integrity, and protection of personal data.[50]

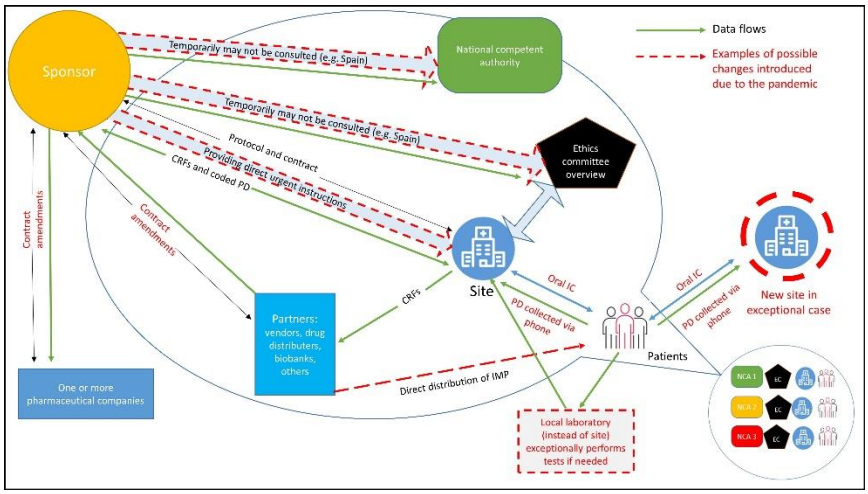

Figure 3 Management of pan-European (academic) clinical trials during the COVID-19 pandemic

3.2.1 Communication with Authorities

Following risk identification and evaluation, it is up to the sponsor to decide which risks to reduce and how.[51] Under the CTD, changes to the conduct of a clinical trial can be made following two procedures.[52] First, the sponsor has the right to introduce two types of amendments, substantial and non-substantial. Substantial amendments (SA) are changes that are likely to impact the safety of patients, change the interpretation of the scientific documents, or are otherwise significant.[53] SAs must be approved by the national competent authorities (NCAs) and ethics committees (ECs) of the Member States concerned. Non-substantial amendments (non-SAs) constitute all other amendments that do not fall under the definition for SA. Although sponsors are not obliged to notify non-SAs, they must keep a record of all such measures.[54] The second procedure consists of urgent safety measures (USMs). These are needed to protect patients against immediate hazard

[48] Article 2(h) of the CTD defines protocol as 'a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments'. See also Ravindra Bhaskar Ghooi et al., 'Assessment and classification of protocol deviations', *Perspect. Clin. Res.* 7(3) (2016) 132-136.

[49] A protocol deviation is defined by as 'any change, divergence, or departure from the study design or procedures defined in the protocol', see ICH E3 Q&A R1. Furthermore, the Q&A also describes important protocol deviations as 'a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being'.

[50] EU Guidance (Version 3), p. 6, *supra* note 14.

[51] Principle 5 ICH GCP E6 R2.

[52] Article 10 of the CTD. See also Communication from the Commission, 'Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1) 2010/C 82/01', https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52010XC0330%2801%29.

[53] Article 10(a) of the CTD.

[54] See CT-1 2010/C 82/01, Art. 3.6.

emerging from a new event.[55] USMs may be introduced without prior notification, but the sponsor is obliged to inform *ex post* the NCAs and the ECs. There is no one-size-fits-all answer as to which of the two procedures is best suited to address the various risks introduced by the ongoing pandemic. The immediate hazard for one patient might be completely different than for another, depending on their location, guidance from the NCA, the impact of the pandemic on the hospital, etc. Moreover, while in theory USMs may seem easier to execute, it could be argued that in practice the administrative strain is equal to the one associated with SAs. Following the implementation of an USM, authorities have to be informed as soon as possible via email or phone.[56]

