Expanded Access Investigational New Drug (IND) Application Protocol:

Use of Diphtheria Antitoxin (DAT) for Possible Diphtheria Cases

BB-IND 11184

Protocol CDC IRB # 4167

Version Number 12.0
February 9, 2023

IND Sponsored by Centers for Disease Control and Prevention (CDC)

This expanded access IND protocol for DAT from the CDC contains information intended to guide treating clinicians regarding the use of investigational DAT and should only be used for the stated purpose and scope of the IND protocol in accordance with the applicable IND regulatory requirements. This document, and the contents within the document, should not be altered or reproduced without prior authorization from the CDC.

PROGRAM CONTACT INFORMATION

Principal Investigator: Erin Tromble, MD
Meningitis and Vaccine Preventable Diseases Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
1600 Clifton Road NE, Mailstop H24-8
Atlanta, GA 30329
Office: (404) 498-5020
E-mail: lzn6@cdc.gov

Regulatory Affairs: CAPT Yon Yu, Pharm.D.
Regulatory Affairs and Clinical Guidelines Team Lead
Division of Preparedness and Emerging Infections
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Road NE, Mailstop H24-11
Atlanta, GA 30329
Office: (404) 639-3046
E-mail: fkb8@cdc.gov

TABLE OF CONTENTS

1.0 OBJECTIVE

The purpose of this expanded access Investigational New Drug (EA-IND) protocol is to provide access to investigational diphtheria antitoxin (DAT) for treatment of suspected diphtheria cases, and for prophylactic use under exceptional circumstances in an exposed contact, in the absence of Food and Drug Administration (FDA)-approved drugs for treatment or prophylaxis of diphtheria.

2.0 BACKGROUND

Diphtheria is a clinical syndrome caused by an exotoxin produced by the bacterium *Corynebacterium diphtheriae*; non-toxin-producing strains of *C. diphtheriae* are not associated with the syndrome but can cause localized inflammation. Most commonly, toxigenic infection results in respiratory or cutaneous disease. Diphtheria is transmitted from person to person by respiratory droplets or contact with discharges from skin lesions. The severe local and systemic manifestations of respiratory diphtheria result after diphtheria toxin binds to a wide range of cells, including epithelial, nerve and muscle cells. The toxin interferes with enzymes necessary for protein synthesis, leading to cell damage and death. Local effects include severe inflammation and pseudomembrane (a firmly-adherent leather-like exudate that looks like a membrane) formation in the nose, and/or pharynx and/or larynx, which can progress to life-threatening airway obstruction. Systemic effects may occur from absorption of diphtheria toxin and include myocarditis, polyneuritis, and, rarely, renal failure.

There are four biotypes of *C. diphtheriae:* gravis, mitis, belfanti and intermedius. All four biotypes are capable of producing an identical exotoxin. No difference in pathogenicity has been demonstrated among the four biotypes. Some strains of *Corynebacterium ulcerans* can also produce an identical diphtheria toxin. A respiratory diphtheria-like illness can result from an infection caused by toxin-producing strains of *C. ulcerans.*[1] The onset of disease is insidious. Following an incubation period of 1-5 days, low-grade fever begins and a pharyngeal pseudomembrane develops over 2-3 days, along with lymphadenopathy and diffuse systemic toxicity, resulting in a rapid, thready pulse, weakness, and irritability. Although the systemic effects of diphtheria can occur in the first week of illness, they usually occur later (1-2 weeks after onset for myocarditis, 2-8 weeks for neuritis).

The hallmark of suspected respiratory diphtheria is a low-grade febrile, membranous pharyngitis of insidious onset. In a minority of instances, respiratory diphtheria can result from an isolated diphtherial infection in the larynx or nasal lining. Other diseases that can occasionally produce a similar membranous pharyngitis include streptococcal pharyngitis and infectious mononucleosis. Patients who have been treated with immunosuppressive drugs can present with a membrane that mimics diphtheria. Isolated diphtherial laryngitis can usually be differentiated from *Haemophilus influenzae* type b epiglottitis, spasmodic croup, or the presence of a foreign body by the gradual onset of diphtherial disease. Differentiation of isolated diphtherial laryngitis from viral laryngotracheitis or bacterial tracheitis can be difficult on the basis of symptoms alone.

DAT was first produced in the 1890s and is still being produced using serum from horses that are hyperimmunized with diphtheria toxoid. The evidence for efficacy of equine-based DAT for the treatment of respiratory diphtheria is based on observations and studies done several decades ago. Mortality rates for clinical diphtheria frequently exceeded 50% in the pre-antitoxin era. Almost as soon as antitoxin was available, clinical experience showed dramatic declines in mortality in groups of patients treated with antitoxin compared to historical control groups or groups treated at hospitals not using antitoxin. In one controlled trial in which patients at a hospital were allocated to antitoxin treatment or no antitoxin treatment on an alternating day schedule, mortality in treated patients was 3.3% compared to 12.2% in untreated patients.[2] It was also shown that early treatment is critical, with the degree of protection from DAT inversely related to the duration of clinical illness preceding its administration. Mortality increased progressively based on the interval from onset of illness to treatment, with a sharp increase from 4% mortality in those treated with antitoxin within 24-48 hours to 16.1% in those treated on the third day of

illness.[3] Mortality rates continued to increase with more prolonged intervals, reaching 29.9% in those treated 7 or more days after onset. Current thinking is that toxin fixes to susceptible cells early in disease and fixed toxin is not neutralized by antitoxin.[4]

