T3 MANUAL OF OPERATIONS

TABLE OF CONTENTS

CHAPTER 21

DRUG DISTRIBUTION CENTER PROCEDURES

21.1 INTRODUCTION

The DDC (Drug Distribution Center) is responsible for packaging, labeling and shipping study drugs to the Clinical Centers, Satellites and Co-Equal sites, and acting, along with the Study Chairman's Office, as liaison to the pharmaceutical company. The DDC assures the quality of the drugs, monitors drug usage, recalls outdated medication kits, and disposes of both used and unused medication kits. In addition, the DDC assists the Data Coordinating Center in monitoring drug related problems. The address for the T3 Drug Distribution Center is:

Cindy L. Colling, R.Ph., M.S.
T3 Drug Distribution Center
CSPCRPCC (151-I)
VA Medical Center
2100 Ridgecrest Drive, SE
Albuquerque, NM U.S.A. 87108
(505) 265-1711, Ext. 2580

21.2 PRINCIPAL INVESTIGATOR'S RESPONSIBILITY FOR DRUG ACCOUNTABILITY

A complete and accurate accounting of all investigational drugs is the responsibility of the Principal Investigator of the Clinical Center. The DDC will provide recording forms, instructions, and assistance as necessary for the investigators to assure accountability for the T3 study drugs and will monitor the performance of the Clinical Centers, Satellites and Co-Equal sites in this regard. Hospital staff may require that their pharmacy assist the investigator in this responsibility. Following completion of the study, the DDC will provide the Principal Investigator with a comprehensive report of all drugs received, distributed to and returned by each hospital.

21.3 DESCRIPTION OF MEDICATION KITS AND OTHER ITEMS PROVIDED BY DDC

T3 study drugs are provided to patients in the form of individually assigned patient medication kits. The kits are assembled and shipped from the DDC at the direction of the Data Coordinating Center. Medication kits contain T3 study drug and three of the items needed to prepare and label the infusion. Exhibit 21-1 lists all the items needed to prepare and infuse the T3 study drug and indicates whether the item is supplied by the DDC or is taken from the Clinical Center's stock. Any item not supplied by the DDC should be obtained and routinely stocked in a designated location within the treatment area.

Each medication kit contains: two 50 mg vials of either T3 study drug or an inert substance (placebo); one 100 ml vial of water for injection (USP preservative free); one empty Viaflex® 150 ml infusion bag; one peelable label for the infusion bag; one set of instruction sheets for preparing and administering the T3 study drug; and two Nomogram Dosing Charts.

Items that will be needed, but are not provided, in the kit are:

1. Syringes, needles and alcohol prep pads.
2. One infusion pump.
3. Administration sets compatible with the infusion pump (if applicable).
4. Blood collection and mailing tubes.

An unblinding envelope is mailed with each medication kit. These envelopes should be kept in a secure location, and not in the same location as the randomization mailers. It is recommended that access to these envelopes be limited to a designated study investigator who will have responsibility for ensuring that these envelopes are used only if the patient has a "severe clinical event" and treatment can not proceed without knowledge of treatment assignment. The only foreseen instance of unblinding a treatment assignment is when a patient experiences a suspected Q-wave myocardial infarction in close time proximity to the study drug infusion. These unblinding envelopes must be returned to the Data Coordinating Center for visual inspection when the completed Form 04 (Admission and Treatment Assignment Form) is sent to the Data Coordinating Center. Clinical Center staff should be made aware that the seal on the unblinding envelope should not be disturbed except in the rare instance that the envelope is used to reveal treatment assignment.

T3 patient identification cards and stickers will be supplied by the Data Coordinating Center. One card should be completed and given to each patient prior to discharge from the hospital. Patients should be instructed to present the card to any non-T3 study physician or dentist they see for treatment during the course of the study. Additional cards can be obtained by calling the Data Coordinating Center.

