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Decentralized clinical trials: current developments in CEE and Turkey

The rapid development of technologies and solutions in the healthcare sector is contributing to the proliferation of decentralised clinical trials ("**DCTs**"). The aim of DCTs is for clinical trials to be conducted more effectively and conveniently – for patients, sponsors and investigators – through the use of digital technologies. In addition, with hospital visits temporarily limited and staff capacities overwhelmed, the challenges associated with the Covid-19 pandemic have significantly underscored the necessity of performing certain elements of clinical trials remotely.

DCTs can be interpreted as clinical trials fully or partially executed remotely, i.e. by using telemedicine solutions with the participation of the relevant healthcare providers. Contrary to traditional clinical trials, patients enrolled in a fully remote DCT remain at home throughout the full duration of the DCT. However, presently the healthcare systems of a number of countries are not yet ready to implement fully remote DCT-related technologies. Instead, they can perform hybrid clinical trials, which encompass certain telemedicine features in addition to traditional clinical trial elements that require on-site patient visits.

Approaches to DCTs differ among European countries. In mid-December 2022 the first version of the EU Recommendation Paper on Decentralized Clinical Trials was published by the European Commission, the Heads of Medicines Agency and the European Medicines Agency (the "**Recommendation Paper**").

European Union

An ongoing effort is evident at the EU level to harmonize procedures concerning the conduct of DCTs. This is currently being carried out by way of a policy document – not by legislative means – within the framework of the Accelerating Clinical Trials in the EU (ACT EU) initiative.

The first DCT-related EU guidance was issued during the Covid-19 pandemic, titled Guidance on the Management of Clinical Trials During the Covid-19 Pandemic (the "**EU COVID Guidance**"). Such EU COVID Guidance provided recommendations concerning adjustments to clinical trial elements in order to continue to conduct ongoing clinical trials during a time when pandemic-related restrictive measures applied in the majority of EU countries.

On 13 December 2022, the Recommendation Paper was published, drafted by experts from the HMA Clinical Trial Coordination Group, EC Clinical Trial Expert Group and the EMA GCP Inspectors Working Group. The aim of the Recommendation Paper is to continue to facilitate the use of decentralised elements in clinical trials, irrespective of pandemics and the related necessary restrictive measures. The first part of the Recommendation Paper includes detailed guidance on certain DCT elements that may be used in clinical trials, including the remote provision of information towards trial subjects, electronic informed consent forms, the delivery and administration of Investigational Medicinal Products ("**IMPs**") at the trial subject's home and remote monitoring.

The annex to the Recommendation Paper includes an overview of Member State's national provisions on DCTs.

The Recommendation Paper includes an emphasis on the importance of reliable and accurate data, equivalent to those obtained during on-site procedures. The Recommendation Paper further highlights that the responsibilities of sponsors, investigators and other parties associated with the conduct of a clinical trial should be clearly defined in the trial protocol, as well as a delegation of tasks to other parties (e.g. in connection with the delivery of IMPs). More specifically, the Recommendation Paper sets out that any trial-specific task delegated to a third-party service provider should be specified in a written agreement between the responsible parties and the relevant third-party service providers. Digital information leaflets are also recommended to be prepared by sponsors so that trial participants are fully aware of the use of different kinds of digital technologies. Furthermore, procedures regarding remote informed consents should be in place and contain a communication plan setting out the obligations of the relevant stakeholders.

Considering the increased usage of digital tools and solutions in the healthcare sector, the Recommendation Paper will likely be subject to future updates to reflect the status of DCT usage in the EU.

Bulgaria

Bulgarian law does not yet regulate DCTs. However, during the Covid-19 pandemic the local regulatory authority, the Bulgarian Drug Agency (*Изпълнителна Агенция по Лекарствата*, "**DA**") issued guidance to companies conducting clinical trials that permitted a certain hybrid regime for clinical trials. Many restrictions were imposed by the Bulgarian government on the healthcare system directly as a result of the pandemic, with the DA strongly recommending: rescheduling visits or replacing them with telephone calls, identifying solutions for the delivery of medication to patient homes, remote monitoring, and postponing the initiation of new clinical trials or new investigation centres. A state of emergency in Bulgaria was in force in this respect until April 2022. The DA has not provided any further guidance or confirmed the continuing application of its previous recommendations.

No legislative developments concerning DCTs are presently observed.

Croatia

Croatian law still does not regulate DCTs. During the Covid-19 pandemic, the Croatian Ministry of Health (the "**Ministry**") issued several volumes of guidance on conducting clinical trials ("**Guidance**") in response to the issuance of the EU COVID Guidance. Each volume reflected the severity of the given pandemic, with both local and global restrictions imposed towards the public, especially in dealings with healthcare professionals.