The management of a patient with suspected diphtheria includes:

1) Administration of DAT as soon as possible after assessing for hypersensitivity to horse serum; early administration of DAT is critical for survival.[5]
2) Establishing the diagnosis through appropriate bacterial cultures;
3) Administration of antibiotics; and
4) Appropriate supportive care including special attention to maintaining an adequate airway in the presence of laryngeal or extensive pharyngeal membranes and to careful monitoring for cardiac rhythm disturbances or other manifestations of myocarditis.

Respiratory diphtheria is currently a rare disease in the United States. The last cultured-confirmed case of respiratory diphtheria caused by toxigenic *C. diphtheriae* was reported in 1997; 3 cases of diphtheria-like respiratory illness caused by toxigenic *C. ulcerans* were reported from January 2000 through December 2022. In 2003, a fatal probable case of respiratory diphtheria was imported from Haiti, a country that is endemic for the disease.[6] There is evidence that toxigenic strains of diphtheria continue to circulate in at least limited areas of the United States.[7] Access to DAT is essential to ensure urgent and effective treatment of all cases of suspected diphtheria.

3.0 PRODUCT INFORMATION

With the discontinued manufacturing of a U.S. licensed DAT product by Connaught in 1997, an investigational, equine-based DAT product, manufactured by the Instituto Butantan (IB) in São Paulo, Brazil, is FDA-authorized for treatment use under this IND program for patients suspected with diphtheria in the United States. The IB-manufactured DAT is a sterile, transparent (clear) serum solution supplied in 10 mL ampoules containing 10,000 International Units (IU) per vial. The composition of DAT is summarized in **Table 1**. DAT must be stored in the refrigerator at 2 - 8°C (36 – 46°F; DO NOT FREEZE).

Table 1. DAT Composition – Each 10 mL Ampoule

Ingredient	Content
Diphtheria Antitoxin (DAT) immunoglobulin antigen-binding fragments	10,000 IU
Phenol	35 mg (maximum)
0.85% physiological solution	10 mL

As the IB-manufactured DAT is primarily produced for national use in Brazil, its ampoule and carton labels are in Portuguese but bears the following auxiliary label in English:

Diphtheria Antitoxin (IND 11184)
Manuf: Instituto Butantan Lot: ##### Exp: SEE LETTER or xxxxx

CAUTION: New Drug – limited by Federal law to investigational use

USE ONLY AFTER CONSULTATION WITH CDC: shipment contains 10 ampoules, which may be more than is necessary for treatment

Also included:

Histamine for Sensitivity Testing LOT_____ EXP _____

Distributed By: CDC Drug Service (H23-6), Atlanta, GA 30333 (404) 639-3670

Although the manufacturer-indicated, provisional expiry is 3 years from date of manufacture, FDA has authorized use beyond the provisional, 3-year dating based on supportive stability test results on IB-manufactured lots of DAT to date. In situations of FDA-authorized use of DAT beyond the manufacturer-indicated provisional expiry date, a "Dear Healthcare Provider (HCP)" letter will be used to inform the HCPs of expiry extended use based on FDA's review of supportive stability and potency testing. The CDC's auxiliary label will include product expiry information accordingly (e.g., specific date or "See Letter" in situations of expiry extension).

DAT, provided by CDC under the IND upon receipt and review of treating clinicians' request, is packaged containing ten 10-mL ampoules of DAT, 1 vial of histamine and IND protocol with required paperwork. Refer to **Section 6.0** for DAT preparation and administration procedures. Follow the instructions regarding investigational product accountability and disposition upon completion of patient's DAT therapy, including handling of unused ampoules (see Appendix 6).

4.0 IND PROGRAM DESCRIPTION

This IND program is to allow DAT treatment for patients with possible diphtheria infection. Clinicians with possible diphtheria patients needing to request DAT should contact the CDC's Emergency Operations Center (EOC) at 770-488-7100. The CDC diphtheria duty officer will release DAT if the patient meets eligibility criteria based on the discussion with the treating/requesting clinicians. It is the clinical decision of the treating clinician to request and administer DAT. The treating clinician may decide against DAT treatment based on any clinical changes to the patient's condition since requesting DAT or per clinician's judgement.

In requesting and obtaining DAT, the treating clinician is agreeing to serve as a site investigator under the IND and acknowledging to comply with FDA IND regulations. Please refer to Section 7.0 of this protocol for treating clinicians' responsibilities for patient monitoring, adverse event reporting, and case report from completion).

