This toolkit will be updated as additional information is released by FDA.

The rapidly evolving information related to the Emergency Use Authorization for CCP is expected to result in updates, including changes to the:

- FDA’s May 1, 2020 Investigational CCP Guidance for Industry, and
- FDA’s webpage, Recommendations for Investigational COVID-19 Convalescent Plasma.
Events of August 23, 2020

1- FDA provided this statement:
“One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19. On August 23, 2020 FDA issued an Emergency Use Authorization (EUA) for COVID-19 Convalescent Plasma. In addition, the Recommendations for Investigational COVID-19 Convalescent Plasma page provides information on the pathways available outside of the EUA for administering or studying the use of COVID-19 convalescent plasma. It is critical to continue to enroll and complete randomized clinical trials to fully answer the questions about the effectiveness of convalescent plasma...Health care providers or acute care facilities should obtain COVID-19 convalescent plasma from an FDA-registered blood establishment.”

2- EUA request for CCP sponsored by the Office of the Assistant Secretary for Preparedness and Response.

3- FDA News Release: FDA Issues Emergency Use Authorization, stating:
“Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients as part of the agency’s ongoing efforts to fight COVID-19. Based on scientific evidence available, the FDA concluded, as outlined in its decision memorandum, this product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.”

“The EUA remains in effect until the termination of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19. The EUA may be revised or revoked if it is determined the EUA no longer meets the statutory criteria for issuance.”

COVID-19 Convalescent Plasma
Reduction in Death at 7 Days

Non-intubated patients treated within 72 h age 80 or less (n=1018)

Statistically significant 37% reduction in mortality in those treated with high titer convalescent plasma (p=.03)

High titer corresponds approximately to Ortho VITROS S/C level ≥ 12

MORE INFORMATION is provided in the news release.
4- FDA posted the Clinical/decision memorandum - REFER to the memorandum for detailed information supporting these Conclusions:

- COVID-19 Convalescent Plasma may be effective in the treatment of COVID-19 and it is reasonable to believe that the known and potential benefits of CCP outweigh the known and potential risks of the product for the proposed EUA.
- Current evidence suggests clinical benefit is most likely in patients treated early in the course of the disease (e.g., prior to intubation) and with the use of CCP with higher antibody levels or neutralization activity.
- Current data are limited by the unavailability of validated assays of antibody levels or neutralization activity in CCP. Based on the available data, it is reasonable to use the Ortho VITROS IgG assay with an S/C cutoff of 12 or greater as a manufacturing potency test to qualify high titer units of CCP.
- Based on the available evidence, CCP without a result of 12 or greater in the Ortho VITROS assay meets the criteria for issuance of an EUA because, among other things, it is reasonable to believe it may be effective in treating COVID-19 and the known and potential benefits of the product outweigh its known and potential risks. Such units must be labeled as “COVID-19 Convalescent Plasma of Low Titer.” Health care providers can decide whether to use these units based on an individualized determination of potential benefit and risk.
- Randomized controlled trials are required to show definitive evidence of safety and efficacy and to determine the optimal product attributes and appropriate patient populations for the use of COVID-19 Convalescent Plasma.

5- Fact Sheets – “The EUA requires that fact sheets providing important information about using COVID-19 convalescent plasma in treating COVID-19 be made available to health care providers and patients, including dosing instructions and potential side effects. Possible side effects of COVID-19 convalescent plasma include allergic reactions, transfusion-associated circulatory overload, and transfusion associated lung injury, as well as the potential for transfusion-transmitted infections.”

- The Fact Sheet for health care providers includes a description of the product and information such as drug interactions, side effects, risks, benefits and risk-benefit assessment. The Fact Sheet also includes the following:
  
  **Dosage**
  Health care providers will administer COVID-19 convalescent plasma according to standard hospital procedures and institutional medical and nursing practices. Clinical dosing may first consider starting with one convalescent plasma unit (about 200 mL), with administration of additional convalescent plasma units based on the prescribing physician’s medical judgment and the patient’s clinical response. Patients with impaired cardiac function and heart failure may require a smaller volume or more prolonged transfusion times.