The Guidance mostly referenced and followed the EU COVID Guidance. Accordingly, Croatia supported EU efforts, especially concerning the Remote Source Data Verification ("rSDV") system. Implementation of the rSDV in Croatia is subject to prior approvals by the Ethical Committee and by the Ministry. A sponsor must deliver to the Ethics Committee and the Ministry a detailed request to implement an rSDV containing a description of the method of implementation and a new version of the informed consent, reflecting the framework set out under the EU COVID Guidance. Under its published Guidance, the Ministry has enabled the introduction of extraordinary measures for ongoing and approved clinical trials. The approved measures include performing check-ups, where possible, via telephone calls or video calls instead of on-site visits, and the delivery of medicines to patient home addresses in direct response to specific requests for distribution of particular medicines, along with all necessary precaution measures. The latter measure requires patients to issue a special purpose written consent via e-mail or, exceptionally, via telephone.

In connection with the Covid-19 pandemic, the Ministry decided to temporarily suspend approvals of new trial sites for existing clinical trials along with approvals of new clinical trials, save for those connected with the ongoing Covid-19 pandemic itself. The Ministry also urged sponsors to temporarily stop recruiting new patients for ongoing clinical trials. These decisions were revoked in the latest Guidance (volume 3), reflecting the easing of pandemic restrictions before and during the summer of 2022.

Czech Republic

Czech law does not yet regulate DCTs. However, during the Covid-19 pandemic, the local regulatory authority, the State Institute for Drug Control (*Státní ústav pro kontrolu léčiv*; "**SÚKL**"), permitted a certain limited hybrid regimen of clinical trials in light of the health-related restrictions imposed by the Czech government. This temporary regimen was abolished by the SÚKL following the government's easing of pandemic restrictions during spring 2022.

In August 2022, the SÚKL published an Opinion by the SÚKL Medicinal Products Clinical Trial Department on Ongoing Clinical Trials in Connection with Covid-19, dated 5 August 2022 (the "**Opinion**"). Via this Opinion the SÚKL enabled the introduction of extraordinary measures for ongoing and approved clinical trials. The authorised measures include: performing check-ups via telephone calls instead of on-site visits; dispensing an Investigational Medicinal Product for a longer period than originally planned, or ensuring its shipment via courier service; and using outsourced laboratory, home care or general practitioners to take samples from trial subjects. Furthermore, the Opinion allows that patient information may be provided by other means than by face-to-face meetings, i.e. by telephone calls or by e-mail, provided that a record is kept of the provision of such information. The SÚKL also sets additional conditions for the adoption of these measures. For instance, the delivery of an Investigational Medicinal Product is authorised only for products that do not need to be diluted or reconstituted before administration – since such procedures must be performed by healthcare professionals.

Notably, the Recommendation Paper provides that an informed consent form (ICF) may be signed by patients in the Czech Republic via qualified electronic signatures within the meaning of the eIDAS regulation. However, the current approach of the SÚKL is arguably quite strict and requires that a patient signs an ICF in person and on-site.

Hungary

Hungarian law does not expressly regulate DCTs. During the Covid-19 pandemic, the National Institute of Pharmacy and Nutrition ("OGYÉI") issued a guidance on the continuation of clinical trials during the Covid-19 pandemic (the "OGYÉI's COVID Guidance"), which provides for certain DCT elements that may be applied in the course of clinical trials during the Covid-19 pandemic. This OGYÉI's COVID Guidance generally reflected the EU COVID Guidance, supplementing this with OGYÉI interpretations. Although the OGYÉI's COVID Guidance is no longer in effect post-Covid-19 pandemic, it can nonetheless serve as a reference for the OGYÉI when approving protocols in the post-Covid era.

Subsequently, the OGYÉI also issued a short, non-building guidance document specifically governing DCTs, irrespective of the Covid-19 pandemic (the "**DCT Guidance**"). According to this DCT Guidance, certain DCT elements may be permitted by the OGYÉI subject to a case-by-case assessment.

As a general rule, DCT elements need to be explained and well substantiated in the given protocol to enable the OGYÉI to properly evaluate the feasibility of applying DCT elements in the given clinical trial.

According to the DCT Guidance, video and telephone visits may be permissible; however, a physical face-to-face meeting between the trial participant and the principal investigator remains mandatory during the consent procedure. The collection of study data by electronic methods is permitted, such as ePROs that can be delivered to a patient's home by courier.