21.4 CUSTODY AND STORAGE LOCATION OF MEDICATION KITS

Patient medication kits must be readily available for use 24 hours per day. **THE MEDICATION KITS DO NOT REQUIRE REFRIGERATION**. However, they should be stored within the following temperature range: 2-30**E** C or 36-86**E** F. Protect the lyophilized T3 study-drug vials during storage from excessive exposure to light by keeping them in the kit box until the time of assignment.

Each kit box measures 7" x 4" x 3 1/2." Allow enough storage space for five to eight kits when participating in the T3A protocol and 10 to 15 kits when participating in the T3B protocol.

The medication kits should be stored together and readily retrievable. The Pharmacy or IV Service within the Pharmacy may be able to adequately respond to T3 needs, but at most Centers, storage in or near the treatment area may be necessary. Inventory levels for the kits will be closely monitored by the DDC. The Research Coordinator should call the DDC when the number of kits remaining reaches the designated kit re-order level (see Section 21.8, ORDERING MEDICATION KITS FROM DDC).

21.5 PREPARING AND ADMINISTERING THE T3 STUDY DRUG

The dose of T3 study drug will be 0.8 mg/kg (not to exceed 80 mg). One-third of the total dose (not to exceed 20 mg) is to be administered as an IV push bolus. Administer the infusion dose over 90 minutes. Refer to the Nomogram Dosing Charts (Exhibit 21-2 and 21-3) for determining the TOTAL DOSE of T3 study drug, the BOLUS DOSE, the INFUSION DOSE and the corresponding DRIP RATE.

[NOTE: It is recommended that only one vial of T3 study drug be reconstituted when the total dose of T3 study drug is 50 mg or less (the remaining vial can be used in case of preparation error, etc.)].

Five points in particular need to be emphasized concerning the preparation and administration of study drug. First, the T3 study-drug infusion must be started as soon as possible after patient eligibility has been established and informed consent obtained. The appropriate medication kit (based on the Treatment Allocation Mailer Assignment) should be obtained and readied for preparation. Any necessary equipment or supplies not provided in the medication kit should be obtained immediately from the Clinical Center's supplies. Directions for preparing and administering the

infusion are enclosed in each kit (Exhibit 21-4). Preparation of the T3 study drug should begin immediately upon completion of patient eligibility and consent. **[NOTE: The T3 drug solution can be used for up to eight hours following reconstitution when it is stored between 36-86EF or 2-30EC. Do not store any remaining unused portion for future use.]**

Second, the T3 study-drug lyophilized powder is subject to formation of foam and bubbles during reconstitution. Extreme caution must be exercised to avoid this problem. Slowly add the Sterile Water for Injection, USP (preservative free) to the vial of lyophilized powder, directing the stream of diluent into the lyophilized cake. Only Sterile Water for Injection, USP (Preservative free) should be used for 1:1 dilutions. Swirl and/or invert the vial **gently** to aid reconstitution. ***DO NOT SHAKE***. Shaking or other agitation will cause foam and bubbles to form. Slight foaming when reconstituting is not uncommon. If foam or bubbles do form, place the vial(s) upright on a flat surface and let stand undisturbed for several minutes. This is usually sufficient time to allow for the dissipation of any large bubbles. Care must also be exercised when transferring the T3 study drug solution into the IV infusion container, to again eliminate the problem of foam and bubbles. Forcing, shaking or agitating the solution will cause foam and bubbles.

[NOTE: Do not add any other medications to syringes or infusion bags containing the T3 study drug.]

Third, caution must be exercised in the choice of an IV pump. Although any IV pump, Harvard pump or radiographic injector can be used, the drop-dependent devices must be closely monitored. The IVAC type infusion is recommended. The drug may increase the drop size, thereby speeding up the rate of infusion beyond what is expected. If a drop counting device is used for the T3 study-drug infusion, closely observe the actual rate of infusion and adjust accordingly. Also, as mentioned above, radiographic injectors may cause problems with the T3 study-drug infusion. Aspirating the drug into the injector may prove difficult and can result in delays in starting the infusion. Injector type devices may also present significant dead space depending on the tubing used. Each Clinical Center, Satellite or Co-Equal site intending to use an injector should measure this volume and if found to be significant, make plans to compensate for the problem.