The EU guidance on the management of clinical trials during the COVID-19 pandemic addresses communication with authorities, among several other key topics.[57] Priority must be given to clinical trial applications for the treatment or prevention of COVID-19 and to SA applications to existing clinical trials necessary as a result of the pandemic. Regarding ongoing trials, the guidance discusses three scenarios. First, USMs may be taken without prior notification when immediate actions are required to protect patients against immediate hazard. Second, SA applications must be submitted if changes are likely to affect the safety and well-being of trial participants but said changes do not require immediate action. Finally, the sponsor is expected to notify NCAs and ethics committees as soon as possible about changes unrelated to patient safety.[58] Over-reporting is discouraged, and in case of SAs and USMs, a single submission by the sponsor with an aggregated list of changes is acceptable. [59]

National guidelines, although similar in spirit, have their own specificities, which take priority over the EU's recommendations.[60] It is interesting to note that the last version of the EU guidance shows a will to address the shortcoming that the lack of a coordinated approach presents for pan-European research. Namely, whereas Version 2 stated that it 'aims to serve as an EU-level harmonized set of recommendations', Version 3 uses much stronger language, namely 'Member States are encouraged to implement the harmonised guidance to the *maximum possible extent* [our emphasis] to mitigate and slow down the disruption of clinical research in Europe during the public health crisis'.

To illustrate just the tip of the ongoing complexity,[61] we will use the direct delivery of IMP as an example. Normally, delivery of medicines occurs at the hospital site under the responsibility of a pharmacist or a physician. During the pandemic, the EU guidance foresees the possibility that IMP is shipped from the site directly to patients' homes.[62] It further specifies that patients' personal data should not be provided to the sponsor, hence no direct distribution from the sponsor is possible. However, the sponsor should bear the cost of the shipment and should provide logistical assistance to the trial site. Furthermore, the guidance provides that in exceptional cases, the IMP may be shipped to the patient by a third party located in the EU/EEA, contracted by the sponsor to store and distributed IMP to the sites (distributor).

All countries who issued guidance agree that IMP can be delivered directly to the patient. However, NCAs are not necessarily in agreement *from where* it can be shipped. The prevalent

[55] Article 10(b) of the CTD.
[56] See CT-1 2010/C 82/01, Art. 3.9.
[57] Other topics are initiating new trials, changes to ongoing trials (*supra* note 50), safety reporting, risk assessment, agreement with and communication between sponsors, trial sites and trial participants, changes to informed consent, changes in the distribution of the IMPs, changes in the distribution of in vitro diagnostic and medical devices, changes to monitoring, changes to auditing, protocol deviations, reimbursement of exceptional expenses, initiation of new trials aiming to test new treatments for COVID-19. See EU guidance (Version 3), *supra* note 14.
[58] *Ibid.*, pp. 8-9.
[59] *Ibid.*, p. 3.
[60] *Ibid.*, p. 1.
[61] For the illustrative purposes of this article, a limited overview of national guidelines will be provided.
[62] EU guidance (Verison 3), pp. 10-14, *supra* note 14.

opinion is that direct distribution can occur only from the site (e.g., Belgium,[63] France,[64] Italy[65]). However, Denmark[66] and the United Kingdom[67] allow the sponsor to perform it directly, without involving the investigator or hospital pharmacies. While this may already be seen as introducing a degree of complexity for pan-European clinical trials, the situation is further complicated by the question *how* this specific change should be reported. Should it be treated as a non-substantial amendment, a SA, a USM? The EU guidance provides a concrete recommendation for the cases when a distributor delivers the IMP: a SA, or an USM (when exceptional emergency situation requires the change). Different countries have chosen varying approaches (see Table 1 for a complete overview of EU/EEA). Belgium says this is non-SA,[68] France prescribes USM, followed by a submission of SA for authorisation to the French NCA and concerned EC within 15 days of implementation of the measure, and Italy sees this as SA.[69] In the case of Denmark, no notification is necessary if the IMP is shipped from the site, but an USM is required if the sponsor sends the drug out directly.[70] Finally, the UK NCA prescribes that direct delivery is non-SA, however oral consent is needed in order to provide the patient's address to the sponsor.[71]

Looking beyond the IMP example, some countries apply a more generalised approach to COVID-19 related measures (Slovakia,[72] for instance, recommends that changes due to the pandemic that will have a significant impact on the risk-benefit balance of the trial, are listed as USM, Italy[73] – that all should be addressed as notified SA without need for evaluation), while others do not (e.g., France,[74] UK,[75] Denmark).[76]