5.0 PATIENT ELIGIBILITY FOR DAT

5.1 Therapeutic Use

Patients who have suspect or confirmed diphtheria are eligible to receive DAT. The Council of State and Territorial Epidemiologists in 2019 approved of the following criteria for case identification and classification:

Clinical case definition for diphtheria: an upper respiratory tract illness with an adherent membrane of the tonsil(s), pharynx, larynx, and/or nose; or, infection of a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa)

Laboratory criteria for diagnosis: Isolation of *C. diphtheriae* from a clinical specimen from any site and confirmation of toxin-production by Elek test or by another validated test capable of confirming toxin-production

Case classification: For reporting purposes, cases are classified as suspect or confirmed:

Suspect: an upper respiratory tract illness with an adherent membrane of the tonsil(s), pharynx, larynx or nose that is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case

Confirmed: an upper respiratory tract illness with an adherent membrane of the tonsil(s), pharynx,

larynx or nose, and isolation of toxin-producing *C. diphtheriae* from the nose or throat, or epidemiologic linkage to a laboratory-confirmed case of diphtheria
OR
An infection at a non-respiratory anatomical site (e.g., skin, wound, conjunctiva, ear, genital mucosa) with isolation of toxin-producing *C. diphtheriae* from that site

A patient's eligibility for treatment will be determined through discussion between the CDC diphtheria duty officer and the treating clinician.

DAT should be released and administered without delay to:

A. All cases of respiratory diphtheria with laboratory-confirmed toxigenic *C. diphtheriae* or respiratory diphtheria-like cases with laboratory-confirmed toxigenic *C. ulcerans.*

B. Suspect cases. Respiratory diphtheria should be strongly considered in a suspect case-patient who is toxic in appearance and one or more of the following:
   - is without another clearly established diagnosis
   - has rapidly worsening illness
   - has history of recent travel to a country where diphtheria is endemic or epidemic
   - was exposed to travelers from countries with endemic or epidemic diphtheria
   - has history of recent contact with dogs, cats, or dairy animals,
   - was never vaccinated or is not up-to-date with diphtheria toxoid vaccination

   For possible cases which are considered to have a low probability for diphtheria, the duty officer will encourage the treating clinician to consider other diagnoses. However, the final decision to request and administer DAT to a patient lies with the treating clinician.

C. Case-patients who have isolated or localized lesions in non-respiratory anatomical sites (e.g., skin, wound, conjunctiva, ear, genital mucosa) from which toxigenic *C. diphtheriae* is obtained, and in whom there are signs of systemic toxicity (fever, tachycardia (myocarditis), and weakness (neuropathy)). Otherwise, DAT treatment is not routinely indicated for treatment of non-respiratory infection; toxigenic sequelae are rare when the infection is limited to the skin or other non-respiratory sites, and when the case-patient is up-to-date on vaccination with diphtheria toxoid.[8]

5.2 Prophylactic Use

DAT is used prophylactically only under exceptional circumstances. Eligibility for prophylactic use of DAT will be limited to the following situations:

1. An individual who:
   - Has had known exposure to toxigenic *C. diphtheriae* (or possibly other toxigenic *Corynebacteria*) AND
   - Is not up-to-date for vaccination against diphtheria AND
   - Cannot be kept under surveillance for the development of clinical symptoms or is not available for follow-up of results of culturing for the diphtheria organism.
2. An individual who has suspected or known injection of diphtheria toxin (e.g., laboratorians). Needle sticks do not qualify as injections.

Each request for use of DAT for prophylaxis will require detailed discussion of all possible options with the diphtheria duty officer. Under the rare circumstances when these conditions are met, the

recommended prophylactic dose of DAT is 10,000 units (after appropriate sensitivity testing). Patients in situation #1 above also should be given prophylactic antibiotics and appropriate up-date vaccination with diphtheria toxoid. Patients in situation #2 do not need prophylactic antibiotics because they have not been exposed to the bacteria.

6.0 DAT TREATMENT PROCEDURES

6.1 Informed Consent/Parental Permission

Written informed consent in compliance with 21 CFR 50 should be obtained before any program-related procedures are initiated. Consent via the enclosed Informed Consent/Parental Permission Form (**Appendix 1**) must be obtained from the patient before DAT is administered if the patient is able to give consent. If the patient is unable to give consent, consent must be obtained from the next-of-kin or legal guardian/representative. The treating clinician or designee will provide information on DAT in lay terms to the patient. Information about the nature of the program, the means by which the program is to be conducted, and the risks to the patient will be provided.

A single Informed Consent/Parental Permission Form will be used to obtain consent from adults or parental permission for minors. Waiver of assent for older children (7–17 years of age) has been granted by the CDC Institutional Review Board (IRB) for all patients under this protocol for the DAT administration. Parental permission will be sought in accordance with 21 CFR 50.55(c) for all minors aged 17 years and younger (permission of only one parent is required). Please see **Appendix 1**. The ultimate responsibility for decision-making for use of this product in minors lies with the parent or guardian.

If a patient is unable to respond and make wishes known about DAT treatment, and no next-of-kin or legal guardian/representative is available, and the patient's illness is life-threatening, per 21 CFR 50.23 "Exception from General Requirements", informed consent may be deemed not feasible, and the treating clinician can make the determination to administer DAT. Per 21 CFR 50.23, the patient's treating clinician, acting as the site investigator, and a clinician who is not otherwise participating in this treatment protocol, must document the following on the consent form:

1. Patient is confronted by a life-threatening situation necessitating the use of DAT.
2. Informed consent cannot be obtained from the patient because of an inability to communicate with or obtain legally-effective consent from the patient.
3. Time is not sufficient to obtain consent from the patient's legal representative.
4. There is no alternative method of approved or generally recognized therapy available that provides an equal or greater likelihood of saving the life of the patient.