IMPs and non-IMPs (such as laboratory kits) may also be delivered to patient homes provided that such home deliveries are approved by the OGYÉI.

Romania

Romanian law does not yet regulate DCTs. However, during the Covid-19 pandemic, the local regulatory authority, the Romanian National Agency for Medicines and Medical Devices (*Agenția Națională a Medicamentului și a Dispozitivelor Medicale din România*; "**ANMDMR**"), did authorise a limited hybrid regime for clinical trials in light of the health-related restrictions imposed by the Romanian government – when at this time, consultations, treatment and interventions in hospitals and other clinics were restricted, except for emergency situations. According to the notice published by ANMDMR addressed to companies conducting clinical trials, the regime was established during the state of emergency only (which lasted until May 2020).

During this period, scheduled visits by trial subjects enrolled in clinical trials were not permitted, unless, on a case-by-case basis, where the principal investigator concluded that an emergency existed and any delay could affect the safety of the trial subject. In all other non-urgent situations, ANMDMR strongly recommended the following: rescheduling visits or replacing them with telephone visits; identifying solutions for the delivery of medication to the patient homes; remote monitoring; postponing the initiation of new clinical trials or new investigation centres.

Although the Health Law No. 95/2006 regulates telemedicine as a means of providing health care, it only refers to prophylactic and curative medicine, without expressly referencing the extent to which such a procedure could also be used in clinical trials.

To date, no further communications have been published by ANMDMR concerning DCT-related measures, and no new relevant regulations have been adopted.

Serbia

Serbian law does not yet regulate DCTs. During the Covid-19 pandemic, the Medicines and Medical Devices Agency of Serbia (*Agencija za lekove i medicinska sredstva Srbije,* "**ALIMS**") issued its Recommendations for Sponsors of Clinical trials (the "**Recommendation**"), introducing the possibility of using certain DCT elements in clinical trials.

According to the latest available version of the Recommendation, dated 24 March 2021, and which is subject to ongoing updating, DCT elements in clinical trials may include the remote provision of information towards trial subjects in re-consenting procedures and obtaining re-consents via electronic communication means – but still only if the given clinical trial centre is affected by the Covid-19 pandemic. Moreover, remotely obtained re-consent must be confirmed on-site during the next subsequent visit by the trial subject at the clinical trial centre.

Other Covid-19-related ALIMS recommendations include rescheduling visits or replacing them with telephone calls and questionnaires to be sent to trial subjects, identifying solutions for the delivery of medication to the patient homes, and remote monitoring. All decisions on aligning activities during clinical trials during a pandemic are based on a risk assessment conducted by the sponsor.

Furthermore, although the Healthcare Act (Official Gazette of the RS, no. 25/2019) does not stipulate explicit provisions on telemedicine, the Serbian government's Programme on Digitalization in the Healthcare System of the Republic of Serbia for the 2022-2026 period recognizes the need to introduce telemedicine in the primary healthcare sector. Currently, no evident plans exist to use telemedicine in clinical trials under regular circumstances.

Slovakia

In Slovakia, the set of Guidelines for Clinical Trials During the Emergency Situation of COVID-19 (the "**ŠUKL Guidelines**"), as published by the State Institute for Drug Control (*Štátny ústav pre kontrolu liečiv; "**ŠUKL**"*) on 9 April 2021, are still in effect. The ŠUKL Guidelines enable the introduction of decentralized measures for ongoing and approved clinical trials.

It is possible, upon reaching an agreement with the sponsors and patients involved in a given clinical trial, for check-ups to be performed via telephone or video calls instead of on-site visits; moreover, on-site check-ups can be cancelled or postponed, and/or the intervals between on-site check-ups can be prolonged; and IMPs can be delivered to patients by an authorised distributor (direct delivery of an IMP to patients is in general not permissible in Slovakia). Remote source data verification in Slovakia is only permissible for the following types of clinical trials:

- clinical trials involving the treatment or prevention of Covid-19,
- clinical trials investigating serious or life-threatening diseases,
- clinical trials in situations where the absence of source data verification may represent an unacceptable risk for patient safety or a risk to the credibility/integrity of trial results,
- clinical trials involving vulnerable persons such as children, or those who are incapacitated, to provide informed consent temporarily (e.g. trials in emergency situations), or full consent (e.g. to patients with advanced dementia),
- pivotal (registration) clinical trials.

After the rescinding of a state of emergency, ŠUKL Guidelines specify that the sponsor of the given clinical trials should take certain measures such as increasing the number of monitoring visits at clinical trial centres, or the re-monitoring of source data, in order to mitigate the data integrity impact caused by the concomitant pandemic-related reduction of monitoring at clinical trial centres.