  **Administration**
  Administer COVID-19 convalescent plasma infusion through a peripheral or central venous catheter according to standard institutional medical and nursing practices for the administration of plasma ([http://www.aabb.org/tm/coi/Documents/coi1017.pdf](http://www.aabb.org/tm/coi/Documents/coi1017.pdf)).
Storage
COVID-19 convalescent plasma, may be stored frozen at -18°C or colder, and has an expiration date one year from the date of collection. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.

- The Fact Sheet for patients provides general information to inform the patient and patient’s parents/caregivers.

6- The EAP website www.USCOVIDplasma.org has this message posted:

“The Mayo Clinic-led expanded access program will be discontinuing new physician and new patient enrollments. COVID-19 convalescent plasma remains available through emergency use authorization.”

➢ Table 1 on the following page will be updated as new information is released by FDA.
➢ The information is current as this document is posted on the AABB website.
TABLE 1. AUGUST 23, 2020 REVISIONS TO FDA’S WEB PAGE:
Recommendations for Investigational COVID-19 Convalescent Plasma

NOTE: The rapidly evolving information related to the EUA is expected to result in additional changes to this August 23, 2020 web page and the May 1 2020 Investigational COVID-19 Convalescent Plasma Guidance. AABB will continue to update resources as new information becomes available.

FDA issued an EUA for convalescent plasma on August 23, 2020. Please check back for updates to this page in the near future.

No change in information from 05 01 2020

FDA has issued guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. The guidance provides recommendations on the following:

- pathways for use of investigational COVID-19 convalescent plasma
- patient eligibility
- collection of COVID-19 convalescent plasma, including donor eligibility and donor qualifications
- labeling, and
- record keeping

Because COVID-19 convalescent plasma has not yet been approved for use by FDA, it is regulated as an investigational product. A health care provider must participate in one of the pathways described below. FDA does not collect COVID-19 convalescent plasma or provide COVID-19 convalescent plasma. Health care providers or acute care facilities should instead obtain COVID-19 convalescent plasma from an FDA-registered blood establishment.

<table>
<thead>
<tr>
<th>FDA’s August 23, 2020 Web Page Update</th>
<th>Replacing May 1, 2020 Web Page Information</th>
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<tbody>
<tr>
<td>KEY TO HIGHLIGHTED INFORMATION</td>
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<tr>
<td>• New information is highlighted below</td>
<td>• Information from May 1 webpage not included in the August 23, 2020 update is highlighted below</td>
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<td>• Information that did not change but was moved is highlighted</td>
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| FDA issued an EUA for convalescent plasma on August 23, 2020. Please check back for updates to this page in the near future. |

<table>
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Excerpts from the guidance document are provided below.

**No change in information from 05 01 2020**

**Background**

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States (U.S.) from threats including emerging infectious diseases, such as the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic. One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19. Convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19) is being studied for administration to patients with COVID-19. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic. Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials.

**No change in information from 05 01 2020**

**Pathways for Use of Investigational COVID-19 Convalescent Plasma**

The following pathways are available for administering or studying the use of COVID-19 convalescent plasma:

1. **Clinical Trials**

Investigators wishing to study the use of convalescent plasma in a clinical trial should submit requests to FDA for investigational use under the traditional IND regulatory pathway (21 CFR Part 312). CBER’s Office of Blood Research and Review is committed to engaging with sponsors and reviewing such requests expeditiously. During the COVID-19 pandemic, INDs may
be submitted via email to CBERDCC_eMailSub@fda.hhs.gov.

### No change in information from 05 01 2020

#### 2. Expanded Access

An IND application for expanded access is an alternative for use of COVID-19 convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (21 CFR 312.305). FDA has worked with multiple federal partners and academia to open an expanded access protocol to facilitate access to COVID-19 convalescent plasma across the nation. Access to this investigational product may be available through participation of acute care facilities in an investigational expanded access protocol under an IND that is already in place.