If time is not sufficient to obtain the independent clinician determination required above in advance of administering DAT to the patient, and in the treating clinician's opinion, immediate use of DAT is required to preserve the life of the patient, the determinations of the treating clinician shall be made and, within 5 working days after the use DAT, be reviewed and evaluated in writing (via documentation of the above criteria) by a clinician who is not participating in this treatment protocol and reported to CDC.

This IND protocol has been reviewed and approved by the CDC IRB and a local institution/hospital may elect to defer to CDC's IRB approval (see Appendix 7). However, if the institution/hospital IRB elects to review this IND protocol rather than rely on CDC IRB's review, the documentation of the above evaluation must be submitted to the institution/hospital IRB within 5 working days of DAT administration. For hospitals that are precluded by local law or institutional policy from relying on another IRB, or

hospitals that otherwise decide to perform their own IRB review, administration of DAT should not be delayed while waiting for local, hospital IRB review; FDA regulations allow, given the emergency situation, that a hospital does not need to obtain IRB approval before administration if this is the hospital's first time using DAT (after administering DAT they need to report to their hospital IRB within 5 working days). Subsequent DAT use at the same facility requires IRB approval (21 CFR 56.104(c)).

6.2 Precautionary measures

DAT is an equine serum product and precautionary measures are recommended for all patients.

Patients with the following history may be at increased risk of developing serious anaphylactic reactions upon receipt of equine-origin serum administered subcutaneously (SC), intramuscularly (IM), or intravenously (IV):

- Asthma, allergic rhinitis, or urticaria
- Asthma, allergic rhinitis, or urticaria or other symptoms of distress when in proximity to horses
- Previous injection of serum of equine origin

All patients should have the following:

- An appropriate history taken for factors suggesting increased risk
- Sensitivity testing to DAT* (see Section 6.3)
- Careful monitoring during sensitivity testing and DAT administration for evidence of hypotension and bronchoconstriction

Patients with a history suggesting increased risk should have the following:

- Initial sensitivity testing (scratch/prick skin test and ID test) with a reduced dose (1:1,000)* (see Section 6.3.A and B)
- Very careful monitoring during sensitivity testing and DAT administration for evidence of hypotension and bronchoconstriction

*Patients with positive or equivocal sensitivity testing to DAT should have *desensitization* performed (see Section 6.4).

Personnel who test for sensitivity to or administer DAT should be trained to treat anaphylactic reactions. The necessary medications, equipment, and staff competent to maintain the patency of the airway and to treat cardiovascular collapse must be immediately available.

6.3 Tests for Sensitivity to DAT

A test for sensitivity to DAT should be carried out prior to each time DAT is administered. Sensitivity to DAT may be assessed by two methods:[9,10] the scratch, prick, or puncture skin test is followed by an intradermal (ID) test if the skin test is negative. This order is recommended as the skin test is thought to be safe while the ID test has been reported to cause fatal anaphylactic reactions.

A. Scratch, prick, or puncture skin test

After cleaning a skin site on the volar surface of the patient's forearm with alcohol and air drying, make a superficial scratch, prick, or puncture using a sterile needle or other sterile sharp instrument, breaking the skin but not drawing blood.

In persons with a *negative history* for animal allergy and no prior exposure to animal serum, apply one drop of a 1:100 dilution of the serum in normal saline to the site.

In patients with a *positive history* for animal allergy or prior exposure to animal serum suggesting increased risk, apply one drop of a 1:1,000 dilution of the serum in normal saline to the site. If the test is negative, repeat it using a 1:100 dilution.

Positive (histamine) and negative (physiologic saline) control tests should also be applied to similar scratch, prick, or puncture sites. A positive scratch test is a wheal with surrounding erythema at least 3 mm larger than the negative control test, read at 15-20 minutes. The histamine control must be positive for valid interpretation; a positive response consists of a wheal at the scratch site surrounded by an erythematous area. If the scratch test is negative, an ID test is performed. If the scratch test is positive, follow procedures for desensitization (Section 6.4).

B. ID test

In persons with a *negative history* for animal allergy and no prior exposure to animal serum, administer a reduced dose of 0.02 ml of 1:100 saline-diluted serum ID; this quantity should raise a small ID wheal.

In patients with a *positive history* for animal allergy or prior exposure to animal serum suggesting increased risk, administer a reduced dose of 0.02 ml of 1:1,000 saline-diluted serum ID; this quantity should raise a small ID wheal. If the test is negative, repeat it using a 1:100 dilution.

Positive (histamine) and negative (physiologic saline) ID control tests should be applied. Interpretation of the ID test is done as with the scratch test.

