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DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Public health, country knowledge, crisis management
Health Security

Guidance on the mutual acceptance of EU Digital COVID Certificates issued to participants of clinical trials for COVID-19 vaccines

The present document is the outcome of discussions held in the Technical Working Group on EU Digital COVID Certificates for clinical trial participants, adopted by the Health Security Committee on 5 October 2022.

5 October 2022

1. Introduction

The topic of EU Digital COVID vaccination certificates for participants in clinical trials for COVID-19 vaccines has been raised in past Health Security Committee meetings. On 15 June 2022, DG SANTE presented Regulation 2022/1034 for the EU Digital COVID Certificate[1] (EU DCC), extending the EU Digital COVID Certificate system until the end of June 2023.

The new Regulation states that Member States may issue an EU DCC to persons participating in ongoing clinical trials for COVID-19 vaccines, as long as the trial has been approved by Member States' ethical committees and competent authorities. Such certificates may be accepted by the Member States in order to waive restrictions to free movement:

"*Member States may also issue vaccination certificates to persons participating in a COVID-19 vaccine clinical trial that has been approved by Member States' ethical committees and competent authorities, regardless whether the participant received the COVID-19 vaccine candidate or the dose administered to the control group. The information about the COVID-19 vaccine to be included in the vaccination certificate in accordance with the specific data fields set out in point 1 of the Annex shall not undermine the integrity of the clinical trial.*

Member States may accept vaccination certificates issued by other Member States in accordance with the fourth subparagraph in order to waive restrictions to free movement put in place, in accordance with Union law, to limit the spread of SARS-CoV-2, unless their acceptance period has expired or they have been revoked following the conclusion of the clinical trial, in particular on the grounds that the COVID-19 vaccine was subsequently not authorised or that the vaccination certificates were issued for a placebo administered to the control group as part of a blinded trial."

Moreover, the Health Security Committee (HSC) has been tasked with ensuring coherence over the acceptance of these certificates across the EU:

"*[…] To ensure a coherent approach, the Commission should be empowered to ask the Health Security Committee, the European Centre for Disease Prevention and Control (ECDC) or the European Medicines Agency (EMA) to issue guidance with regard to the acceptance of certificates issued for a COVID-19 vaccine undergoing clinical trials that has not yet been granted a marketing authorisation pursuant to Regulation (EC) No 726/2004, which should take into account the ethical and scientific criteria necessary for carrying out clinical trials.*"

[1] Regulation (EU) 2022/1034 of the European Parliament and of the Council of 29 June 2022 amending Regulation (EU) 2021/953 on a framework for the issuance, verification and acceptance of interoperable COVID-19 vaccination, test and recovery certificates (EU Digital COVID Certificate) to facilitate free movement during the COVID-19 pandemic (OJ L 173, 30.6.2022, p. 37).

In the context of this mandate, the Commission set up a HSC Technical Working Group on EU DCC issued to COVID-19 clinical trial participants. The main tasks of this technical working group are:

- To draft guidance on a coherent approach for the mutual acceptance of EU Digital COVID vaccination certificates issued to clinical trials participants of COVID-19 vaccines that have not yet been granted a marketing authorisation. This guidance will include a list of ongoing clinical trials for COVID-19 vaccines. The guidance, to be drafted based on discussions within the Technical Working Group and input from its participants – namely, nominated representatives of EU/EEA Member States, ECDC, EMA, and the Trials Coordination Board - will be put forward to the HSC for formal agreement by EU/EEA countries;
- To review new data and information submitted on ongoing clinical trials for COVID-19 vaccines and, where necessary, to put forward proposals for updates to the guidance and/or list of clinical trials for COVID-19 vaccines for which EU DCC of vaccination should be mutually accepted across the EU Member States;
- To participate in discussions regarding ethical and scientific criteria related to clinical trials for COVID-19 vaccines.

2. Acceptance of EU Digital COVID Certificates of vaccination issued to participants of clinical trials

General considerations and work of the Health Security Committee

During the COVID-19 pandemic, the Commission has strived to put in place coordinated rules across Member States to ensure free and safe intra-EU travel. The EU Digital COVID Certificate (EU DCC) was born out of a need to facilitate free movement, at a time when Member States were imposing travel restrictions.

The question of certificates for participants in clinical trials has been brought up in various forums, including in the Health Security Committee (HSC). During discussions in the HSC, not all countries felt concerned by the issuance of certificates if no trials are taking place nationally, resulting in the fact that there may not be any requests for such certificates at national level. However, where certificates are being issued, it is important that they are recognised and accepted also in other Member States.

A HSC survey on the mutual acceptance of EU vaccination certificates for participants in clinical trials was presented on 1 June 2022, containing 23 replies[2]. Although there was an overall trend towards a wider acceptance of clinical trials, the majority of EU/EEA countries still had no defined view on the subject. The responses also showed a divergence of opinions regarding the inclusion of clinical trials, e.g. all trials vs EU/EEA only, or how to deal with multi-country trials.