Having thus provided a flavour of the diverging rules, it must be further noted that the guidance on how to notify is complicated in a three-fold way. First, as shown above, each country may assess differently the same change, consequently, different reporting will be prescribed. Second, within one single country, the approaches for addressing various risks stemming from COVID-19 could be weighted differently, and numerous reports (as USMs or SAs) may be required. Finally, each individual site has its own constraints. Due to different hospital capacities and priorities, some of the considered measures (e.g. whether to stop recruitment, or not; whether to implement video calls instead of visits) may differ from one site to another. Henceforth, filing clear SAs or USMs may be even more complicated than initially foreseen.

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[63] Federal Agency for Medicines and Health Products (FAMHP), 'Addendum to the Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic', 29 April 2020, https://www.afmps.be/sites/default/files/content/national_guidance_corona_20200429c_clean.pdf, retrieved 18 August 2020.

[64] L'Agence nationale de sécurité du médicament et des produits de santé (ANSM), 'Covid 19 - Ongoing clinical trials', last updated 20 May 2020, https://www.ansm.sante.fr/Activites/Essais-cliniques/COVID-19-Ongoing-clinical-trials/(offset)/1, retrieved 20 August 2020.

[65] Agenzia Italiana del Farmaco (AIFA), 'Gestione degli studi clinici in Italia in corso di emergenza COVID-19 (coronavirus disease 19), Versione 2 del 7 aprile 2020', https://www.aifa.gov.it/documents/20142/871583/Comunicato_gestione_studi_clinici_in_emergenza_COVID-19_07.04.2020.pdf/34d8c749-a329-990b-9ce3-2ea044cecc80, retrieved 20 August 2020.

[66] Danish Medicines Agency, 2020, 'Extraordinary measures for clinical trials due to COVID-19', https://laegemiddelstyrelsen.dk/en/news/2020/extraordinary-measures-for-clinical-trials-due-to-covid-19/~/media/259AC11DD4CB438F9966E0C06396E47A.ashx, 24 April 2020, last updated 2 July 2020 (Version 6.0), retrieved 24 August 2020. The option to deliver IMP directly is valid until 1 December 2020, an extension is possible.

[67] Medicines and Healthcare products Regulatory Agency (MHRA), 'Managing clinical trials during Coronavirus (COVID-19)', https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19, 19 March 2020, last updated 21 May 2020, retrieved 24 August 2020.

[68] *Supra* note 63.

[69] *Supra* note 65.

[70] *Supra* note 66.

[71] *Supra* note 67.

[72] SUKL, 'Mimoriadne Opatrenia Pre Klinické Skúšania v Dôsledku Covid-19', https://www.sukl.sk/hlavna-stranka/slovenska-verzia/klinicke-skusanie-liekov/pokyny/mimoriadne-opatrenia-pre-klinicke-skusania-v-dosledku-covid-19?page_id=5303, 16 March 2020, last updated 29 May 2020, retrieved 24 August 2020.

[73] *Supra* note 65.

[74] *Supra* note 64.

[75] *Supra* note 67.

[76] *Supr*a note 66.

Based on a comparison of all available national guidance documents, the authors conclude that Spain's approach to the emergency is the most pragmatic one. According to the Spanish guidance, all exceptional measures taken by the sponsor do not require approval on a case-by-case basis as SAs.[77] In the four months following the date on which the pandemic is considered to have ended in Spain, a report of the exceptional measures taken for each trial must be communicated to the NCA and the ethics committee for drug research.[78] While in the beginning of April, Spain was the only country following such an approach, by May 2020, Denmark[79] and Belgium[80] had changed their guidelines in a similar vein.