A positive skin test indicates the probability of sensitivity with some correlation between the severity of the reaction on skin testing and the likelihood and severity of reaction to the DAT. However, a negative skin test does not preclude the possibility of an adverse reaction and DAT should still be administered cautiously. In addition, antihistamines (and possibly other drugs such as tricyclic antidepressants) administered previously can interfere with the results of skin testing for periods of one day or longer depending on the antihistamine.

6.4 Desensitization

Patients with positive sensitivity testing to DAT or with a history suggesting increased risk from DAT administration (even with a negative or equivocal sensitivity test) should undergo *desensitization*. Tables 3 & 4 (appended) serve as guides for desensitization. See Table 3 for the IV regimen and Table 4 for IM, SC and ID regimens provided at the end of this protocol.[7] The IV route is considered safer because it offers better control.

The personnel performing desensitization need to have the expertise to treat anaphylaxis and the necessary equipment and medications available. Some clinicians recommend concurrent treatment with an oral or IM antihistamine with or without IV administration of a corticosteroid such as hydrocortisone or methylprednisolone. The protection from anaphylaxis afforded by giving DAT according to the desensitization treatment schedule requires that no interruption occur in the sequence of administration of doses; *if an interruption occurs the protection is lost*.

6.5 DAT Administration

Route

The IV route is the preferred route of administration of DAT, especially in severe cases. The antitoxin dose should be mixed in 250 –500 mL of normal saline and administered slowly over 2 – 4 hours, closely

monitoring for anaphylaxis. The antitoxin may be given IM in mild or moderate cases.

Temperature
Antitoxin should be warmed to 32 – 34°C (90 – 95°F) before injection. Warming above the recommended temperature should be carefully avoided because the DAT proteins will denature.

Dosage
A. Perform sensitivity tests, and desensitization if necessary.
B. Give the entire treatment dose of antitoxin IV in a single administration (except for series of injections needed for desensitization).
C. The recommended DAT treatment dosage ranges are:

Table 2. Pediatric and Adult DAT Dose[8]

Diphtheria clinical presentation	DAT dose in IU (# of ampoules)
Pharyngeal or laryngeal disease of 2 days duration	20,000 – 40,000 (2-4)
Nasopharyngeal disease	40,000 – 60,000 (4-6)
Extensive disease of 3 or more days duration, or any patient with diffuse swelling of neck	80,000 – 100,000 (8-10)
Skin lesions only (rare case where treatment is indicated)	20,000 – 40,000 (2-4)

D. Give children the same dose as adults.
E. Repeated doses of DAT after an appropriate initial dose are not recommended and may increase the risk of adverse reactions.

Appropriate antimicrobial agents in full therapeutic dosages should be started immediately upon suspicion of respiratory diphtheria (and ideally after specimen collection). For cutaneous diphtheria, antitoxin is rarely required (see Section 5.1.C); attention should focus on wound hygiene and antimicrobial agent treatment. The antibiotic of choice for treatment of either respiratory or cutaneous diphtheria is erythromycin or penicillin, which may be given in the following dosages over a duration of 14 days:

Intramuscular procaine penicillin G, 25,000-50,000 units/[kg/d] for children and 1.2 million units/d for adults, in two divided doses; parenteral or oral erythromycin, 40-50 mg/[kg/d], with a maximum of 2 g/d, in 4 divided doses; oral penicillin V, 125-250 mg four times daily.

Any person with clinical symptoms of diphtheria should receive DAT as soon as it can be made available, without waiting for bacteriologic confirmation of the diagnosis. Supportive treatment should be continued until all local and general symptoms are controlled.

Prophylactic regimen
Prophylactic treatment with DAT can be considered for contacts but is recommended only in exceptional circumstances. (Please reference Section 5.2). Such exceptional circumstances should be discussed in detail with the CDC diphtheria duty officer. If it is concluded that a close contact may benefit from receiving DAT, DAT can be administered in addition to antimicrobial prophylaxis and immunization with diphtheria toxoid. Before administering DAT:
A. Perform appropriate sensitivity tests.
B. If sensitivity testing is negative, give 10,000 units IM.

C. If sensitivity testing is positive, proceed with desensitization schedule outlined in Section 6.4, and then administer 10,000 units of DAT IM.

6.6 Possible adverse reactions following administration of DAT

Anaphylactic Reaction
Although onset and severity are highly variable, anaphylaxis usually begins in susceptible patients within minutes after exposure to DAT; in general the more rapid the onset, the more severe the reaction. The major manifestations are 1) cutaneous, including pruritus, flushing, urticaria, and angioedema; 2) respiratory, including hoarse voice and stridor, wheeze, dyspnea, and cyanosis; and 3) cardiovascular, including a rapid, weak pulse, hypotension, and arrhythmias. Anaphylaxis is a major medical emergency.

In the event of an anaphylactic reaction, treatment will depend on the nature and severity of the reaction. Parenterally-administered epinephrine is the primary drug for all types of reactions. Antihistamines should also be given. Additional medications, depending on the severity of the reaction may include corticosteroids, alpha-adrenergic blocking agents, aminophylline, and beta-2 agonists.[7]

Febrile Reaction
When fever occurs, it usually develops twenty minutes to one hour after exposure to DAT. It is characterized by a chilly sensation, slight dyspnea and a rapid rise in temperature. Most febrile reactions are mild and can be treated with antipyretics alone; severe reactions may require other measures (tepid water baths, etc.) to reduce the temperature.

