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Clinical trials at the times of covid-19 in a public law perspective: telemedicine and changes to informed consent.

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Abstract IT: *La diffusione del covid-19 ha avuto un impatto sulla conduzione delle sperimentazioni cliniche in diversi modi: fin dall'inizio si è assistito a un più ampio utilizzo della telemedicina e sono stati messi in atto metodi alternativi di espressione del consenso informato per la partecipazione alle sperimentazioni cliniche. L'analisi della legislazione e delle indicazioni esistenti, sviluppate a diversi livelli, nazionale, sovranazionale e nazionale di Stati non europei, ci ha permesso di presentare una serie di riflessioni.*
All'interno di un'ipotetica futura infrastruttura normativa in materia di telemedicina, il tema del consenso informato elettronico potrebbe assumere un'importanza sempre maggiore ed essere concepito come implicito nell'uso delle tecnologie, in senso lato, attraverso l'utilizzo di strumenti, quali videoconferenze, e-mail, fax, ecc. e, in senso stretto, attraverso l'uso di software e piattaforme specifiche che utilizzano sistemi chiave per validare e verificare l'autenticità, la correttezza e la veridicità del processo elettronico così seguito.

Abstract EN: *The spread of covid-19 has impacted on the conduct of clinical trials in different ways: since the beginning there has been a wider use of telemedicine, and alternative methods of expressing informed consent have been put in place for participation in clinical trials. The analysis of existing legislation and indications, developed at different levels, national, supranational and non-European States domestic frameworks, has allowed us to present a series of reflections. Within a future hypothetical regulatory infrastructure concerning telemedicine, the issue of electronic informed consent could become increasingly important and be conceived as implied by the use of technologies, in a broad sense, through the use of tools, such as video conferences, emails, faxes, etc., and, strictly speaking, through the use of specific software and platforms that use key systems in order to validate and verify authenticity, correctness, and truthfulness of the electronic process thus followed.*

Sommario: 1. Introduction. – 2. State of the art in the relevant sectors for the purposes of the investigation. – 2.1. The framework of telemedicine at the European level. – 2.2. Informed consent in clinical trials. – 3. The interconnection of sectors at the time of covid-19. – 3.1. The supranational guidelines in the health emergency. – 3.2. The national guidelines in the health

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emergency. – 3.3. Indications from non-European States domestic farmeworks. – 4. Concluding remarks.

1. Introduction.

At the end of 2019, the coronavirus spread from China to the rest of the world, impacting greatly on the health and social systems of many countries. At first, many routine health activities were suspended, and existing resources were subsequently focused on fighting the effects of the pandemic. Access to health facilities and research centres was limited in order to avoid the spread of the infection, and the main objective during the different waves of the contagion was to fight against the virus and treat those who were affected. Many health trials were either suspended or cancelled as the resources for clinical research were allocated to the search for vaccines and effective therapies against the coronavirus.

The conduct of clinical trials has been impacted in different ways: since the beginning there has been a wider use of telemedicine, and alternative methods for expressing informed consent have been implemented for participation in clinical trials.

The pandemic was characterised by high diffusivity of a respiratory virosis, leading to a much greater susceptibility among those who were frail or with chronic conditions. This highlighted the difficulty of balancing existing principles in the field of clinical research with a requirement to carry out an even greater case-by-case evaluation in order to protect and prioritise the rights of those involved in the trials.

The most relevant issues concerned the need for clinical research precisely at a juncture such as that of the pandemic, and also the significant criticalities that emerged from the trials of drugs and vaccines for covid-19 at a time when the respiratory virus had not yet been the subject of an exhaustive etiopathological description and a cure for the respiratory infection it caused did not yet exist[1].

One of the basic needs that the pandemic highlighted was for protection of the most vulnerable, even beyond the indications of the European Union Charter of Fundamental Rights - see Articles 24 "Rights of the child"; "Rights of the elderly"; "Integration of people with disabilities"; the guarantee of scientific research, as required by Article 13 of the EU Charter of Rights; the need for "a high level of protection of human health" to be guaranteed for all in the

[1] On these aspects, see A.C. SHAH, S.M. BADAWY, *Telemedicine in pediatrics: systematic review of randomized controlled trials*, in *JMIR pediatrics and parenting*, 4, 2021; G.B. TIRAPELLI, G. BAIOCCHI, *Telemedicine and cancer research during the COVID-19 pandemic*, in *Journal of Surgical Oncology*, 1, 2021; T.R. MEHTA, *Application of telemedicine in research (clinical trial case)*, In S. Beladakere Ramaswamy-S.M. Bhagavan-R. Govindarajan (eds.), *Learning Teleneurology Basics*, Cham, 2021; B.E. BUNNELL, G. SPRAGUE, S. QANUNGO, M. NICHOLS, K. MAGRUDER, S. LAUZON, J. S. OBEID, L. A. LENERT, B. M. WELCH, *An exploration of useful telemedicine-based resources for clinical research*, in *Telemedicine and e-health*, January 2020; L. PALAZZANI, *Consenso informato alla ricerca clinica nell'ambito della pandemia Covid-19: tra bioetica e biodiritto*, in *Rivista di biodiritto*, 3, 2020.

definition and implementation of all policies and activities of the Union, as established by Article 35 of the EU Charter of Fundamental Rights.
In the same way, the Oviedo Convention on Human Rights and Biomedicine of 1997 establishes some rules to protect those who do not have the ability to consent to a research (Art. 17).
Scientific research during a health emergency may require the modification of existing standards and push towards a simplification of measures. These may be valid only for the emergency period but may subsequently lead to possible systematisation in more appropriate regulatory forms[2].
The World Health Organization (WHO) in the "Ethical standards for research during public health emergencies: distilling existing guidance to support COVID-19" stated that scientific research constitutes an ethical imperative during health emergencies because some research can be usefully and validly conducted only in an emergency context[3].
Along similar lines, the Nuffield Council affirmed the ethical need for research in health emergencies to be guided by three fundamental values: equal respect; help to reduce suffering; and fairness[4].
The Position of the European Network of Research Ethics Committees (EUREC) on the Responsibility of Research Ethics Committees during the covid-19 pandemic states, in turn, that the pandemic represents an extraordinary challenge for medical research and that new technologies can offer a substantial contribution to scientific research[5].