3.2.2 Communication with Patients

Informed consent (IC) is the core ethical requirement for the conduct of clinical research,[81] put in place to protect the fundamental rights to human dignity and integrity of individuals. Pursuant to the CTD and without prejudice to national provisions, IC must be obtained in written form after the trial participant has been informed about the nature, significance, implications, and risks of the clinical trial. Oral consent is acceptable only in exceptional cases and must be obtained in the presence of at least one witness.[82] Discussions about the use of electronic methods for seeking, confirming, and documenting IC (eConsent) are ongoing, with evidence suggesting that eConsent may improve patients' understanding of some aspects of the study.[83] In the UK, for example, electronic methods for documenting consent are acceptable and can be considered to be in writing. [84] However, eConsent is not yet widely used due to concerns about security/confidentiality, lack of well-established processes, and global acceptance of e-signatures.[85]

In order to implement the urgent changes to the trial conduct, the EU acknowledges that there may be a need to again obtain consent for the participation of trial participants who have already been included in the trial.[86] The guidance supports alternative means of obtaining re-consents, such as oral consent via phone, supplemented with e-mail confirmation. However, it also stresses that any consent obtained in this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity.[87] Moreover, they accept the use of eConsent, but only when already established as a standard practice under national legislation.

Most of the national guidance examples follow the EU's line. Hungary explicitly forbids eConsent, and provides no possibility to diverge from the national law during the emergency.[88] The Netherlands allows consent to be deferred as an exception when patients are unable to

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[77] Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), 'Medidas excepcionales aplicables a los ensayos clínicos y estudios observacionales para gestionar los problemas derivados de la emergencia por COVID-19', https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/2020-medicamentosusohumano-3/medidas-excepcionales-aplicables-a-los-ensayos-clinicos-para-gestionar-los-problemas-derivados-de-la-emergencia-por-covid-19/, last updated 1 July 2020, 24 August 2020.

[78] *Ibid.*

[79] *Supra* note 66.

[80] *Supra* note 63.

[81] Article 3 of the CTD, Principle 1.28 ICH GCP E6 R2.

[82] Article 3(d) of the CTD.

[83] Erin Rothwell et al., 'A randomized controlled trial of an electronic informed consent process', *Journal of Empirical Research on Human Research Ethics* 9(5) (2014) 1-7.

[84] The UK Health Research Authority (HRA) & The Medicines and Healthcare products Regulatory Agency (MHRA), 'Joint statement on seeking consent by electronic methods', 2018, https://www.hra.nhs.uk/about-us/news-updates/hra-and-mhra-publish-joint-statement-seeking-and-documenting-consent-using-electronic-methods-econsent/, retrieved 20 August 2020.

[85] Jennifer Lentz et al., 'Paving the way to a more effective informed consent process: Recommendations from the Clinical Trials Transformation Initiative', *Contemporary Clinical Trials* (49) (2016) 65-69.

[86] EU guidance (Version 3), p. 11, *supra* note 14.

[87] *Ibid.*

[88] The National Institute of Pharmacy and Nutrition (OGYÉI), 'Information on the continuity of clinical trials under COVID-19 (coronavirus)', 5 May 2020, https://ogyei.gov.hu/tajekoztatas_klinikai_vizsgalatok_folytonossagarol_a_covid_19_koronavirus_alatt__20200505, retrieved 24 August 2020.

provide it, but only following a mandatory approval by the ethics committee.[89] As it is not clear, however, whether all ethics committees are able to continue their work remotely, such a condition could be an obstacle to trial continuity. Denmark specifically emphasises the need to strengthen communication with patients during the pandemic, as their increased levels of anxiety and concern are to be expected.[90]

3.3 *What about Data Protection?*

Both the EDPB and the European Commission affirmed recently that the requirement for IC pursuant to the clinical trials legislation must not be confused with consent as one of the possible legal bases for processing of personal data under the GDPR.[91] Moreover, in the context of clinical research, they encouraged the use of other legal bases, finding that it may be hard to satisfy the requirement that consent is 'freely given'.[92]