Serum Sickness
The symptoms of serum sickness are fever, maculopapular skin rashes, or urticaria in milder forms (90% of instances) with arthritis, arthralgia, and lymphadenopathy also possible in more severe forms. Rarely, angioedema, glomerulonephritis, Guillain-Barré syndrome, peripheral neuritis, or myocarditis can occur. The onset of symptoms is usually 7 to 10 days (range 5 –24 days) after initial exposure to DAT. Onset can be as short as several hours to 3 days after administration of DAT in persons who have received a dose of animal serum in the past; these individuals are also more likely to develop serum sickness. Mild cases of serum sickness frequently resolve spontaneously over a few days to 2 weeks. Medications that may be helpful include antihistamines, non-steroidal anti-inflammatory drugs, and corticosteroids.[7]

Febrile reactions and serum sickness are not IgE-mediated and therefore are not predicted by skin testing. The frequency of anaphylaxis and serum sickness is partially dependent on the frequency of previous administration of animal serums in the population; this frequency is now low. Recent data on the frequency of adverse reactions to horse serum products is extremely limited due to their infrequent use. In a review of 1,433 diphtheria cases treated with antitoxin between 1940 and 1950, the frequency of adverse reactions was as follows: anaphylaxis, 0.6% (without any fatalities); febrile reactions, 4.0%; and serum sickness, 8.8%.[6]

Given the potential risk of serious adverse reactions related to DAT administration, DAT should be administered under close monitoring in a setting with appropriate medical intervention if needed.

The clinical determination regarding DAT treatment should be based on risk-benefit assessment and the clinical status of the patient. Given the life-threatening nature of respiratory diphtheria and the toxin neutralizing effect of DAT, treatment with DAT may potentially reduce morbidity and enhance survival of patients with diphtheria.

7.0 REQUIRED PATIENT MONITORING AND REPORTING OF ADVERSE EVENTS

7.1 Patient Monitoring

Since DAT is an investigational product, treating clinicians have certain responsibilities regarding the use of DAT and must comply with the FDA regulations. This includes performing patient evaluation and monitoring, and recording and reporting requested information to CDC, such as any occurrence of serious adverse events (SAEs) during and following DAT administration as described in **Section 7.2**.

The treating clinician is responsible for completing and returning the following forms within 14 days of DAT administration.

REQUIRED FORMS:

- Adult Informed Consent/Parental Permission and Child Assent Forms (**Appendix 1**)
- Information for Close Contacts (**Appendix 2**)
- CDC Diphtheria Worksheet (**Appendix 3**)
- Diphtheria Antitoxin Treatment and Adverse Effects Form (**Appendix 4**)
- Form **FDA 1572** (Statement of the Investigator) with a treating clinician's CV (**Appendix 5**)
- Investigational Product Accountability and Disposition Form (**Appendix 6**).

Once completed, forms and any supplemental information should be transmitted by fax (404-718-4528) to CDC Meningitis and Vaccine Preventable Diseases Branch.

7.2 Definitions of Adverse Events (21 CFR 312.32)

Adverse Event (AE): Any untoward medical occurrence with the use of DAT in humans, whether or not considered related to DAT. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of DAT, without any judgment about causality.

Adverse Reactions (AR): Any AE for which there is a reasonable possibility that DAT caused the AE. It is a subset of all AEs for which there is a reasonable possibility that DAT caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between DAT and the AE.

Suspected Adverse Reaction: Any AE for which there is a reasonable possibility that DAT caused the AE. It is a subset of all AEs for which there is a reasonable possibility that DAT caused the event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction."

Unexpected: An AE is considered "unexpected" if it is not listed in this protocol or is not listed at the specificity or severity observed.

Serious Adverse Event (SAE): An AE or suspected adverse reaction is considered "serious" if, in the view of either the treating clinician or CDC, it results in any of the following outcomes:

- death
- a life-threatening AE (An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the treating clinician or CDC, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused a death.)
- inpatient hospitalization or prolongation of existing hospitalization (excluding the hospitalization due to diphtheria infection)
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect (if DAT is administered during pregnancy)

Serious and Unexpected Suspected Adverse Reaction (SUSAR): An adverse reaction that is both unexpected (not consistent with the observed or expected risk information applicable to DAT) and also meets the definition of "serious" described above.

NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes previously listed.

7.3 Recording and Reporting Adverse Events

Treating clinician reporting requirements to CDC:

The treating clinician, serving as the site-investigator for DAT, must report all AEs by means of the Diphtheria Antitoxin Treatment and Adverse Effects Form (Appendix 2). These may include AEs that the patient reports spontaneously, those the clinician observes, and those the clinician elicits in response to open-ended questions. SAEs and SUSARs (see Section 7.2 for definitions) must be reported to CDC within 24 hours of occurrence or as soon as possible by contacting the CDC diphtheria duty officer who was consulted at the time of DAT release. If this individual cannot be reached, the CDC Emergency Operations Center should be contacted at 770-488-7100 to reach the CDC diphtheria duty officer on call.