2. State of the art in the relevant sectors for the purposes of the investigation

It is the case that in the matter of informed consent in clinical trials, legislation has been consolidated and applied to the main aspects requiring regulation; however, in the sector of telemedicine there is currently no homogeneous legal framework at the European Union level.
We will therefore proceed to describe the state of the art in the related sectors and then look more closely at the effects of the interconnection between sectors

[2] See the work of the International Coalition of Medicines Regulatory Authorities (ICMRA), i.e. the regulatory agencies of the European Union, the United States and numerous other jurisdictions, aimed at implementing measures to speed up the development, production and distribution of safe and effective vaccines. See www.icmra.info.
[3] Cfr. World Health Organization, Ethical standards for research during public health emergencies: distilling existing guidance to support COVID, 2020, 1.
[4] "The ethical compass is made up of three very widely shared values: Equal respect: treating others as moral equals, including respecting their dignity, humanity and human rights; Helping reduce suffering: acting in accordance with fundamental duties, founded on solidarity, and humanity, to help those in need or suffering from disease; and Fairness: including both duties of non-discrimination in the treatment of others, and of the equitable distribution of benefits and burdens". See Nuffield Council on Bioethics, Research in global health emergencies: ethical issues, 2020, 76 ff.
[5] Position of the European Network of Research Ethics Committees (EUREC) on the Responsibility of Research Ethics Committees during the COVID-19 Pandemic, 27 April 2020. Point 6 of the Position specifies that the technologies to be used must have been designed in order to guarantee the protection measures established by the European regulation on privacy (the so-called privacy by design).

that occurred during the time of covid-19. In particular, it is important to consider the consequences and changes that relate to the question of informed consent in clinical trials.

2.1. The framework of telemedicine at the European level

At the level of European Union legislation, telemedicine includes aspects relating to both health services and information services. For this it is possible to refer to the regulations concerning these two areas[6]. The European Commission defines telemedicine as "the provision of healthcare services, through the use of ICT, in situations where the health professional and the patient (or two health professionals) are not in the same location. It involves secure transmission of medical data and information, through text, sound, images, or other forms needed for the prevention, diagnosis, treatment and follow-up of patients"[7]. As a health service, telemedicine falls within the scope of Articles 56 and 57 of the Treaty of the Functioning of the European Union (TFEU) and is therefore subject to the principle of free movement of health services. For this reason, Directive no. 2011/24 on cross-border care, and, in particular, Article 14 on online healthcare, are relevant. With respect to information and telecommunication services, the following documents are relevant: the Information Society Services Directive no. 98/34/EC; the e-commerce directive n. 2000/31/EC; the directive on privacy in electronic communications n. 2002/58/EC; the 2017/745/EU Regulation on medical devices; the 2016/679/EU Regulation on data protection and, finally, the Proposal for a Regulation of the European Parliament and of the Council on the European health data space (COM/2022/197 final)[8]. In addition, the EU legislation on electronic identification[9] and security of networks and

[6] V.L. RAPOSO, *Telemedicine: The legal framework (or the lack of it) in Europe*, in *GMS health technology assessment*, 12, 2016; C.S. PATTICHIS, ET AL., *Wireless telemedicine systems: an overview*, in *IEEE Antennas and Propagation Magazine*, 2002, 143-153; T.J. SOMMER, *Telemedicine: a useful and necessary tool to improving quality of healthcare in the European Union*, in *Computer methods and programs in biomedicine*, 1995, 73-77; V. SALIBA, ET AL., *Telemedicine across borders: a systematic review of factors that hinder or support implementation*, in *International journal of medical informatics*, 2012, 793-809.

[7] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, On telemedicine for the benefit of patients, healthcare systems and society/COM/2008/0689 final/. See also EU Commission, e-Health: making healthcare better for European citizens: an action plan for a European e-health area, COM/2004/356 of 30 April 2004.

[8] See Information Society Services Directive no. 98/34/EC; Directive 2000/31/EC of the European Parliament and of the Council of 8 June 2000 on certain legal aspects of information society services, in particular electronic commerce, in the Internal Market (Directive on electronic commerce); Directive 2002/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications); the 2017/745/EU Regulation on medical devices; the 2016/679/EU Regulation on data protection; the Proposal for a Regulation of the European Parliament and of the Council on the European health data space (COM/2022/197 final).

[9] Regulation (EU) n. 910/2014 of the European Parliament and of the Council of 23 July 2014 on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC.

information systems[10] offers a range of opportunities for the use of digital technologies in health and care fields, but, it must be specified, it does not have as its primary purpose the regulation of telemedicine. In addition, there is a reference to the Commission communication on the digital transformation of health and care of April 2018 which aims to increase digitalisation in the health and care sector[11]. Even if, pursuant to Article 168 of the TFEU, the responsibility for the organisation and provision of health services and telemedicine remains a state competence, the European Union has a role to play in its support for national policies. In particular, the Commission specifically has a role in the coordination of policies in order to promote convergence towards common solutions. The directive on patients' rights relating to cross-border healthcare[12] established the online healthcare network (eHealth network) to advance the use of technologies in healthcare according to standards of adequacy, respect for privacy, and interoperability of eHealth solutions[13]. In recent years, European Union cooperation has focused on the search for a legal framework for the secure transmission and sharing of health data. This is in compliance with the General Date Protection Regulation (GDPR) and aims to develop an infrastructure of interoperability between the electronic systems of the Member States. The main references at European Union level are represented by the "E-health Action Plan 2012-2020: Innovative healthcare for the 21st century"[14]; "The Digital Single Market Strategy: eHealth"[15] in which telemedicine is included in the section 'Boosting competitiveness through interoperability and standardization, Recommendations of the Commission's study on Big Data in Public Health, Telemedicine and Healthcare'.
The covid-19 pandemic has resulted in an increase in telemedicine services, both for therapeutic activities and for clinical trials. To a certain extent, these have compensated for the inability, for public health reasons, to access health facilities and research centres. The necessary use of telemedicine services highlighted the criticalities already existing in the sector, among which are: the absence of legislation at European Union level and the fragmentation of

[10] Directive (EU) 2016/1148 of the European Parliament and of the Council of 6 July 2016 concerning measures for a high common level of security of network and information systems across the Union.
[11] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on the digital transformation of healthcare and assistance in the digital single market, citizen empowerment and the creation of a healthier society, COM/2018/233 final.
[12] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.
[13] The e-Health network is a European network which, pursuant to Article 2 of the Commission decision no. 2019/1765 of 22 October 2019, "connects the national authorities responsible for online healthcare designated by the Member States and pursuing the objectives set out in Article 14 of Directive 2011/24 / EU", namely online healthcare.
[14] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, eHealth Action Plan 2012-2020 - Innovative healthcare for the 21st century, COM(2012) 736 final.
[15] See Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on enabling the digital transformation of health and care in the Digital Single Market; empowering citizens and building a healthier society, COM(2018) 233 final.

national regulations; the criticalities concerning the interoperability of infrastructures within member countries and at European Union level; problems concerning the confidentiality and privacy of health data; the nonexistence of consolidated health practices on the subject; and the doubts of health professionals on aspects related to responsibility in a context in which many regulatory uncertainties remain.

2.2. Informed consent in clinical trials

Concerning informed consent in clinical trials, the confusion of relevant norms has stratified over time. The basic requirement underlying legislation on this subject was to establish a series of fundamental principles, from a legal and ethical point of view, aimed at guaranteeing the autonomy and rights of people in clinical trials and their rights. These principles would include: the rights of the most vulnerable; respect for the protection of human dignity; the integrity of the person; respect for privacy and family life; and the protection of personal data[16]. The international[17] and European Union standard[18] of informed consent in trials provides for detailed information on the nature and objectives of the trial. It includes the risk/benefit balance of the trial, the existence or not of therapeutic alternatives to clinical trials, a series of guarantees relating to participation, and the possibility to withdraw from the trial. There is also the need for written, personal, conscious, current, specific consent, expressed in advance of the person's enrolment in the trial, and the review of the trial protocol and related documentation by an independent and competent ethics committee for the trial. The protection of human dignity and the right to the integrity of the person are explicitly recognised in Article 1 and in Article 3 of the Charter of Fundamental Rights of the European Union.