Fourth, the T3 study-drug infusion should be administered through a separate IV line using a heparin lock.

Fifth, the bolus dose should not be administered using a filter needle and in-line filters should not be used while infusing the T3 study drug. Use of certain in-line filters as part of the intravenous delivery system may lead to substantial reductions in the amount of study drug delivered to the patient. This phenomenon appears to be related to filter component material rather than pore size or flow rate. Since in-line filters are not required during T3 study-drug administration, their routine use should be avoided.

21.6 DAMAGED AND UNUSABLE DRUGS

21.6.1 Medication Kits Damaged During Shipment

Immediately upon receipt from the DDC, each medication kit should be opened and inspected for damages. If any of the vials (T3 study drug or sterile water) are received broken, call the DDC as soon as possible for replacements.

21.6.2 Medication Kits Rendered Unusable During Preparation

Once a medication kit is assigned, if the T3 study drug is not available at the time of administration (due to contamination, preparation error, breakage, leakage, etc.), the patient will not receive the drug. When this situation occurs, **NO OTHER MEDICATION KIT WILL BE PREPARED OR ADMINISTERED IN PLACE OF THE UNUSABLE KIT.** The patient, however, will continue to be followed according to the protocol, and management strategy for T3B.

21.6.3 Documenting Loss of T3 Study Drug

A Documentation of Loss of T3 Study Drug Form (T3 Form 5F) must be completed for all losses of patient medication kits caused by accidental breakage or other reasons. In addition, this form is to be used for any patient who does not receive a full dose of T3 therapy from a patient medication kit. The original of this form should be sent to the Data Coordinating Center with a copy to the Drug Distribution Center. The medication kit and unblinding envelope should also be sent to the Drug Distribution Center. The seal on the unblinding envelope should not be disturbed, even if the drug is not used.

21.7 DRUG USE RECORDS

Drug use records for T3 consist of two documents: the individual patient's Admission and Treatment Assignment Form (T3 Form 04) and a form provided by the DDC, the Medication Kit Assignment Record (Exhibit 21-5). The Medication Kit Assignment Record is a list of patient kits received from the DDC. Each time a kit is assigned, the investigator, Research Coordinator or pharmacist will make an entry. One of these forms will be included with each shipment of kits. When all the kits listed on the form have been assigned, the white copy should be returned to the DDC and the yellow copy retained by the Research Coordinator or investigator.

21.8 ORDERING MEDICATION KITS FROM DDC

The medication kits will be shipped to the Principal Investigator or his/her designate. An inventory level of five to eight medication kits should be maintained at each Clinical Center participating in the T3A protocol and 10 to 15 kits should be maintained at each Clinical Center participating in the T3B protocol. A smaller inventory can be maintained at the local Clinical Center's discretion.

The DDC will monitor inventory levels at each Clinical Center, Satellite and Co-Equal site. Research Coordinators should call the DDC to re-order medication kits when the number of kits remaining at the Center reaches the designated re-order level. **The designated reorder level for T3A Centers will be three kits and for T3B Centers, will be five kits.** [NOTE: Canadian sites should monitor their kit levels quite closely, since shipments from the DDC could be delayed through Customs.] Additional kits will be sent immediately upon request.

21.9 RETURNING MEDICATION KITS TO DDC

All used medication kits must be returned to the DDC, whether or not all the study drug was infused. All used kits should be returned on at least a quarterly basis. Returned kits should include the T3 study-drug vials (full, empty, partial), the sterile water vial (full, empty, partial), and the infusion bag (full, empty, partial). **Due to the possibility of injury and/or disease transmission (i.e., hepatitis B, HIV, etc.) to DDC personnel from returned kits, all IV tubing, angiocaths, needles, syringes, etc. should be removed from the T3 study drug infusion bag before returning the kit box to**

the DDC. When the study is completed, the DDC will request that all remaining medication kits (both used and unused) be returned to Albuquerque promptly.