However, confusion between the two types of consent still persists,[93] and an example may be found in the EU COVID-19 related guidance. The guidance prescribes that patients should provide oral consent for the provision of their contact details to a distributor (in case of direct IMP delivery).[94] The prescription essentially means that in this specific case, consent is imposed as the lawful ground for the processing of personal data (patients' names and addresses). In our view, a better suited legal basis could be Art. 9(2)(c) of the GDPR, 'processing necessary to protect the vital interests of the data subjects'. This provision applies to the processing of sensitive data. Distributors know the type of diseases investigated in the trial, hence they can infer sensitive health data, even though they will only be provided with non-sensitive data (patients' names and addresses). In principle, vital interest should be used only where the processing cannot be manifestly based on another legal basis[95] and when data subjects are incapable of giving consent.[96] However, Recital 46 also states that 'some types of processing may serve both important grounds of public interest and the vital interests of the data subject as for instance when processing is necessary (…) in situations of humanitarian emergencies, in particular in situations of natural and man-made disasters'. The current pandemic can be seen as such a humanitarian emergency.

Following from this, it is relevant to pay attention to any discussions on the interplay of data protection and clinical research rules that might be ongoing during the pandemic.

The EU guidance discusses data protection in the context of emergency changes to the conduct of clinical research monitoring. Examples include converting site visits into phone visits, and adapting the on-site monitoring plan when it is impossible to follow,[97] or supplementing it with centralised monitoring, if possible and meaningful. So-called remote source data verification

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[89] Central Committee on Research Involving Human Subjects, 'Recommendations for the conduct of clinical research at the time of restrictive measures due to the coronavirus', https://english.ccmo.nl/publications/publications/2020/04/28/recommendations-for-the-conduct-of-clinical-research-at-the-time-of-restrictive-measures-due-to-the-coronavirus, last update 25 June 2020, retrieved 24 August 2020.

[90] *Supra* note 66.

[91] EDPB Opinion 3/2019, p. 5, European Commission Questions and Answers, Question 4, *supra* note 25.

[92] EDPB Opinion, *ibid.*, p.. 6, European Commission, *ibid.*

[93] For instance, at the national level, several countries either oblige the data controller to use consent as the legal basis for the processing of data in the clinical trial context or impose substantial obstacles to the health researcher who does not use consent. This is the case, e.g., in Germany (see Section 40(1)(3)c) of the German Medicinal Product Law), and Ireland. See Niamh Clarke et al., 'GDPR: an impediment to research?', *Irish Journal of Medical Science* 188(4) (2019) 1129–1135.

[94] EU guidance (Version 3), p. 13, *supra* note 14.

[95] Recital 46 of the GDPR.

[96] Art. 9(2)(c) GDPR.

[97] In clinical trials, monitoring is "the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)", see principle 1.38 ICH GCP E6 R2. The monitoring plan is a document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial (Principle 1.64 ICH GCP E6 R2).

(SDV)[98] (e.g., providing the sponsor with electronic copies of medical records or remote access to electronic medical records) is also discussed. Whereas Version 2 of the guidance simply asserted that remote SDV is not allowed in most Member States as it introduces the risk of infringement of participants' rights, Version 3 provides more practical guidance. Remote SDV may be considered only during the pandemic, and only for a limited number of trials, namely (1) trials involving COVID-19 treatment or prevention, or (2) pivotal trials investigating serious or life-threatening conditions with no satisfactory treatment option.[99] It is up to the principle investigators to determine whether the situation at their sites allows for any of the options for remote SDV listed in the guidance.[100] From a practical standpoint, remote SDV is more burdensome, as it requires an update of the monitoring plan and other relevant documents, staff training, and study site resource (already under strain during the pandemic). When Version 2 was issued, only the UK supported remote SDV. At the moment of writing this contribution, eight countries allow it.[101] The focus remains on respecting confidentiality, adequate documentation, and upholding security.