The Charter of Fundamental Rights of the European Union establishes in Article 3 paragraph 2 letter a) that in the field of medicine the principle of free and informed consent of the person must always be respected in the manner defined by law. The Convention for the protection of human rights and the dignity of the human being with regard to the applications of biology and medicine (Convention on Human Rights and Biomedicine signed in Oviedo in 1997) establishes in Article 5 the general rule that no intervention in the field of

[16] See S.J.L. EDWARDS, ET AL., *Informed consent for clinical trials: in search of the "best" method*, in *Social science & medicine*, 1998, 1825-1840; N.T. TAM, ET AL., *'Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis*, in *Bulletin of the World Health Organization*, 2015, 186-198; T.C. DAVIS, ET AL., *Informed consent for clinical trials: a comparative study of standard versus simplified forms*, in *JNCI: Journal of the National Cancer Institute*, 1998, 668-674; M. KUTHNING, F. HUNDT, *Aspects of vulnerable patients and informed consent in clinical trials*, in *GMS German Medical Science*, 2013.

[17] World Medical Association (WMA), *Declaration of Helsinki*, 1964, reviewed version of 2013; Council of Europe, *Convention on Human Rights and Biomedicine*, 1997, Article 5 and Additional Protocol concerning Biomedical Research, 2004; UNESCO, *Universal Declaration on Bioethics and Human Rights*, 2005, Article 6.

[18] The regulatory reference point is represented by European Union Regulation No. 536/2014 of 16 April 2014 on the clinical trial of medicinal products for human use, which repeals Directive 2001/20/EC. See also Charter of Fundamental Rights of the EU, 2000, Article 3.

health can be carried out unless the person concerned has given free and informed consent, and Article 8 provides for an exception in the case of an urgent situation[19]. The exceptions to the standard, thus generally reconstructed,[20] include some exceptions to the requirement of writing and to the principle of prior consent in emergency situations[21]. In Considerando no. 36 of regulation no. 536 of 2014[22] it is specified that the regulation provides for specific rules in relation to informed consent even in emergency situations[23]. Regulation no. 536/2014 then dedicates Article 35 to "Clinical Trials in Emergency Situations" and establishes how it is possible to acquire informed consent to participate in a clinical trial and that information relating to the clinical trial can be provided after the decision to include the subject in the clinical trial provided that said decision is taken on the occasion of the first intervention on the subject. A series of conditions are then established, such as the presence of scientific reasons consistent with the potential participation with a significant direct benefit in terms of improving health and well-being conditions or reducing suffering; absence of previously expressed objections to participation; minimisation of risk and discomfort, in comparison to the

[19] Article 8 of the Oviedo Convention states that "When due to an urgent situation, the appropriate consent cannot be obtained, any medical intervention that is essential for the benefit of the health of the person concerned can be immediately proceeded with."

[20] In Considerando no. 30 of the European Union regulation no. 536 of 2014 on clinical trials of medicinal products for human use and which repeals Directive 2001/20/EC, it is specified that, in accordance with third countries guidelines, the informed consent should be issued in writing. Where the subject is unable to write, consent can be recorded using suitable alternative means, such as audio or video recordings.
In Article 29, the regulation establishes certain consent requirements that must be documented in writing, dated and signed by the participant in the trial.
This provision provides that if the subject is unable to write, the consent can be provided and registered by means of suitable alternative instruments, in the presence of at least one impartial witness. In this case the witness affixes his/her signature and the date on the informed consent document. The subject, or, if the subject is unable to provide informed consent, his or her legally designated representative, receives a copy of the documentation (or registration) with which the informed consent was obtained.

[21] On the transformations that have affected informed consent in clinical trials during covid-19, see the monographic volume dedicated to Informed consent in clinical trials in the context of the Covid-19 pandemic. Ethical and legal challenges, in Biolaw Journal, 2021, n. 2, special issue.

[22] The Regulation n. 536 of 2014, which repeals directive no. 2001/20, was published in the Official Gazette of the European Union of 27 May 2014 entered into force on 16 June 2014, but its application is subject to the activation of the EU portal, first expected in 2020, but postponed first due to the reallocation of the EMA headquarters to Amsterdam as a result of Brexit and then due to the spread of covid-19.
Article 98 of the Regulation provides for a three-year co-regulation period, in which the two provisions, Directive and Regulation, will coexist, and it will therefore be possible to conduct a trial by adhering to one or the other.

[23] Such situations concern, for example, cases in which the patient suddenly finds oneself in clinical conditions which, due to multiple trauma, stroke or heart attack, endangers his/her life by requiring immediate medical intervention. In such cases it may be appropriate to intervene in the context of an ongoing clinical trial, already approved. In certain emergency situations, it is, in fact, impossible to obtain informed consent before the intervention. The regulation establishes certain rules which, subject to very strict conditions, allow the enrolment of the patients in question in a clinical trial. The latter must have a direct relationship with the clinical condition due to which it is not possible to obtain, within the therapeutic window, the prior informed consent of the subject or his/her legally designated representative. Any objections previously expressed by the patient must be respected and the informed consent of the subject or the legally designated representative must be obtained as soon as possible.

standard of care and treatment. However, consent must be given as soon as possible; that is, when the subject returns to the conditions to express it. It can be expressed in unwritten form with an impartial witness and research approval from an ethics committee.

3. The interconnection of sectors at the time of covid-19

The internatational and supranational documents in the context of a health emergency refer to alternative ways of using information and communication technology with which the trials can be conducted and with which informed consent can be obtained.

The first area includes the possibility of employing information and communication technology to share the health data of the participants in the trial. It can be used for carrying out check-ups through video calls, telephone calls, and for remote verification of data and documents related to the trial. The second area includes the possibility of using information and communication technology in order to collect electronic informed consent in the case of enrolment into a new trial, or in the case of renewed consent following substantial changes to the protocol.

The Bioethics Committee of the Council of Europe (DH-BIO), in the document *Statement in the Context of the COVID19 Crisis*, underlines how the case of "compulsory isolation" for a seriously infectious disease, such as a pandemic, falls within the exceptions to the informed consent for reasons of public health protection[24]. This exception is provided for by Article 8 of the Oviedo Convention on Human Rights and Biomedicine of 1997 concerning emergency situations, which include the pandemic. The document states that in such conditions, when the appropriate consent cannot be obtained, any medical intervention that proves to be of direct benefit to the individual is allowable. These emergency rules show how oral or photographed/videotaped consent in the presence of witnesses (selected according to impartial criteria justified by the investigator) is considered acceptable.