[2] Responses received by: SK, SE, FI, DE, CZ, AT, NL, SI, PL, DK, LV, EL, LT, IE, HU, MT, CY, RO, FR, EE + IS, NO, LIE

Following the adoption of the new Regulation 2022/1034 on 29 June 2022, it is now possible for Member States to issue EU DCC to persons participating in ongoing clinical trials for COVID-19 vaccines which have not yet been granted a marketing authorisation, as long as they are approved by Member States' ethical committees and competent authorities. Equally, Member States may accept certificates issued by other Member States in order to waive restrictions to free movement due to the COVID-19 pandemic, where these are in place.

The Commission may adopt implementing acts establishing that COVID-19 certificates issued by a third country are to be considered as equivalent to certificates issued by Member States in accordance with the DCC Regulation ('equivalence decisions'). It therefore follows that Member States may also accept vaccination certificates covered by an equivalence decision issued by third countries to persons participating in a COVID-19 vaccine clinical trial.

Furthermore, to preserve the integrity of clinical trials and ensure the validity of the studies, including in terms of data blinding and confidentiality, the new Regulation states that, where Member States issue EU DCC for a given clinical trial, all participants are entitled to receive vaccination certificates irrespective of the dose received, i.e. whether they were administered the candidate vaccine or, if the participants were part of a control group, a different vaccine or a placebo.

The Commission Implementing Decision (EU) 2021/1073 on technical specifications was also amended accordingly and adopted on 8 September. This was to ensure that the rules for populating the EU Digital COVID Certificate were updated to reflect the possibility to issue vaccination certificates for participants of clinical trials. The following designation will apply in case of doses administered as part of a clinical trial: "*CT_clinical-trial-ID*".

However, to avoid a confusing scenario where different Member States would accept or not a given certificate, it is necessary to agree on a common approach across all Member States with regard to the acceptance and implementation of these certificates. As per the Regulation 2022/1034, the Health Security Committee is asked to issue guidance on such a common approach.

In light of a possible next wave of the COVID-19 pandemic during the upcoming autumn and winter months, Member States may reintroduce, where necessary and proportionate, travel restrictions, including the requirement to present an EU DCC.

It is therefore important to agree on a common understanding regarding these certificates, to guarantee clarity for participants in clinical trials. Clinical research plays a fundamental role in the development of vaccines and in public health in general. Voluntary participation in clinical trials should be encouraged. There is a concern that participation would be hindered, and consequently the studies themselves would be impacted, if participants are denied access to EU DCC for vaccination, or if that EU DCC is

not accepted in other Member States. Organisers of clinical trials have flagged this matter previously.

This work is also very relevant outside of the COVID-19 pandemic and the EU DCC, as it may set agreements and principles for future epidemics or pandemics, where the ambition will be to develop vaccines globally within 100 days.

Proposed guidance of the mutual acceptance of EU Digital COVID Certificates of vaccination issued to participants of clinical trials

There are a number of arguments in favour of a **'general acceptance' approach** (= all vaccination certificates issued for ongoing clinical trial participants included in a common list are accepted under the same conditions as other DCC vaccination certificates for the purpose of lifting free movement restrictions) , namely:

- The EU DCC may be reintroduced if the COVID-19 pandemic evolves (possibility of an autumn/winter peak). It remains important to ensure that everyone can obtain a valid EU DCC;
- The speed at which vaccines can be developed (e.g. against a future variant that evades current immunity) depends on the success of recruiting a large number of trial participants within the shortest period possible;
- Based on the lessons learnt with the authorisation of the first generation of COVID-19 vaccines, it had become increasingly difficult to attract participants to trials of new vaccines, given the uncertainty regarding their ability to travel;
- Trial participants should therefore be incentivised with equal opportunities for travel, particularly as numbers of trial participants are comparatively small (e.g. 46 000 globally for authorising Pfizer/BioNTech, 24 000 for AstraZeneca).
- Also, the risk will only be limited to the duration of the trial itself. Upon conclusion of the trial, if the new vaccine gets authorised, participants may benefit from a new EU DCC of vaccination for the authorised vaccine. If this is not the case, certificates may be revoked, in line with the current rules set out in the Regulation. In a situation where the candidate vaccine is denied authorisation following a review process by the regulatory body (national or EMA), or if the vaccination certificate was issued for a placebo administered to the control group as part of a blinded trial, the HSC recommends that the EU DCC for trial participation should be revoked.
- In the current scenario of vaccine development, control group participants are also vaccinated with an authorised vaccine. There are no placebo groups anymore;
- The large benefits of trial participation therefore greatly outweigh the potential risk of participants travelling during the period of the clinical trial;
- **Global perspective** (EU DCC equivalence decisions): Due to its global success, the EU DCC will continue to be an important incentive for potential participants in global trials, which will eventually benefit the public health in the EU;

- Lessons learnt from the first generation of COVID-19 vaccines that were authorised in the EU show that the corresponding trials took place almost exclusively outside the EU (e.g. in the US, UK, Argentina, Brazil, Mexico, South Africa, Turkey). We must therefore ensure in the future that (a) relevant clinical trials also take place in the EU and (b) provide incentives for trial participation both across the EU and for key global trials, on which EU access to new vaccines depends and which would be in our own EU interest.