An important question pertains to what data protection authorities contribute to the discussion. All have been active, issuing timely guidance. The EDPB, in particular, adopted several relevant documents, including guidance on the processing of health data for the purpose of scientific research in the context of the pandemic.[102] Naturally, the focus is on research efforts against COVID-19, and especially on contact tracing apps,[103] hence detailed analysis of the documents is outside the scope of this contribution. Nevertheless, the information they provide is useful in the context of ongoing non-COVID-19 related trials. It was repeatedly affirmed that data protection rules do not hinder measures taken in the fight against the pandemic.[104] However, it remains of utmost importance to preserve data protection principles and maintain transparency, data quality, and trust.[105] Concerning transparency and the information obligation (Art. 13 and 14 GDPR), it is useful to briefly go back to the EU clinical trials guidance requirement that oral consent should be sought in order to provide contact details to a distributor for the direct delivery of IMP. It could also be argued that there is confusion between the GDPR information obligation and consent, whereby consent as a legal basis for data processing is prescribed in cases where transparency would suffice.

At the national level, DPAs' guidelines prioritise topics similar to the ones considered at EU level,[106] namely the tracking of location data, processing of (health) data by public authorities,

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[98] Source data is all information in original records and certified copies of original records of original findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of a trial. (1.51 ICH GCP E6 R2). Source data verification is the process of ensuring that the data reported for analyses accurately reflect the source data at the clinical trial site. See Nicole Sheetz et al., 'Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials', *Therapeutic Innovation & Regulatory Science* 48(6) (2014) 671–680.

[99] EU guidance, p. 16, *supra* note 14.

[100] *Ibid.*

[101] Austria, Denmark, Italy, Latvia, The Netherlands, Norway, Poland, and Spain. It is not as clear with respect to Ireland, as the guidance states that remote SDV is '*generally* not acceptable'. See Table 1 for a complete overview.

[102] European Data Protection Board (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', adopted 21 April 2020.

[103] See EDPB 'Guidelines 04/2020 on the use of location data and contact tracing tools in the context of the COVID-19 outbreak', adopted 21 April 2020; See also the EU toolbox for the use of mobile applications for contact tracing and warning, developed by EU Member States, supported by the Commission, and part of a common coordinated approach to support the gradual lifting of confinement measureshttps://ec.europa.eu/commission/presscorner/detail/en/ip_20_670. Relevant here is *Commission Recommendation (EU) 2020/518 of 8 April 2020 on a common Union toolbox for the use of technology and data to combat and exit from the COVID-19 crisis,* https://ec.europa.eu/commission/presscorner/detail/en/ip_20_626, retrieved 20 August 2020.

[104] EDPB, 'Statement on the processing of personal data in the context of the COVID-19 outbreak', adopted 19 March 2020*;* EDPS, 'Statement on Monitoring spread of COVID-19', adopted 25 March 2020.

[105] *Ibid.*

[106] See an overview by Christina Etteldorf, 'EU Member State Data Protection Authorities Deal with COVID-19: An Overview', *European Data Protection Law Review* 6(2) (2020), 265-280. See also the repository of data protection

employment and data protection implications in the home office, (unsolicited) government contact via electronic communication, notifications about the infection of a person. As observed by Etteldorf, however, the views of DPAs often diverge.[107]

Finally, it remains to be seen whether EDPB, EDPS, and the DPAs would more specifically address the conduct of non-COVID-19-related research during the emergency. Nevertheless, the current state of affairs already indicates the need for strengthened dialogue between the different institutions that have a role in the regulation of clinical trials.

4 Conclusion

In this article, we have outlined a part of the challenges that clinical research faces during the pandemic. As observed, the current hurdles primarily have their basis in the pre-existing legal and regulatory frameworks, and the ongoing dialogue (or lack thereof) between competent authorities. The contribution aimed to raise awareness by systematising discrepancies, and to open up a discussion that is broader than the current times. Questions emerge, inter alia: Looking ahead, what will the crisis teach us, and what lasting changes it may bring? Could the broader acceptance of remote/decentralised clinical trials be foreseen? [108] Or a broader implementation of eConsent? What about the further harmonisation of the EU clinical research framework?[109] After all, the most recent EMA 2025 strategy, which was worked out in the three years preceding the pandemic, addresses the need for 'advancing international harmonization'. [110] Dis-harmonisation in times of a crisis is not merely a burden or a pitfall but introduces dangers in itself. The pandemic reduced the capacity for 'business as usual' worldwide, with employees working remotely, balancing work and family, with limited access to appropriate technical and other infrastructure. Lockdowns were introduced to avoid saturating the hospitals. Similarly, the diversity of conflicting measures may require 'confinement' in future to prevent saturating those involved in research. All organisations are expected to have a business continuity plan (BCP) to prepare for the unexpected disruptions in their activities. It is worth pondering the introduction of 'clinical trials BCP' for the EU, which would allow rapid decision-making in a harmonised way in times of crisis. The evolution throughout the different versions of the EU guidance provides grounds for optimism, as it shows a pull in the direction of more coordination.