CDC reporting requirements to FDA and CDC IRB:

All SAEs and SUSARs reported to CDC will be reviewed by the CDC Principal Investigator and treating clinician, acting as the site investigator, to assess and determine causality to DAT. In making the causality assessment, the CDC Principal Investigator and treating clinician will discuss the information available for each reported SAE/SUSAR while considering the temporal relationship between DAT administration and the SAE/SUSAR, the evidence for other causes of the SAE/SUSAR, and the known safety information about DAT.

Association with DAT will be classified into four causality categories:

- Related: A clinical or medical event, including laboratory test abnormality, occurring in a plausible time relationship to DAT administration, and cannot be explained by underlying disease/condition or concurrent drugs
- Possibly related: A clinical or medical event, including laboratory test abnormality, with a reasonable time sequence to administration of DAT, but could also be explained by underlying disease/condition or concurrent drugs
- Unlikely to be related: A clinical or medical event, including laboratory test abnormality, with a temporal relationship to DAT administration that makes a causal relationship improbable, and underlying disease/condition or concurrent drugs provide plausible explanations
- Not related: A clinical or medical event, including laboratory test abnormality, after careful medical consideration, are clearly and incontrovertibly due to causes other than DAT

Of the SAEs determined to be SUSARs (Serious and Unexpected Suspected Adverse Reaction; see Section 7.2 for definition), those that are fatal or life-threatening should be reported to FDA by CDC as soon as possible, but no later than 7 calendar days after CDC's initial receipt of the information (21 CFR 312.32(c)(2)). Other SUSARs should be reported to FDA by CDC within 15 calendar days of initial receipt or after determining that the information qualifies for reporting under 21 CFR 312.32(c)(1). All three (3) of the following definitions contained in the FDA requirement for expedited reporting must be met to qualify for expedited reporting to FDA by CDC: 1) Serious, 2) Unexpected, and 3) Suspected Adverse Reaction. AEs that do not meet the requirements for SUSAR expedited reporting will be reported to FDA in the IND Annual Report.

CDC will also report all SUSARs to CDC IRB according to CDC IRB's policy and procedures.

8.0 LABORATORY TESTING

Although the decision to administer DAT in a suspected case of respiratory diphtheria must frequently be made in the absence of confirmatory laboratory evidence, it is essential to obtain the specimens to confirm the diagnosis early in the course of illness, and if possible, before the administration of antibiotics. The recommended specimens include the following:

A. Throat, membrane (swabs or fragments), and nasal swab specimens for diphtheria culture. These are plated on special media (tellurite-containing media). The testing laboratory must be notified to look for *C. diphtheriae* so that the appropriate, special medium is used, and laboratory personnel must have the necessary expertise to process cultures for *C. diphtheriae*. In patients who have not yet had specimens collected for culture, or who have had cultures processed that were negative for *C. diphtheriae*, the CDC diphtheria duty officer may recommend that existing or new specimens be sent directly to the CDC Diphtheria Laboratory for culture and polymerase chain reaction (PCR) testing. Testing by PCR has the capability of identifying the *tox* gene of *C. diphtheriae* from swabs or from membrane specimens when cultures are negative. Tissue and swabs for culture and PCR should be maintained in transport medium or in a sterile container kept moist with sterile, non-bacterial static saline until they reach the laboratory. Specimens for culture and PCR *should not be placed in formaldehyde.*

   All *C. diphtheriae* strains isolated should be forwarded to the CDC Diphtheria Laboratory (telephone 404-639-1231) for confirmation and toxigenicity testing.

B. A serum specimen can be obtained from the patient before antitoxin administration and tested for diphtheria antibodies (IgG). A low titer level (< 0.01 IU/ml) indicates susceptibility but does not confirm the diagnosis. A high titer (> 0.1 IU/ml) suggests that a diagnosis is less likely to be diphtheria.

9.0 LOCAL AND STATE HEALTH DEPARTMENT NOTIFICATION

It is a requirement that cases of suspected diphtheria (e.g., cases for whom DAT is requested) and known contacts be reported to local and state health departments. A clinician who requests and administers DAT should notify the local and state health departments. The CDC duty officer will also notify the state health department of any DAT that is released.

Public health officials will assist in identifying contacts at risk of infection, will often obtain nasal and throat swabs for cultures, and will facilitate antibiotic prophylaxis of contacts (oral erythromycin or penicillin) when necessary to prevent spread to other members of the community. All asymptomatic, unimmunized contacts of patients with diphtheria should receive prophylactic antimicrobial therapy after specimens for cultures are obtained. If testing confirms *C. diphtheriae* in a contact, this contact should receive another course of antibiotic treatment, and repeat nasal and throat swabs for culture should be obtained following the second treatment course, to confirm eradication of the bacteria. Immunization with diphtheria toxoid should be given, if not up-to-date, and surveillance for illness continued for seven days. This is the standard of care for contacts of a diphtheria case. Please see "Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures: recommendations of the Immunization Practices Advisory Committee (ACIP)" MMWR 1991:40 (No. RR-10)[8] for additional details.