The supranational guidelines establish that digital technology for informed consent must be implemented (avoiding paper documents, improving and speeding up information for patients).

The European Medicines Agency (EMA) in the Guidance on the Management of Clinical Trials During the Covid-19 Pandemic document stresses that patients must be informed about alternative methods to written consent (e.g. oral consent, in the presence of a witness, deferred consent, renewal of consent or reconfirmation for changes to the protocol by telephone or e-mail, to avoid the participant having to be exposed to unnecessary risks). Informed consent obtained through these methods must be reconfirmed, through standard procedures, as soon as possible, and the reasons for the impossibility of the

[24] Committee on Bioethics (DH-BIO), *Statement on human rights considerations relevant to the COVID-19 pandemic*, 14 April 2020.

participant's usual informed consent must be appropriately motivated and recorded by the researcher. From the forecasts contained in supranational and third countries documents, some possible developments emerge that have some substantial implications in terms of informed consent in trials.

3.1. The supranational guidelines in the health emergency

The European Medicine Agency (EMA) published its guidelines on the subject and its fourth version is dated 4 February 2021[25]. The guidelines proposed some simplification and flexibility measures, valid only for the duration of the covid-19 pandemic, in order to guarantee the integrity of the trials, the rights, the safety, the well-being of the trial participants, and the safety of the staff during the global health emergency. The guidelines take into consideration the impact that covid-19 has had on the trials in progress and on those yet to be started. In these two situations there are different rules for acquiring consent or for obtaining a renewal of consent from patients already included in the trial. The guidelines give an indication of some possible changes that may affect informed consent deriving from the particular health emergency of the pandemic and which are required by the use of telemedicine and information and communication technology. When a participant in the trial could access the research centre, the guidelines suggested a resort to other measures, through which it was possible to maintain social distancing, or establish contact by telephone or video link, by which it was possible to identify events and ensure continuous medical monitoring. The EMA also restated the need to consider the limitations and risks that these methods may have and which may require specific measures to protect personal data. When considering new trials, the EMA recommended postponing trials except in the case of trials involving a cure or vaccines against covid-19 or therapies for diseases for which there are no validated treatments. In the case of trials in progress a series of measures was recommended: such as the change from physical visits to remote contact by telephone or video; postponement or cancellation of visits if not strictly necessary; a temporary halt to the trials; the interruption or slowdown in the recruitment of new participants; the extension of the duration of the experimentation; the postponement of the trials; the closure of the trial centres; or the transfer of trial participants to safer centres. Unless it is connected to the implementation of urgent security measures, the modification of the collection processes for informed consent must be reviewed and approved in advance by the competent ethics committees. In the event that the sponsor plans a new trial to test new treatments for covid-19, alternative procedures should be sought to obtain informed consent if it is not appropriate for the physical document of consent to leave the isolation room and it is therefore not usable as

[25] Cfr. EMA, *Guidance on the management of clinical trials during the Covid-19 pandemic*, 4 February 2021. See also EMA, *Recommendation paper on decentralised elements in clinical trials*, 13 December 2022.

documentation of the experimentation. On this point, during the covid-19 pandemic, the EMA provided a series of indications as follows: first of all, if it is not possible to collect written consent from the participant, for example due to physical isolation due to covid-19, the consent should be given orally by the participant in the presence of an impartial witness (the guidelines refer to Article 2 (j) of Directive 2001/20/ EC). In these cases, the witness is required to sign and date the form and the investigator is responsible for recording how the selection of the witness was made. Additionally, the participant and investigator can sign and date separate informed consent forms. Anything that occurs will be filed in the investigator's log and the participant's signed form will be sent as soon as possible.
In case of life-threatening conditions, when it is not possible to obtain informed consent, it will be deferred and acquired later, once this is allowed by national law. In these cases, the investigator will record the reasons why it was not possible to obtain informed consent from the participant prior to enrolment. It may be required to obtain a renewal of consent from those already included in the trial. If the re-consent procedure becomes necessary for the implementation of changes to the protocol, due to covid-19 or to security needs for other trials, alternative ways to obtain re-consent in the pandemic period must be considered. These options may include contact with the participant via telephone or video calls, and the collection of oral consent must be documented in the participant's medical record and verified by a confirmatory email. Updated and approved information and informed consent forms must be provided to the participant by the investigator via email, post, or courier prior to obtaining re-consent. Consent obtained in these ways must be documented and confirmed as part of a normal consent procedure at the first useful opportunity when the participant returns to the trial centre. This is the first reference by the EMA to electronic consent in the Guidelines[26]. It states that any validated and secure electronic system already used in the trial in the particular Member State to obtain informed consent can be used as usual practice, if in accordance with national law. This provision opened the way for the development of electronic signed consent (eConsent) through the collection of important "source" information (in this specific case, the date and the patient's consent itself). This consent is viewed with varying degrees of acceptability as it involves advanced technology. Monitoring then presents other peculiar aspects. With respect to monitoring trial activities, the Guidelines looked ahead to some eventualities[27]. The monitoring connected to visits to the research centre could be cancelled or postponed for the purpose of containing the infection[28].

[26] European Medicine Agency, *Guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic*, 4 febbraio, 4 v., 11.
[27] European Medicine Agency, *Guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic*, 4 febbraio, 4 v., 14 ff.
[28] Monitoring is a crucial activity in clinical trials that is conducted by a subject, the monitor, delegated by the promoter of the clinical study, in order to verify at the competent research centre the correspondence of the activities carried out with those described in the research protocol, integrity of the data collected and the correspondence between the source documents (such as reports of

One possibility which may occur refers to centralised monitoring and centralised review of the collected data which could replace actual visits to the research centre.
A second option concerns off-site monitoring activities, which could include phone calls, video calls, emails or other online tools to discuss the study with the investigator and centre staff. These activities could be used to obtain information on the progress of the clinical trial, to exchange information on troubleshooting, to review procedures, and to monitor the status of study participants, as well as to train investigators for trials. A third potential outcome is represented by source data verification remotely (SDV) which can only be used for very few processes in line with national legislation. Remote data verification cannot be performed unless combined with adequate data protection, including data security and personal data protection.[29] Remote data verification can only be considered for some specific trials: where research is being conducted on a treatment or prevention of covid-19; the investigation of serious or life-threatening conditions; where the absence of SDV for critical data would probably entail unacceptable risks for the safety of the participant or the reliability/integrity of the results of the trial; where particularly vulnerable participants are involved, such as children or other subjects who are temporarily (for example in trials in emergency conditions) or permanently (for example in trials in patients with advanced dementia) unable to give their informed consent. In the above cases, the principal investigators should make their own decisions to determine whether or not the situation in their clinical centre allows for one of the following options for remote verification: sharing with the monitor pseudonymised copies of source documents related to the study; direct and adequately controlled remote access to the electronic medical data of study participants; video review of medical records with support from the clinical site team, without sending any copies to the monitor and without the monitor recording images during review.
It was stated during the pandemic that for covid-19 trials that began during a health emergency, when remote data verification was required, it was to be described in the initial protocol application and on the informed consent form. In the case of ongoing trials, an amendment for remote data verification should be presented, in line with national rules or national temporary emergency measures, by means of a substantial modification[30].

instrumental and laboratory tests, medical letters, clinical diary and therapeutic plans) and the data entered in the research data collection forms.