The DDC recommends that kits be returned to Albuquerque via the U.S. Postal Service (Canadian sites should use the equivalent service). If other types of carrier services are utilized (i.e., Federal Express, DHL, Emery, Express Mail™, etc.), the sender will be responsible for all shipping charges incurred.

EXHIBIT 21-1

ITEMS NEEDED FOR T3

T3 Study Drug Preparation and Blood Coagulation Tubes

Items 1-9 should be available in the treatment area at all times. Shelf or cabinet space should be reserved or clearly designated for T3 items. The items listed below should routinely be stocked on the designated shelf or in the designated cabinet.

NON REFRIGERATED	SUPPLIED BY
1. T3 Medication Kits (contents listed in 21.3)	Drug Distribution Center
2. Syringe, 50 ml	Clinical Center
3. Needles	Clinical Center
4. Prep pads	Clinical Center
5. One IV pump or other rate controlling device	Clinical Center
6. IV administration sets compatible with the pump	Clinical Center
7. Vacutainer needles	Clinical Center
8. "Mailing" Tubes (red top, green top, and lavender top)	Coagulation Core Lab
9. Unblinding envelopes	Drug Distribution Center
OTHER ITEMS (Need Not Be in Immediate Treatment Area	
10. Patient Identification Cards	Data Coordinating Center
11. Patient ID Labels	Data Coordinating Center

REFRIGERATED	SUPPLIED BY
1. Blood Collection "Draw" Tubes (red top, green top, and lavender top)	Coagulation Core Lab

EXHIBIT 21-2

NOMOGRAM DOSING CHART A

When prepared as directed, the final concentration of T3 is: **1 mg/1 ml**

1. Reconstitute the vial(s) with 50 ml of sterile water (Conc. = 1 mg/ml)
2. Withdraw and administer the "Bolus Dose" (Column 3)
3. Withdraw the "Infusion Dose," (Column 4). For doses of 58 mg or less add the additional diluent (Column 5) to the infusion bag using either normal saline or 5% dextrose (additional diluent).
4. Infuse at the corresponding drip rate (Column 6)

(1) Wgt (Kg)	(2) Total Dose (mg)	(3) Bolus (mg)	(4) Infusion Dose (mg)	(5) Additional Diluent (ml)	(6) Drip Rate (ml/hr)
40	32	11	21	21	28
41	33	11	22	22	30
42	34	11	23	23	30
43	34	11	23	23	30
44	35	12	23	23	30
45	36	12	24	24	32
46	37	12	25	25	34
47	38	13	25	25	34
48	38	13	25	25	34
49	39	13	26	26	34
50	40	13	27	27	36
51	41	14	27	27	36
52	42	14	28	28	38
53	42	14	28	28	38
54	43	14	29	29	38
55	44	15	29	29	38
56	45	15	30	30	40
57	46	15	31	31	42
58	46	15	31	31	42
59	47	16	31	31	42
60	48	16	32	32	42
61	49	16	33	33	44
62	50	17	33	33	44
63	50	17	33	33	44
64	51	17	34	34	46
65	52	17	35	35	46
66	53	17	36	36	48
67	54	18	36	36	48
68	54	18	36	36	48
69	55	18	37	37	50
70	56	18	38	38	50
71	57	19	38	38	50
72	58	19	39	39	52
73	58	19	39	39	52

EXHIBIT 21-2 (Continued)