10.0 DATA COLLECTION, STORAGE AND USE

A requirement for release of DAT under this IND is that CDC will obtain and store information relating to the patient's illness (including patient identifiers). Data obtained will be shared with the state health departments for public health investigation. In the event of serious adverse reactions, complete medical records may be requested for evaluation by the CDC Principal Investigator from the treating clinician. SAEs and SUSARs will be reported to CDC IRB and FDA. Stored data will be analyzed as needed by CDC staff to prepare annual summary reports for renewal or continuation of the program with the CDC IRB and FDA. The data containing personal identifiers will be stored in locked file cabinets. This information will be kept strictly confidential. Analyzed data may also be published in order to share important findings with the scientific community. Publication of this data will contain only aggregate

data; no identifying information will be included. All forms should be returned directly to the CDC Meningitis and Vaccine Preventable Diseases Branch.

CDC Meningitis and Vaccine Preventable Diseases Branch
Mailstop H24-6
1600 Clifton Rd. NE
Atlanta, GA 30329
Phone: 404-639-3158
Fax: 404-718-4528

Additional Tables for Desensitization to DAT

Table 3. Desensitization to DAT - Intravenous Route[7]

Dose Number*	Dilution of DAT in Normal Saline	Amount of Injection (cc)
1	1:1,000**	0.1
2	1:1,000	0.3
3	1:1,000	0.6
4	1:100**	0.1
5	1:100	0.3
6	1:100	0.6
7	1:10**	0.1
8	1:10	0.3
9	1:10	0.6
10	undiluted	0.1
11	undiluted	0.2
12	undiluted	0.6
13	undiluted	1.0

* Administer at 15-minute intervals.

**1 ml (antitoxin) + 9.0 ml of saline = 1:10 dilution
1 ml (1:10 dilution) + 9.0 ml of saline = 1:100 dilution
0.1 ml (1:10 dilution) + 9.9 ml saline = 1:1000 dilution
[1 ml (1:100 dilution) + 9 ml saline = 1:1000 dilution]

Table 4. Desensitization to DAT - Intradermal, Subcutaneous and Intramuscular Route[7]

Dose Number*	Route of Administration	Dilution of DAT in Normal Saline	Amount of Injection (cc)
1	ID	1:1,000**	0.1
2	ID	1:1,000	0.3
3	SC	1:1,000	0.6
4	SC	1:100**	0.1
5	SC	1:100	0.3
6	SC	1:100	0.6
7	SC	1:10**	0.1
8	SC	1:10	0.3
9	SC	1:10	0.6
10	SC	undiluted	0.1
11	SC	undiluted	0.2
12	IM	undiluted	0.6
13	IM	undiluted	1.0

*Administer at 15-minute intervals.

**1 ml (antitoxin) + 9.0 ml of saline = 1:10 dilution
1 ml (1:10 dilution) + 9.0 ml of saline = 1:100 dilution
0.1 ml (1:10 dilution) + 9.9 ml saline = 1:1000 dilution
[1 ml (1:100 dilution) + 9 ml saline = 1:1000 dilution]

11.0 REFERENCES

1. Centers for Disease Control. Respiratory Diphtheria caused by *Corynebacterium ulcerans*: Terre-Haute, Indiana, 1996. MMWR 1997;46:330 –2.

2. Diphtheria; other corynebacterial and coryneform infections. In Topley and Wilson's principles of bacteriology, virology and immunity (Chapter 60). 5th ed. Baltimore, MD: Williams and Wilkins, 1964:1695 –98.

3. Naiditch MJ, Bower AG. Diphtheria. A study of 1433 cases observed during a ten year period at the Los Angeles County Hospital. Am J Med. 1954;17:229-45

4. Placido Sousa C, Evans DG. British Journal of Experimental Pathology. 1957;38:644-.

5. Farizo KM, Strebel PM, Chen RT, et al. Fatal respiratory disease due to Corynebacterium diphtheriae: case report and review of guidelines for management, investigation, and control. Clinical Infectious Diseases 1993;16:59-68.

6. CDC. Fatal respiratory diphtheria in a U.S. traveler to Haiti--Pennsylvania, 2003. *MMWR Morb Mortal Wkly Rep* 2004: *52*(53), 1285-1286

7. Marston, C. K., Jamieson, F., Cahoon, F., Lesiak, G., Golaz, A., Reeves, M., & Popovic, T. Persistence of a distinct Corynebacterium diphtheriae clonal group within two communities in the United States and Canada where diphtheria is endemic. *J Clin Microbiol 2001: 39*(4), 1586-1590

8. Centers for Disease Control. Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991:40(No. RR-10): (inclusive page numbers).

9. American Academy of Pediatrics. Active and Passive immunization. In: Pickering LK, ed. 2000 Red Book: Report of the Committee on Infectious Diseases, 25th ed. Elk Grove Village, IL: American Academy of Pediatrics;2000:47-51

10. American Academy of Pediatrics. Diphtheria. In: Pickering LK, ed. 2000 Red Book: Report of the Committee on Infectious Diseases, 25th ed. Elk Grove Village, IL: American Academy of Pediatrics;2000:230-34