[29] See EMA, *Guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic*, 4 February 2021, v. 4, 17.

[30] In annex no. 1 to the EMA guidelines other indications have been established to protect the rights and safety of participants: remote access to data can only take place within an EU member country and not from third countries, unless a protection equivalent to that guaranteed by the GDPR is ensured; a risk assessment must be made, also by consulting the reference DPO, and the data to which remote access can be given and the data excluded must be indicated; the staff must inform the participants of the remote access to the data and make sure that the participants have no objections; this process must be recorded in the participant's medical record; if a participant disagrees, it will not be possible to access the data remotely for that participant; remote access must take place through devices that are protected

3.2. The national guidelines in the health emergency

At national level, the guidelines strictly followed the provisions of the EMA regarding the use of telemedicine, oral consent and deferred consent.

While in Europe many documents about clinical trials refer to the need to make use of telemedicine for contacts, control visits to participants, and monitoring of the trial, there are also significant references to digital or electronic consent aimed at enrolling participants in the trial in the first place. The changes to the informed consent process determined by the alternative methods envisaged in order to contain the possibility of contagion are relevant; they refer, as mentioned above, to oral, deferred consent and to the consent given through the technological means available (email, fax, etc.) or through a platform that supports electronic informed consent in circumstances where the national legislation provides for it and regulates its use in accordance with the rules on privacy and on the rights of participants in the trial.

In the Italian Medicines Agency (AIFA) document of 17 September 2020,[31] which followed the documents of 7 April and 12 March 2020, some specifications were provided about the use of telemedicine and informed consent.

Given the persistence of the emergency situation, it was advised that the inclusion and enrolment of new subjects in clinical trials be avoided as much as possible, except for those cases where participation in the study was fundamentally necessary, such as in the absence of a valid therapeutic alternative; or, of course, in cases of enrolment in studies where drugs to combat covid-19 are tested.

Concerning the use of information and communication technologies, the AIFA refers to suitable remote communication mechanisms with the interested parties in order to allow the exchange of all information that would no longer be provided in person. Depending on the case, where it was deemed necessary, telephone and/or video calls were to be used in order to facilitate the disclosure of information on the subject or provide detailed instructions. It recommended that a documented record of communications, of any kind, be kept, which occurred in this emergency situation.

To maintain control over the progress of the experimentation and the conditions of the subjects, it was considered preferable to intensify the exchange of information by strengthening the activities carried out from the outside (off site-monitoring). This external monitoring usually complements the activity of

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against unauthorised access to data; the monitor must sign a confidentiality agreement that commits him/her to destroy the documents drawn up, both physical and electronic, as soon as they have been used for data verification and must undertake not to make any copies (or any recording in the case of video access) of non-pseudonymised documents.

[31] See AIFA Communication (update of the AIFA press release published on 12 March 2020), *Management of clinical trials in Italy during the COVID-19 emergency* (coronavirus disease 19) (Version 2 of 7 April 2020), available at the following link 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.

in situ monitoring, through the use of media such as telephone contact with the site, video conferences, emails and other online communication with the investigator and clinical staff.
In cases where it was necessary to obtain informed consent (activation of new studies or amendment to informed consent for studies already started or for the implementation of emergency measures or simply to avoid exchanges of paper material, a possible source of contagion), and where this was not possible with the usual methods, the AIFA document listed alternative procedures for obtaining this. The implementation of these alternative procedures (telephone contacts, followed by confirmation e-mails or through validated electronic systems) did not provide exemption from obtaining written consent as soon as the situation allowed, on the first occasion in which the subject was present at the centre.
Obtaining consent from the subjects was to be considered privileged over other requests, even in cases where subjects were in isolation; in these situations it is possible to make use of cameras or photographs of the documentation taken through the transparent insulation material.
In the event that obtaining a written informed consent by the patient is not possible, pursuant to Article 3, paragraph 1, letter d) of Legislative Decree 211/2003, a temporary consent in verbal form is accepted. In such cases, the presence of an impartial witness is required to certify that the consent has been given and the informed consent document is signed and dated at the site. It is up to the investigator to certify the method of selection of the impartial witness.
In any case, the rules in relation to discipline on the processing of personal data remain, with particular reference to the acquisition of consent to the processing of the same carried out as part of the clinical trial. According to the principle of accountability, data controllers are required to identify suitable measures and prove the successful acquisition of valid consent to the processing of personal data, for example, by voice recording of the telephone consent or by storing the email.
In other documents published by the national authorities within the European Union, on the basis of the EMA Guidelines to which reference has already been made, there are indications similar to those contained in the AIFA Communication on the management of studies during the covid-19 emergency.
In the Danish Medicine Agency document titled "Extraordinary Measures for Clinical Trials due to COVID-19" updated on 7 October 2020,[32] reference is made to telemedicine but not to electronic consent. Telemedicine is considered as part of the visits that must be carried out via telephone or video conference.
The sponsor, in collaboration with the investigator, should consider the possibility that physical visits are postponed or cancelled, or converted into telephone or video conversations using electronic systems, such as video and

[32] Si veda Danish Medicine Agency, *Extraordinary measures for clinical trials due to COVID-19*, 7 October 2020, abailable at the following link: https://laegemiddelstyrelsen.dk/en/news/2020/extraordinary-measures-for-clinical-trials-due-to-covid-19/~/media/BCC2DBEA7FFE4DFBB9C8A3A5CEFDB069.ashx.

should refer to electronic health records, if the IT systems are secure. Again, it is significant that no reference is made here to digital consent.
Similarly, in the document of the Agence nationale de sécurité du médicament et des produit de santé (ANSM), entitled "Essais clinique en cours" updated 5 August 2021,[33] there is scant reference to telemedicine and none to electronic consent. It states that during the 2021 summer, the epidemic situation made it possible to consider the normal resumption of clinical trials in accordance with the protective measures of research participants and caregivers.
However, the transitional measures proposed by ANSM starting from March 2020 for the conduct of clinical trials could be reactivated as necessary according to the evolution of the health situation and needs identified for the different research sites (depending on the epidemic impact and the burden on care facilities).
The French national recommendations were in line with the European recommendations established and published by the EMA.
It is specified that in the event of the inability to carry out follow-up visits to the research centre, it would still be possible to collect and record information by teleconsultation on an exceptional basis.
With respect to remote monitoring, proposers were invited to read the European recommendations which set the general framework for possible solutions. In particular, it specified that the sending of copies of medical records, even pseudonymised, is not allowed in France. In all cases, the promoter was encouraged to contact the investigators to establish rules of conduct that comply with the European Union framework.
In the case of the German document, adopted by the Federal Institute for Drugs and Medical Devices, reference was made to telemedicine but not to electronic consent[34]. The document stated that if it is intended to convert periodic visits in part or completely to telephone contact or telemedical visits, this must be submitted to the relevant federal higher authority and the relevant ethics committee as a notification of change subject to approval. In the case of change notifications affecting safety reporting, the sponsor is encouraged to include a risk analysis of the effects of these changes on the safety of trial participants and the validity of the data collected. Furthermore, remote access to data is allowed only where it complies with European Union legislation[35].
The sponsor must ensure that remote access to the data has been entered in the study participant's informed consent form and is authorised by the federal authority with a favourable opinion from the competent ethics committee.