NOMOGRAM DOSING CHART A

(1) Wgt (Kg)	(2) Total Dose (mg)	(3) Bolus (mg)	(4) Infusion Dose (mg)	(5) Additional Diluent (ml)	(6) Drip Rate (ml/hr)
74	59	19	40	0	27
75	60	20	40	0	27
76	61	20	41	0	27
77	62	20	42	0	28
78	62	20	42	0	28
79	63	20	43	0	29
80	64	20	44	0	29
81	65	20	45	0	30
82	66	20	46	0	31
83	66	20	46	0	31
84	67	20	47	0	31
85	68	20	48	0	32
86	69	20	49	0	33
87	70	20	50	0	33
88	70	20	50	0	33
89	71	20	51	0	34
90	72	20	52	0	35
91	73	20	53	0	35
92	74	20	54	0	36
93	74	20	54	0	36
94	75	20	55	0	37
95	76	20	56	0	37
96	77	20	57	0	38
97	78	20	58	0	39
98	78	20	58	0	39
99	79	20	59	0	39
100 AND OVER	80	20	60	0	40

EXHIBIT 21-3

NOMOGRAM DOSING CHART B

When prepared as directed, the final concentration of T3 is 1 mg/1 ml:

Wgt (Kg)	Total Dose (mg)	Bolus (mg)	Dose of Infusion (mg)	Drip Rate (ml/hr)
40	32	11	21	14
41	33	11	22	15
42	34	11	23	15
43	34	11	23	15
44	35	12	23	15
45	36	12	24	16
46	37	12	25	17
47	38	13	25	17
48	38	13	25	17
49	39	13	26	17
50	40	13	27	18
51	41	14	27	18
52	42	14	28	19
53	42	14	28	19
54	43	14	29	19
55	44	15	29	19
56	45	15	30	20
57	46	15	31	21
58	46	15	31	21
59	47	16	31	21
60	48	16	32	21
61	49	16	33	22
62	50	16	34	23
63	50	17	33	22
64	51	17	34	23
65	52	17	35	23
66	53	17	36	24
67	54	18	36	24

EXHIBIT 21-3 (Continued)

NOMOGRAM DOSING CHART B

Wgt (Kg)	Total Dose (mg)	Bolus (mg)	Dose of Infusion (mg)	Drip Rate (ml/hr)
68	54	18	36	24
69	55	18	37	25
70	56	18	38	25
71	57	19	38	25
72	58	19	39	26
73	58	19	39	26
74	59	19	40	27
75	60	20	40	27
76	61	20	41	27
77	62	20	42	28
78	62	20	42	28
79	63	20	43	29
80	64	20	44	29
81	65	20	45	30
82	66	20	46	31
83	66	20	46	31
84	67	20	47	31
85	68	20	48	32
86	69	20	49	33
87	70	20	50	33
88	70	20	50	33
89	71	20	51	34
90	72	20	52	35
91	73	20	53	35
92	74	20	54	36
93	74	20	54	36
94	75	20	55	37
95	76	20	56	37
96	77	20	57	38
97	78	20	58	39
98	78	20	58	39
99	79	20	59	39
100 AND OVER	80	20	60	40

EXHIBIT 21-4

THROMBOLYSIS IN MYOCARDIAL ISCHEMIA (T3)

PREPARATION AND ADMINISTRATION SUMMARY

[T3 Study Drug, 50 mg per vial]

A. PREPARATION:

1. Use only Sterile Water for Injection, USP (preservative free) to reconstitute the T3 study drug.

2. Slowly add 50 ml of Sterile Water to each T3 study-drug vial needed (one or both, depending on the dose). Do not let the vacuum in the vial draw the water rapidly from the syringe. Direct the stream of water into the lyophilized powder cake. A 50 ml syringe and an 18 gauge, 1½" needle are recommended for reconstitution and drug transfer.

3. ***DO NOT SHAKE*** the vial to dissolve the powder cake: shaking will cause foaming. Gently swirl and/or invert the vial to aid reconstitution. If foaming occurs, place the vial in an upright position on a flat surface and let stand undisturbed for several minutes. This is usually sufficient time to allow for dissipation of any large bubbles. The concentration of the solution (1:1 dilution) will be **1 mg per 1 ml**.