Taking into consideration the above-mentioned arguments relating to ongoing clinical trials for COVID-19 vaccines, the expert opinion of the Technical Working Group on EU Digital COVID Certificates for clinical trial participants is as follows:

- Member States should agree to a **single approach of mutual acceptance** for all ongoing clinical trials, without differentiation (if listed in Annex to this document). That is, where a EU Digital COVID Certificate of vaccination has been issued to a participant of a clinical trial, all other EU Member States / EEA countries should agree to accept those certificates for the purpose of waiving restrictions to free movement, should those restrictions be in place as a response to the COVID-19 pandemic;

- The above should apply to **all EU/EEA publicly available clinical trials recorded as ongoing in EudraCT or CTIS**, which should be listed in Annex to this document and updated on a regular basis. This list should be provided by EMA and include all trials on COVID-19 vaccines for which information is available on the EU Clinical Trials Register (public interface of EudraCT) or CTIS public portal. It is the responsibility of the Member States to update the information concerning nationally authorised clinical trials through EudraCT or CTIS.

- Considering the global context of the EU Digital COVID Certificate, namely the various equivalence decisions made with third-countries regarding the use of this tool, and that the vast majority of clinical trials took place outside the EU for the first generation of EU-authorised COVID-19 vaccines, a limited selection of **key international trials should also be considered.** Such clinical trials would be added to the list in Annex following the nomination by the respective trial sponsor and following a procedure of prior review for compliance, in terms of relevance and quality, by the Commission, with the help of VACCELERATE[3], the EU clinical research network for the coordination and conduct of COVID-19 vaccine trials.

- Any additions and/or alterations to the common list of clinical trials for COVID-19 vaccines mentioned in this guidance will always be subject to a process of acceptance by the Health Security Committee. This document is intended to

[3] https://vaccelerate.eu/

function as a "living document" where the list of clinical trials in Annex may be updated as required.

List of clinical trials for COVID-19 vaccines

A list of ongoing clinical trials for COVID-19 vaccines is included as an **Annex** to this document. This list is currently restricted to clinical trials on COVID-19 vaccines in the EU/EEA that the national competent authorities (NCAs) have approved on EudraCT or CTIS. Of note, no trials on COVID-19 vaccines were uploaded on CTIS at the time when the present guidance was drafted.

In time, it should be further complemented with key international trials. This process should be overseen by the Commission and include the necessary checks for quality compliance. For the first generation of COVID-19 vaccines, the EU has mainly relied on clinical trials undertaken outside the EU and within a very short time from April - December 2020 (e.g. Pfizer/BioNTech had enrolled 46,331 participants in Argentina, Brazil, Turkey, South Africa and the United States. AstraZeneca involved 23,848 people in the UK, Brazil, and South Africa). It will therefore be crucial to consider the important incentive that an EU DCC represents for potential participants in global trials, which will eventually benefit the public health in the EU.

Taking into account that trials conducted in the EU/EEA would already have been approved by Member States' ethical and scientific committees, there is no requirement to assess again the ethical and scientific merits of individual trials. Trials for which information is available on the EU Clinical Trials Register (the public portal of EudraCT) or the CTIS public portal may be added to the list in Annex by EMA, upon request of European Commission. Of note, the role of EMA is limited to the provision of a list on the currently ongoing EU/EEA clinical trials on COVID-19 vaccines. Member States will be responsible for updating the necessary information regarding clinical trials authorised at national level on EudraCT/CTIS, to ensure that those trials are duly included on the list (Annex).

In the current list in Annex, trials for which information cannot be publicly shared are marked in [yellow] and are anonymised, displaying only information on the EU/EEA countries were the trial is planned to take place. The entries in [yellow] correspond to either 1) trials that have not yet been authorised in the Member States; or 2) phase I trials in adults only (noting that phase I/II trials would already be disclosed on EU-CTR, as well as any phase I that include children).

3. Mechanism for review of ongoing clinical trials for COVID-19 vaccines

Where necessary, the European Commission should put forward proposals for updates to the guidance, in particular where the information in Annex (list of clinical trials) requires reviewing or updating. Such modifications should always be subject to an assessment and final agreement by the Health Security Committee.

In the case of non-EU clinical trial, onus should be placed on the sponsors of ongoing clinical trials for COVID-19 vaccines with regards to taking the appropriate steps to submit a request to the European Commission for inclusion in the list of accepted clinical trials, and to providing the necessary information regarding the trials. The inclusion of such trials should be done on a case-by-case basis and the final decision, in favour or against, should be issued by the EU/EEA countries within the Health Security Committee.