[33] Cfr. Agence nationale de sécurité du médicament et des produit de santé, *Essais clinique en cours*, 5 August 2021 available at the following link: https://ansm.sante.fr/dossiers-thematiques/covid-19-essais-cliniques-en-cours.
[34] Federal Institute for Drugs and Medical Devices, Guidance: Supplementary recommendations to European Guidance on the Management of Clinical Trials during the Covid-19 (coronavirus) pandemic (Version 3.0), 27 marzo 2020.
[35] See Supplementary recommendations of BfArM and PEI to the European Guidance on the Management of Clinical *Trials during the Covid-19 (coronavirus) pandemic*, version 3, 19 May 2020.

In Ireland, the Health Products Regulatory Authority adopted a document updated on 7 April 2021 where there are references to the use of information and communication technology for visits, monitoring of research participants, and monitoring remotely; but, again, no mention of electronic informed consent[36].
This document specified that if a person should be unable to attend the research centre, other measures, such as telephone contact or a home nursing visit, may be necessary to identify adverse effects and ensure ongoing medical care and supervision. However, the limitations of such methods, including the oversight capacity of investigators, should be considered.
Remote monitoring of centres, for example by telephone, video conference and e-mail, have been valued of greater use. These activities allow the monitor to discuss the study with the investigator and centre staff. These activities could be used to gather information on the progress of the clinical trial, to exchange information on troubleshooting, review procedures, and to assess the status of study participants, as well as to train investigators for critical trials.
In the case of monitoring via a video link, a secure connection must be ensured without a recording being made (including the precaution of deleting any temporary or cached files) and screenshots cannot be made.
In the case of remote access to electronic medical records (if available), it must be ensured that access to the monitor complies with certain conditions, including whether access can be limited to the files of only those enrolled in clinical trials.
For new trials where a remote SDV is proposed, the sponsor should ensure that the appropriate wording is included in the informed consent form to outline the circumstances in which the subject's medical notes can be accessed remotely.

3.3. Indications from non-European States domestic frameworks

In non-European countries, the changes to informed consent as a result of the impact of the pandemic on trials are more evident.
In the guidelines of the Australian Ministry of Health of 9 April 2020, titled "COVID-19: Guidance on Clinical Trials for Institutions, HRECs, Researchers and Sponsors",[37] some important indications are provided.
During the health emergency period, in trials that proceed without modification, participants were explicitly given a number of options: continue to participate in the trial; suspend their participation, if possible; or withdraw from the trial.

[36] Cfr. HPRA, Guidance on the Management of Clinical Trials during Covid-19, 7 April 2021, version 8.0, available at the following link http://www.hpra.ie/homepage/medicines/regulatoryinformation/clinical-trials/covid-19-(coronavirus)-and-cts/guidance-on the-management-of-clinical-trials-during-covid-19.
[37] Cfr. Australian Government, Department of Health and National Health and Medical Research Council, COVID-19: Guidance on clinical trials for Institutions, HRECs, Researchers and Sponsors, 9 April 2020.

Participants were informed of any changes to the trial, including medical and other trial procedures, ongoing treatments or care, and any tests or assessments that may have had the potential to impact them.
In studies that have been modified, participants should explicitly be given the following options: participation in the trial, as modified, including alternative mechanisms for engagement such as remote visits, data collection, monitoring, etc.; or suspension of their participation, if possible, or withdrawal from the process.
In a situation where a trial participant should be unable to attend a visit or otherwise fulfil the conditions of participation due to public health directives or government policies (such as limited travel between states and territories), sponsors and researchers were to endeavour to enable the participant to continue participating in the trial. If available, such adjustments were approved as per the guidance provided below for changes. Researchers and sponsors were called on to learn about new approaches to conducting clinical trials, such as decentralised (i.e. tele-trial) trials where participants can be recruited and participate remotely and data can be acquired remotely via available technology. Changes to clinical trials that allow remote verification of data are in the public interest and should be understood as stemming from the obligation to protect the safety of participants, researchers and others involved in research. In harmony with other published guidelines, such changes are to be notified to the Human Research Ethics Committee (HREC), time permitting.
HRECs should consider actively encouraging alternative models of clinical trial conduct where possible and appropriate.
Eligible changes would be at the discretion of the institution and/or HREC and could include the following possible changes: modifying a study to employ virtual visits; telemedicine; electronic informed consent,[38] or otherwise implement tele-trials; changing the "site" to a location outside of a hospital or clinic or allow referral to another hospital or clinic; extending protocol times for visits, procedures, test drug delivery or follow-up to allow for periods of isolation or other disruptions; ensuring that all returned experimental medical product is destroyed in accordance with standard protocols for the destruction of biological hazards. In addition, the institution or ethics committee could include any other changes that do not compromise the safety or well-being of the participants and which are intended for the purpose of safeguarding the health of the participants, researchers and staff or the community, through infection control or by reducing the burden of trial participation for participants or researchers. Remote monitoring visits were encouraged as a first option in all cases, with sponsors and institutions ensuring their facilitation, while taking into account the need to avoid undue burdens on hospitals or institutional resources. These agreements adhered to patient confidentiality protocols already in place.

[38] On the digitalisation of consent see Australian Government, Department of Health, MRFF strategy and priorities, 1 August 2018; Australian Government, Department of Industry, Innovation and science, 'Informed consent', 19 February 2015.

Verification of source data remotely can be done electronically as long as adequate security arrangements are / can be put in place.
It was recommended that should remote monitoring visits not be feasible, clinical research associates could continue to have on-site monitoring visits as long as they were not symptomatic, had not returned from overseas in the past 14 days, and had not had contact with a known case of covid-19, in accordance with the most current guidelines and public health councils of the various territorially competent health departments. The Canadian guidelines updated in May 2021 provided for a series of indications for informed consent[39]. First, they encouraged discussion with the research ethics committee about different informed consent methods for the study, or changes to the study protocol if in-person visits were not possible, These provisions had previously included electronic informed consent or registered telephone consent[40].
The existing guidelines required that consideration be given to accepting a text or email of a copy of a signed and dated written statement for participants who are enrolled remotely (this statement should indicate that they voluntarily accept participation experimentation).
In the case of verbal consent, the potential participant must have the opportunity to ask questions and, if necessary, receive the document in advance, in the presence of a witness. The witness can be a family member (this can be on a conference call) and a scanned copy of the statement can be forwarded to the investigator by email, or a photo of the signed statement can be emailed. If a witness cannot be present, the conversation can be recorded.
On remote data monitoring, the guidelines established the content of the necessary documentation. It included the reason for remote monitoring, the method used to collect the information, the types of data collected, and how the source of the data was verified. While a substantial change to the protocol was not necessary to access remote data , the guarantees envisaged concerned the priority use of remote monitoring. This was to ensure the safety of the participants and the integrity of the data; it also allowed for the possibility of carrying out centralised monitoring and documentation of any changes and their impact.
Participants in the trial would be required to consent to the use of remote access and be certain that their privacy would be protected. The Food and Drug Administration (FDA) document of March 2020 (updated 30 August 2021) provides guidelines for trials at the time of the coronavirus in the US context[41].