4. Use the Nomogram Dosage Charts (Exhibits 21-2 and 21-3) to determine the TOTAL DOSE of T3 (based on the patient's weight in kilograms), the BOLUS DOSE, the INFUSION DOSE, ADDITIONAL DILUENT and the corresponding DRIP RATE. When transferring the T3 study drug to the IV infusion container, be careful not to shake, agitate or force the T3 drug solution since this may cause the solution to foam.

5. Withdraw and administer the "BOLUS DOSE."

6. Withdraw the "INFUSION DOSE," add it to the infusion bag. For doses of 58 milligrams or less; add an equal volume of either normal saline or 5% dextrose.

7. Gently rotate the IV infusion bag to effect a solution.

8. Infuse at the corresponding "DRIP RATE."

EXHIBIT 21-4 (Continued)

THROMBOLYSIS IN MYOCARDIAL ISCHEMIA (T3)

PREPARATION AND ADMINISTRATION SUMMARY

[T3 Study Drug, 50 mg per vial]

B. ADMINISTRATION

1. The TOTAL DOSE of T3 = 0.8 mg/kg (not to exceed 80 mg):

   a. Administer one-third of the total dose (not to exceed 20 mg) as an *IV PUSH BOLUS*.

   b. Administer the *INFUSION DOSE* over 90 minutes.

   c. Add 25-50 ml of either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (preservative free) to the empty IV infusion container and continue infusing at the rate indicated on the Nomogram until the total infusion dose has been administered.

      EXAMPLE: After reconstituting the T3 study drug, the final concentration is 1 mg/1 ml. A patient weighing 80 kg needs a total dose of 64 mg or 64 ml of the drug solution. One-third of this dose, 20 mg or 20 ml of the drug solution, will be administered as an IV push bolus. The infusion dose, 44 mg or 44 ml of the 1:1 drug solution, will be placed in the IV infusion container and administered over 90 minutes (rate = 29 ml/hr*). When the infusion container is empty, add an additional 25-50 ml of either D5W or NS (preservative free) and continue infusing at the same rate (29 ml/hr) until the entire infusion dose has been administered, i.e., 44 ml.

      *If the total dose of T3 is 58 mg or less, a second dilution of the drug is necessary to facilitate ease of administration. This dilution will yield a solution containing 0.5 mg/ml. Refer to the Nomogram Dosing Chart for instructions.

2. Pumps:

   a. An IVAC or similar pump is recommended.

   b. Drop counting devices must be monitored closely for accurate drip rates.

   c. Harvard pumps and radiographic injectors - use care when drawing the drug solution into the syringe to avoid foaming.

EXHIBIT 21-5

MEDICATION KIT ASSIGNMENT RECORD

"THROMBOLYSIS IN MYOCARDIAL ISCHEMIA (T-3)"

CLINICAL SITE:_____

STUDY DRUG: T-3 STUDY DRUG 50 mg per vial OR PLACEBO [GENENTECH, INC.]

KITS RECEIVED FROM D.D.C.		ASSIGNING KITS TO PATIENTS				FINAL DISPOSITION	
DATE	KIT NUMBER	DATE	PATIENT ID #	PATIENT NAME CODE	ORDERED BY PHYSICIAN	DATE	AFTER ASSIGNMENT, KIT SENT TO:

INSPECT EACH DRUG KIT ON ARRIVAL FOR DAMAGE.

CALL THE D.D.C. AT (505) 265-1711, EXT. 2580 FOR IMMEDIATE REPLACEMENT OF ANY BROKEN VIALS OF T-3 STUDY DRUG OR STERILE WATER.

RETURN ALL USED AND UNUSED KITS TO:

T-3 DRUG DISTRIBUTION CENTER
VA CSPCRPCC (151-1)
VA MEDICAL CENTER
2100 RIDGECREST DRIVE, SE
ALBUQUERQUE, NM U.S.A. 87108

White Copy - Drug Distribution Center Yellow Copy - Your Files 8/89