Currently, the following protocol is in place: **National Expanded Access Treatment Protocol**

### No change in information from 05 01 2020

#### 3. Single Patient Emergency IND

Although participation in clinical trials or an expanded access program are ways for patients to obtain access to convalescent plasma, for various reasons these may not be readily available to all patients in potential need. Therefore, given the public health emergency that the COVID-19 pandemic presents, and while clinical trials are being conducted and a national expanded access protocol is available, FDA also is facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of the patient’s physician requesting a single patient emergency IND (eIND) for the individual patient under 21 CFR 312.310. This process allows the use of an investigational drug for the treatment of an individual patient by a licensed physician upon FDA authorization, if the applicable regulatory criteria are met. Note, in such case, a licensed physician seeking to administer COVID-19 convalescent plasma to an individual patient must request the eIND (see 21 CFR 312.310(b)).
The requesting physician may contact FDA by completing Form FDA 3926 ([https://www.fda.gov/media/98616/download](https://www.fda.gov/media/98616/download)) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov.

**NOTE:** To enable electronic completion of the form, download it from your internet browser, save locally, close and re-open. Do NOT ATTEMPT to fill out this form after opening it from your internet browser; the form will not be fillable until downloaded, saved and opened locally. Check either box 3a or 3b to enable form logic and the appropriate fields. For more detailed instructions see the FDA FORM 3926 Instructions ([https://www.fda.gov/media/98627/download](https://www.fda.gov/media/98627/download)). CBER requests that all forms be filled out electronically to facilitate rapid review. Handwritten forms are often hard to read and may delay the processing of the request. Please pay special attention to the following:

- The completed form should include a brief clinical history of the patient, including age, gender, diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements in 21 CFR 312.305 and 312.310.
- The form should include the name of the blood establishment collecting the COVID-19 convalescent plasma.
- Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required.

<table>
<thead>
<tr>
<th>For requests between 8am ET and 8pm ET (Mon-Sun):</th>
<th>For requests between 8am ET and 8pm ET where the provider is unable to complete and submit Form FDA 3926 due to extenuating circumstances, the provider can contact FDA’s Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.</th>
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<tr>
<td>FDA will respond within four hours.</td>
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<td>For requests that are made overnight between 8pm ET and 8am ET (Mon-Sun):</td>
<td>For requests that are made overnight between 8pm EST and 8am EST, in case of a medical emergency, the provider should contact FDA’s Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization from a medical officer.</td>
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<td>- In case of a medical emergency, i.e., when authorization and issuance of an emergency IND</td>
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For requests between 8am EST and 8pm EST (Mon-Sun), the requesting physician may contact FDA by completing Form FDA 3926 ([https://www.fda.gov/media/98616/download](https://www.fda.gov/media/98616/download)) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov. For eIND requests submitted via email during this time frame, FDA will respond within 4 hours.

- The completed form should include a brief clinical history of the patient, including: diagnosis, current therapy, and rationale for requesting the proposed investigational treatment in order to meet the expanded access use requirements in 21 CFR 312.305 and 312.310.
- The form should include the name of the blood establishment collecting the COVID-19 convalescent plasma.
- Providers should complete the form to the extent possible, and FDA will work with the provider if additional information is required.
- Providers are strongly encouraged to fill out the form electronically whenever possible.
- FDA will review the request and, upon authorization, send the requesting physician a confirmatory email that includes the emergency IND number.
- For requests that are made overnight between 8pm EST and 8am EST, in case of a medical emergency, the provider should contact FDA’s Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization from a medical officer.
number is needed before 8 am the next morning, the provider should contact FDA’s Office of Emergency Operations at 1-866-300-4374 to be routed to the appropriate clinical review staff for assistance with submitting the request and issuance of an emergency IND number.

• In case of a non-critical overnight request, the Form FDA 3926 should be submitted by email to CBER_eIND_Covid-19@FDA.HHS.gov for review, and the emergency IND number will be issued by 8 am the next morning.

In situations when the provider is unable to complete and submit Form FDA 3926 due to extenuating circumstances, the requestor must agree to submit an expanded access application (e.g., Form FDA 3926) within 15 working days of FDA’s authorization of the use (21 CFR 312.310(d)(2)). When submitting the expanded access application form the requestor is advised to indicate that the application is a follow-up to a previously granted emergency IND, and to provide the IND number.