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[39] Cfr. Government of Canada, *Management of clinical trials during the COVID-19 pandemic: notice to clinical trial sponsors*, 6 May 2021.
[40] On the electronic informed consent see University of British Columbia Clinical Research Ethics General Guidance Notes, Guidance on electronic consenting, Article 13.2.4; Government of Canada, The personal information protection and electronic documents Act ; Government of Canada, Tri-Council policy statement: ethical conduct for research involving humans – TCPS 2 (2018), Article 3.12, where it is written, "Evidence of consent shall be contained either in a signed consent form or in documentation by the researcher of another appropriate means of consent."
[41] FDA, Guidance on conduct of clinical trials of medical products during the COVID-19 public health emergency guidance for industry, investigators, and Institutional Review Boards, updated 30 August 2021.

The FDA recognised that the covid-19 public health emergency could impact medical product trials. Difficulties could arise, for example, from quarantines, centre closures, travel restrictions, supply chain disruptions for the medical product, or other considerations if centre staff or trial participants became infected with covid-19. The FDA acknowledged that protocol changes could be required and that inevitable protocol deviations were likely due to covid-19 and/or public health protection measures. Since it may not have been possible for study participants to come to the trial centre for protocol-specified visits, sponsors were to consider whether alternative methods for safety assessments could be implemented in order to ensure the safety of participants. These assessments include telephone contact, virtual visits, the use of an alternative centre, for example, laboratory premises or imaging centres.

Changes to a protocol are typically not implemented before review and approval by the ethics committee and, in some cases, the FDA. Sponsors and clinical investigators are encouraged to work with ethics committees as soon as possible in an emergency or if changes to the protocol or informed consent are planned.

FDA regulations generally require that a study participant's informed consent be documented using a written consent form that typically includes the elements of informed consent,[42] approved by the Internal Review Board (IRB) and signed and dated by the study participant or a legally authorised representative at the time of consent.[43] Whenever possible, the guidelines recommend a traditional method for obtaining and documenting informed consent using a signed paper copy of the consent form or the use of electronic informed consent.

The FDA has published guidelines for the use of electronic informed consent in trials for use by ethics committees, investigators and sponsors.[44] The FDA has defined electronic consent as "the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive websites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent"[45].

Electronic informed consent includes the possibility of extensive use of technology or the use of specific dedicated software that complies with a series of technical requirements set out in the Code of Federal Regulation[46]. The

[42] See Code of Federal Regulations, Title 21, Part 50, Sec. 50.25 "Elements of informed consent".

[43] See Code of Federal Regulations, Title 21, Part 50, Sec. 50.27 "Documentation of informed consent".

[44] See FDA, Use of electronic informed consent in clinical investigations (December 2016), periodically updated.

[45] FDA, Use of electronic informed consent: questions and answers, December 2016, page 2.

[46] Electronic systems used to generate electronic signatures on clinical trial records, including informed consent documents, during the covid-19 public health emergency must comply with the requirements outlined in the FDA regulations under the Code of Federal Regulation, Title 21 (Part 11).

The FDA makes it clear that there are multiple off-the-shelf commercial software systems for providing electronic signature services for clinical trials. Suppliers may be able to provide sponsors and other regulated entities with information about this if their systems comply with Part 11. When such information is not available from the supplier and an electronic system is required to comply with Part 11, the sponsor and other entities must take steps to ensure that the electronic system or software in use complies with Part 11 of the Code of Federal Regulations. When an electronic system compliant with Part 11 is not available, regulated entities must have an alternative means of obtaining the required

procedures envisaged are as follows, and are aimed at satisfying the requirements for informed consent in the trials: firstly, a photograph of the signed informed consent document can be transmitted to the trial staff. The patient (or an individual in the room) can take a photograph of the signed informed consent and send it to the investigator. A member of the testing team places the photograph in the study documentation along with a certificate stating how that photograph was obtained and confirming that it is a photograph of the patient's signed informed consent.
Alternatively, a witness can attest to the signature. An unsigned consent form is provided to the patient by a person who has entered the room.
The investigator can organize a three-way phone call or video conference with the patient, an impartial witness and, if desired and feasible, additional subjects requested by the patient (for example, next of kin). Alternatively, instead of requiring a witness, a recording of the conversation can be made.
When investigators have to resort to alternative methods to obtain informed consent it may still be acceptable if those methods allow for an adequate exchange of information and documentation and use a method which ensures that the signer of the consent form is the person intending to enroll as a participant in the clinical investigation; or is the legally authorised representative of the trial participant. For example, the consent form can be sent to the trial participant or their legally authorised representative by fax or email, and the consent interview can then be conducted by telephone when the study participant or their legally authorised representative can read the consent form during the discussion. After the consent discussion, the study participant or their legally authorised representative can sign and date the consent form.
Options for returning the document to the clinical investigator may include fax, or a photographic image sent electronically; or the consent form can be scanned and returned via a secure email account or posted to a secure internet address. This is especially important when there are concerns about sending a potentially contaminated consent document.
Alternatively, the study participant can bring the signed and dated consent form at a later date when they next visit the clinical centre, once travel restrictions to the clinical trial site are eased; or it could be mailed to the clinical investigator. In any case, it must be shown that informed consent was obtained prior to participation in the study.
If a potential trial participant (or a legally authorised representative) is unable to print the informed consent document provided electronically by the investigator, or if an electronic signature process is not available and the potential trial participant must meet certain time-sensitive eligibility criteria, the

signatures (for example, handwritten signatures in ink made on documents, handwritten stylus or hand drawn signatures made on electronic medium documents that are then printed or properly stored).
When handwriting techniques are used, the sponsor and other regulated entities should ensure that all records containing signatures are (1) collected and archived, such as original hard copies or properly certified electronic copies (for example, using a validated process for hard copy scanning) and (2) retained under applicable record retention requirements.