Further studies – from a legal, ethical, and regulatory perspective – are required to zoom in on each of the questions posed, and the discussion for potential strengthened harmonisation is the prerogative of EMA, the European Commission and the EU Member States. In a recent piece for *The Guardian*, Peter C Baker ponders that:

> it's not just the size and speed of what is happening that's dizzying. It's the fact that we have grown accustomed to hearing that democracies are incapable of making big moves

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resources, compiled by The Free University of Brussels (VUB) https://lsts.research.vub.be/en/data-protection-law-and-the-covid-19-outbreak.

[107] Etteldorf, *ibid.*

[108] See e.g., Alison Holland, 'The Covid-19 crisis is the right time to adopt decentralized clinical trials', *MedCityNews*, 19 March 2020, https://medcitynews.com/2020/03/the-covid-19-crisis-is-the-right-time-to-adopt-decentralized-clinical-trials/, retrieved 1 June 2020.
There is no framework for remote clinical trials exists at EU level, but both EMA and FDA have shown support for their future enabling, see EMA, 2020, *EMA Regulatory Science to 2025. Strategic reflection*, https://www.ema.europa.eu/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf; FDA, 'Statement by FDA Commissioner Scott Gottlieb, M.D., on new strategies to modernize clinical trials to advance precision medicine, patient protections and more efficient product development', https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-strategies-modernize-clinical-trials-advance, retrieved 21 March 2020.

[109] Negrouk et al., *supra* note 22.

[110] Philip A. Hines et al., 'A future for regulatory science in the European Union: The European Medicines Agency's strategy', *Nature Reviews Drug Discovery* 19(5) (2020) 293-294, retrieved 24 August 2020.

> like this quickly, or at all. But here we are. Any glance at history reveals that crises and disasters have continually set the stage for change, often for the better.[111]

Could we envisage a change for the better for clinical research as well?[112]

[111] Peter C. Baker, '"We can't go back to normal": How will coronavirus change the world?', *The Guardian*, 21 March 2020, https://www.theguardian.com/world/2020/mar/31/how-will-the-world-emerge-from-the-coronavirus-crisis, retrieved 24 August 2020.

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Table 1 Overview of EU and national approaches (EU/EEA countries) on selected COVID-19 related measures

EU and national guidance	**General rule applicable to COVID-19 related measures**	**Direct delivery of IMP**	**Remote SDV**
EU guidance	Single submission (both USMs and SAs) by the same sponsor is acceptable and encouraged. Over-reporting is discouraged.	Yes, from site to patients, sponsor bears costs of shipment. Patients' personal data should never be provided to the sponsor. Patients' should provide oral consent, confirmed in writing by e-mail. SA (when distributed by distributor), or USM (in exceptional emergency situations).	Considered necessary for very few trials and only during the public health crisis for trials involving Covid-19 treatment/prevention, or in the final data cleaning steps before database lock in pivotal trials investigating serious or life-threatening conditions with no satisfactory treatment option. SA for ongoing trials.
Country (EU/EEA)			
Austria	All measures: notified as urgent safety notification. After the end of the pandemic: a summary report on all measures, submitted as single SA.	Yes. Directly from site, via courier. Sponsor may organise it (not directly). SA if handled via an independent third party.	Allowed in the two exceptional cases established by the EU guidance. SA.