If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., Form FDA 3926) within 15 working days of FDA’s authorization of the use. (21 CFR 312.310(d)(2)).

No change in information from 05 01 2020

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol [External Link]. These criteria include:

• Laboratory confirmed COVID-19
• Severe or immediately life-threatening COVID-19, for example,
  o Severe disease is defined as one or more of the following:
    ▪ shortness of breath (dyspnea),
    ▪ respiratory frequency ≥ 30/min,
    ▪ blood oxygen saturation ≤ 93%,
    ▪ partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300,
    ▪ lung infiltrates > 50% within 24 to 48 hours

Not changed
Life-threatening disease is defined as one or more of the following:
- respiratory failure,
- septic shock,
- multiple organ dysfunction or failure

- Informed consent provided by the patient or healthcare proxy.

Collection of COVID-19 Convalescent Plasma

Health care providers or acute care facilities seeking to use COVID-19 convalescent plasma should include information in the IND submission that the COVID-19 convalescent plasma will be obtained from an FDA-registered blood establishment that follows the donor eligibility criteria and donor qualifications described below in collecting plasma from donors.

1. Donor Eligibility
   a. COVID-19 convalescent plasma must only be collected from individuals who meet all donor eligibility requirements (21 CFR 630.10, 21 CFR 630.15). Note the additional donor eligibility requirements for the collection of plasma by plasmapheresis in 21 CFR 630.15 (b). Donation testing for relevant transfusion-transmitted infections must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).
   b. COVID-19 convalescent plasma is collected from individuals who meet the following qualifications:
      i. Evidence of COVID-19 documented by a laboratory test either by:
         ▪ A diagnostic test (e.g., nasopharyngeal swab) at the time of illness
         OR
         ▪ a positive serological test for SARS-CoV-2 antibodies after recovery, if prior
diagnostic testing was not performed at the time COVID-19 was suspected.

ii. Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.

iii. Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

iv. SARS-CoV-2 neutralizing antibody titers, if available
   ▪ When measurement of neutralizing antibody titers is available, we recommend neutralizing antibody titers of at least 1:160. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.
   ▪ When measurement of neutralizing antibody titers is not available, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date. Although optional for all IND pathways, storing samples for single patient eINDs is not recommended.

Registered and licensed blood establishments that collect plasma intended for transfusion do not need to request a supplement to their license or obtain their own IND to collect and manufacture COVID-19 convalescent plasma for investigational use provided they 1) follow their standard operating procedures for plasma collection and all applicable regulations, and 2) collect plasma from individuals that meet the donor...
qualifications specified above, which would be included in the applicable IND(s) held by a health care provider or other sponsor.

Once manufactured, the COVID-19 convalescent plasma may be distributed for investigational use. Blood establishments do not need to request an alternative procedure or exception under 21 CFR 640.120(a) to collect COVID-19 convalescent plasma.

**No change in information from 05 01 2020**

2. **Labeling**

   a. The container label of COVID-19 convalescent plasma units must include the following statement, “Caution: New Drug—Limited by Federal (or United States) law to investigational use.” (21 CFR 312.6(a)).

   In addition, the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.

   i. FDA recognizes that the current circular of information does not contain specific information about COVID-19 convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.

   b. We recommend the use of a uniform container label for COVID-19 convalescent plasma. In particular, we recommend the use of the International Society of Blood Transfusion (ISBT) format specified in the United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128.

   c. The manufacturing process used and the expiration date on the label for COVID-19 convalescent plasma should be the same as for other plasma products that are of
the same type. For example, COVID-19 Convalescent Plasma, Fresh Frozen, should be frozen within 8 hours after collection, stored at -18C or colder and have an expiration date one year from the date of collection.

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<td>2. Recordkeeping</td>
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A health care provider who is participating in an IND, including an expanded access IND or eIND, must maintain records for the COVID-19 convalescent plasma unit(s) administered to the COVID-19 patient (21 CFR 312.62). Such records should include the unique identification number(s) (e.g., the ISBT donation identification number(s)) of the unit(s).

| Not changed |