investigator may consider using an alternative process to meet FDA requirements for obtaining and documenting informed consent.
The investigator provides the prospective participant (or legally authorised representative) with an electronic version of the informed consent document.
The investigator arranges a phone call or video conference with the prospective participant (or legally authorised representative), the investigator, a witness who is not otherwise connected with the clinical study and, if desired and feasible, additional participants requested by the prospective participant (e.g. example, next of kin). Alternatively, instead of using a witness, the conversation can be recorded[47].
Verbal confirmation is given by the participant (or legally authorised representative) that they have signed and dated a blank piece of paper with a written declaration of voluntary acceptance of participation in the protocol, noting the protocol number and the title of the protocol.
After having signed and dated the newly created document, the trial participant (or legally authorised representative) sends a photograph of the signed and dated statement by fax, text message or e-mail to the investigator; or returns the document to the investigator by post at a later date or for a future visit that he or she may do in person.
When a witness is present, the documentation in the trial records includes an attestation dated and signed by the witness who attended the call that the patient confirmed his or her consent to participate in the trial and signed the document mentioned above.
When using a recording instead of resorting to a witness, the documentation in the trial records includes the recording of the teleconference.
After the signed and dated document has been received by the trial staff, it should be attached to a copy of the consent document that has been reviewed with the participant (or their legally authorised representative) and retained in the documentation as would normally be done for a signed informed consent document.
In addition, a note should be included in the process documentation explaining the circumstances and the reason why informed consent was obtained through alternative methods. The case history for each study participant must document that informed consent was obtained prior to participation in the trial.
This alternative approach must be reviewed and approved by the Institutional Review Board (IRB) overseeing the study as required by FDA regulations[48].
Sponsors intending to use remote assessments as part of a clinical investigation should use appropriate technology and develop procedures for providing technology and technical support to trial participants, investigators, and /or other study staff to facilitate such evaluations. For example, sponsors could develop a plan to support trial participants who are already enrolled in a trial or may be in the future, but who do not have access to appropriate technology

[47] See FDA, Conduct of clinical trials of medical products during the COVID-19 public health emergency, 30 August 2021, 19.
[48] Reference are made to the rules set forth in 21 CFR 50.27, 56.103, and 56.108 (a).

(e.g., cell phones or the Internet), by providing participants in the trial with these services.
FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations[49].
During a health emergency, traditional on-site monitoring may be difficult for reasons such as sites not being able to host monitoring visits (for example, due to staff restrictions or site closures) or monitors may not be in place or able to travel to testing sites. When on-site monitoring visits are not possible, the reason must be documented and available for review by the sponsor and during FDA inspections.
Remote monitoring should be focused on reviewing critical documentation and data source. If the materials identified for review include participants' medical records that would normally be reviewed at the site (and that review is consistent with informed consent documents) then remote review of medical records with trial sites can be performed to complete the revision of the source document. When the study monitor cannot access the site to review critical source documents, requests for revision of source documents that may include private health information should be consistent with the current study monitoring plan or other study-specific document.
During remote monitoring, the study monitor should focus on the testing activities that are essential for the safety of study participants and/or the reliability of the data.
Regarding the retention of copies of source documents used for remote review, it is not necessary to keep certified copies of source documents used for remote review, as long as the clinical investigator retains the original source documents according to FDA regulations for record keeping[50].
Remote monitoring activities, including remote review of source documents, should be documented with the same level of detail as on-site monitoring activities and resulting actions to address issues identified by source document review should be consistent with procedures and processes described in the study monitoring plan.

4. Concluding remarks

The changes affecting informed consent for clinical trials have been accelerated by the covid-19 pandemic. A number of issues and problems are interlinked, and as time goes on, these changes are becoming more and more relevant. It is particularly noticeable in the development of telemedicine and the inevitable rapid changes that were instigated by the use of technologies in healthcare. The lasting legacy will continue well beyond the immediate covid-19 emergency.
The analysis of existing legislation and indications, developed at different levels, national, supranational and third countries level, allows us to present a series of concluding reflections.

[49] Cfr. 21 CFR 312.50, 312.53(d), 312.56(a), 812.40, 812.43(d), and 812.46.
[50] Cfr. 21 CFR 312.62 and 812.140(a).

As we have seen, covid-19 has led to a greater use of telemedicine methods in order to carry out the trials that could not be suspended because they concerned drug-related or other treatment against covid-19; or indeed, other diseases for which there are no alternative therapies.
The use of telemedicine involves several aspects: the contact and relationship with the trial participants; other relevant phases of the trial, such as monitoring the condition of the participants; the monitoring of data and experimentation activities; and the process of acquiring the informed consent if practised through video conferencing tools, video calls, etc.
It has been noted that in all the mentioned guidelines issued during the pandemic, the changes to the traditional methods of conducting trials through the use of telemedicine have been widely accepted, with a series of precautions concerning the protection of privacy and the protection of the safety of the participants. Changes to traditional informed consent through the use of technology, however, have been graded differently in the various countries characterised by different regulatory and cultural contexts.
Starting from the EMA Guidelines, the use of available technology, such as fax and email, for the purpose of obtaining informed consent has certainly been affirmed; however, compared to electronic informed consent, technically understood, the EMA Guidelines refer to the provisions of national regulations which have to provide for the requisite and technical standards necessary for the use of software or platforms that support the existing electronic consent systems.
As we have seen, the European nation states, on the basis of the EMA Guidelines, refer to telemedicine and the use of technologies for informed consent (informed consent acquired via email, fax, etc.) but do not refer in their Guidelines to electronic informed consent; they merely refer to the provisions of the EMA Guidelines.
In this regard, there are very different indications from other parts of the world, both in the West (United States and Canada) and in the East (Australia). Here, the reference to the use of technology in the context of informed consent is broader and more technical than what we have seen happening in Europe. The provision of management of the trials through the alternative methods of telemedicine corresponds to remote management of informed consent, which includes electronic informed consent. These are countries that have regulated or begun to regulate the use of software or platforms in the context of electronic informed consent and have defined the requirements and technical standards to comply with rules on privacy and the protection of participants in the trial. On one hand, there is a cultural factor that differentiates the non-European approach from the European Union one, and, on the other hand, there may also be a more strictly normative issue. In fact, we have seen that in the telemedicine sector, which combines health services with communication and information services, at the European Union level there is still no homogeneous legislation that addresses the existing technical-regulatory problems.

There is no doubt that looking beyond the covid-19 pandemic, within a future hypothetical regulatory infrastructure concerning telemedicine, the question of electronic informed consent could be addressed. It could be inserted into the context of the changes to informed consent that are implied by the use of technology. This includes the use of tools such as video conferencing, email, fax, etc., and particularly through the use of specific software and platforms that use key systems in order to validate and verify the authenticity of the electronic signature thus produced.

One of the areas to be addressed will obviously concern risk management related to the use of technology. Risk management is the main theme of fundamental European Union regulatory blocks on the subject, such as that on privacy (regulation no.679 of 2016) and on artificial intelligence (proposal for a regulation of the European Commission of 21 April 2021). Naturally, this is a complex regulatory framework from which any legislation on telemedicine and electronic informed consent can and must be developed, taking into account the need for speeding up and simplification. This issue is increasingly important for clinical trials, while one must never forget that the ultimate goal of clinical trials is the protection of the health and safety of people in general, and of participants in trials, in particular.