Slovak laws allow for the obtaining of a required informed consent without an in-person meeting by the clinical trial participant and the investigator. However, in such a case, the qualified electronic signature of the investigator and participant are required, according to Act No. 272/2016 on trust services for electronic transactions in the internal market.

Turkey

Turkish law does not currently provide for any specific regulation of DCTs. Certain DCT features have been referenced in a number of regulatory actions introduced by the Turkish Medicine and Medical Devices Authority ("**TITCK**") issued in response to the Covid-19 pandemic. Most notably, this includes the Guidelines on Measures to be Taken in Clinical Trials Due to the Covid-19 Pandemic (most recently updated on 5 May 2022). Such regulatory actions, however, are seemingly specific to imposed quarantine or curfew conditions. In such conditions, TITCK allows for the following methods in Turkish clinical trials: (i) remote monitoring activities, (ii) the delivery of a product to the participant at home, and (iii) the use of telephones for communication, or home visits, rather than participant visits to a research centre.

Outside of imposed quarantine or curfew conditions, only remote monitoring activities appear to be permissible in clinical trials subject to the Turkish regulatory framework. Turkish good clinical practice guidelines provide that monitoring activities during, before and after trials must generally be conducted on-site. The guidelines do not detail the scope of on-site requirements and, when taken together with other regulatory instruments, it can be concluded that under certain circumstances monitoring activities can be conducted remotely. Evidently, remote monitoring components can be included in Turkish clinical trials, provided that (i) the participant consents to such activities, (ii) it is appropriate under the circumstances of the clinical trial, and also factoring-in the safety of participant, and (iii) the confidentiality of data and compliance with Turkish Personal Data Protection Law are ensured.

Nonetheless, Turkish law is very strict on the principle that the participant's informed consent is required to be obtained at an in-person meeting between the given research investigator and participant. This principle prohibits the use of electronic means in obtaining informed consent forms. In its "frequently asked questions" (FAQs) section, a document concerning clinical trials issued by TITCK on 1 December 2019 (and updated on 30 April 2021), made clear that electronic means can only be used at the stage of providing information to participants, but are not valid for obtaining informed consent forms within the meaning of the Clinical Trials Regulation.

Ukraine

DCT's are not yet regulated under Ukrainian law. However, on 28 September 2020, the regulatory authority, the State Expert Center of the Ministry of Health of Ukraine (*Державний експертний центр МОЗ України*, "**SEC**") issued its Updated Recommendations for Conducting Medicinal Clinical Trials Under the Extended Quarantine in Ukraine (the "**COVID Recommendations**"), developed in line with the COVID Guidance of the European Medicines Agency *(EMA, Version 3 as of 28 April 2020).* Quarantine rules in Ukraine are currently extended until 30 April 2023. The COVID Recommendations have also been affirmed via the SEC's Recommendations for Conducting Clinical Trials During Martial Law in Ukraine as of 1 June 2022 (the "**Martial Law Recommendations**"). Currently, martial law in Ukraine is in effect until 19 February 2023 (further extensions are likely).

Under the COVID Recommendations and the Martial Law Recommendations (jointly the "**Recommendations**") conducting off-site monitoring (e.g. check-ups via phone calls, e-mail, or other online tools (telemedicine) instead of on-site visits is permissible, as is rSDV, provided that the respective provisions are reflected in the given clinical trial documentation (ICF, rSDV procedure, etc). An ICF can be signed physically and/or remotely (e.g. by a qualified e-signature which is equal to an original signature under Ukrainian law) and sent by e-mail or by regular post. If signing the updated ICF is not possible, oral consent can be provided by the trial participant (e.g. via a video conference with the healthcare personnel) and the respective note to this effect is made on the primary documents (a duly signed ICF must be obtained as soon as possible). The updated clinical trial documentation is then sent by e-mail to the SEC and/or respective ethics committee; the originals can be provided at a later stage (as soon as possible). Moreover, an IMP can be delivered to trial participants by an independent distributor, and an examination of trial participants can be performed by laboratories outside of the clinical trial location, provided that an agreement to this effect is concluded between the third-party providers and the sponsor.

On 28 July 2022 a new Law on Medicines (the "**Medicines Law**") was adopted, designed to harmonize Ukrainian regulations and EU standards. The Medicines Law will come into force in stages; the majority of provisions come into force within 30 months after martial law is rescinded. According to unofficial sources, considering the increased relevance of DCTs, the respective regulations will likely be adopted before the end of martial law.

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