Belgium	Sponsors asked to keep listing of all mitigation measures. Delayed reporting recommended (exception: permanent amendments and USM).	Yes, not directly from sponsor. Non-SA, to be submitted with next SA.	Not allowed
Bulgaria	N/A	Yes. Notification to NCA and EC.	N/A
Croatia	N/A	N/A	N/A
Cyprus	N/A	N/A	N/A
Czech Republic	N/A	Yes, from site to patient, organised by sponsor. NCA and EC should be informed.	Not allowed.
Denmark	No notification requirements for changes covered by the national COVID-19 guidance. When the situation is stabilised, sponsors are obliged to submit notifications describing all actions taken in	Yes. No notification requirement. There is a temporary possibility for the sponsor to distribute directly to patients (valid until 1 September 2020), in this case - USM.	Allowed in the two exceptional cases established by the EU guidance. Sponsor is responsible for ensuring that remote SDV complies with GDPR. In this connection, a separate risk assessment must be prepared regarding data protection for the established procedures.

	the trial due to the pandemic.		
Estonia	N/A	Yes, only from site to patient. Notification to NCA via email with justification.	Not allowed.
Finland	N/A	Yes. Notification to NCA of fundamental change to research plan.	N/A
France	N/A	Yes. USM followed by SA. For delivery of non-self-administering drugs: SA.	N/A
Germany	N/A	SA to NCA and EC, patient consent required	N/A
Greece	N/A	Yes, from site to patient. Patients should give oral consent, confirmed via email or audio message. Changes can be applied immediately, followed by informing NCA and EC as soon as possible.	Not allowed.
Hungary	USM	Yes, USM.	Not allowed.
Iceland	N/A	N/A	N/A
Ireland	N/A	Yes, site to patients; sponsor may provide assistance and advice.	Generally not acceptable due to data protection and ethical consideration.

Italy	Notified SA (no evaluation) their cessation.	Yes. Notified SA to EC.	Allowed. The methods must be described in a specific standard operating procedure (SOP) and approved by the data protection officer of the site.
Latvia	USM	Yes. (Reported to NCA)	Allowed.
Liechtenstein	N/A	N/A	N/A
Lithuania	Sponsors are advised to follow the EU guidance	N/A	N/A
Luxembourg	N/A	N/A	N/A
Malta	No specific guidance, except that COVID-19 clinical trials will be prioritized with accelerated assessment	N/A	N/A
Netherlands	Logistical changes (e.g. phone visits instead of physical visits, direct delivery of IMP, remote SDV) are NOT considered SA. Protocol deviations or introducing USM can take place without prior approval, but have to be	Yes, only from site to patient. Should be recorded in writing, no need to inform EC. Patient's consent obligatory.	Allowed in the two exceptional cases, established by the EU guidance.

	notified immediately to the EC.		
Norway	USM. All measures must be well documented and included in an appendix to the protocol, to be submitted as on overall change notification when the situation is stable.	Yes, not directly from sponsor. USM. It should be described in a supplement or an appendix to the protocol (same way as other changes) and should be submitted collectively in a change notification to the NCA.	Allowed in the two exceptional cases established by the EU guidance.
Poland	Recommended to treat measures as USM, but long-term changes that have to be implemented over time should be submitted as SA.	Yes. USM. Possible that no consent is required, but only notification to NCA and EC.	May be considered by the sponsor as a last resort, limited to situations critical to patient safety.
Portugal	N/A	Yes. Non-SA to EC and duly recorded in the study documents.	N/A
Romania	N/A	NCA recommends identifying solutions for	N/A

		transmitting medication to the patient's home	
Slovakia	Recommended: USMs and notified without delay.	Yes, not directly from sponsor.	Not allowed.
Slovenia	USM	Yes, USM	N/A
Spain	Any exceptional measures must be duly documented in the trial file. In the four months following the date in which it is considered that the COVID-19 crisis has ended in Spain, the sponsor must communicate for each trial a report on the exceptional measures adopted that will be sent to the NCA and EC.	Yes.	Allowed in the two exceptional cases, established by the EU guidance. Prior authorisation from NCA or EC not needed, nor patient's consent.
Sweden	USM	Yes, but not directly from sponsor.	N/A

United Kingdom	N/A	Yes. Possible directly from sponsor. Patient's oral consent required to providing contact details for shipping purposes. Non-SA.	Allowed.