Appendix 2. Protocol of the Treatment of Lead-exposed Children Trial

1. PURPOSE AND RATIONALE

1.1. Introduction

The adverse effects of exposure to high levels of lead have been known for hundreds of years. Only recently, however, have the effects of relatively low level exposures to lead on development, blood pressure levels, and other health endpoints been recognized. Epidemiologic studies[1,2] have, for example, reported deficits of three to seven intelligence quotient (IQ) points per 10 micrograms per deciliter (μg/dL) increase in average blood lead concentration in cognitive test scores of exposed children tested at ages four to eleven. Primate and human neurodevelopmental research has provided evidence that attention, learning, short-term memory, and executive function may be the selectively deficient domains of cognition that underlie these IQ differences.[3] The Clean Air Science Advisory Committee of the Environmental Protection Agency[4] has recommended 10 μg/dL as the maximum safe blood lead concentration for an individual child. The U.S. Centers for Disease Control and Prevention[5] has also recommended 10 μg/dL as the blood lead level of concern; values above this level trigger a series of actions including monitoring of exposed children, steps to prevent further exposure, and assessment of the utility of treatment.

Children living in inner cities in the United States, along with those living in older homes with leaded paint, are at highest risk of exposure to lead. The U.S. Agency for Toxic Substances and Disease Registry[6] estimates from 1984 census data that over 12 million children are at risk from leaded paint alone. Unfortunately, little is currently known about the developmental effects of treatment of children with elevated blood lead concentrations. Lead chelation with a variety of agents is known to reduce blood lead concentrations acutely, but the concentration may rebound to as much as 70% of its baseline value within weeks to months after treatment, often requiring repeated courses of treatment. Strategies for treating children with elevated blood lead concentrations and for assessing the developmental effects of those treatments are urgently needed. The Treatment of Lead-Exposed Children (TLC) Trial has been designed to assess the effects of lead chelation with succimer in children aged 12 to 32 months at the beginning of treatment as measured by developmental status three years after the initiation of treatment.

1.2. Study Objectives

1.2.1. Primary Objective

To compare the effects of lead chelation with the drug succimer and placebo therapy on developmental status, as measured by full-scale deviation IQ score measured using the Wechsler Preschool and Primary Scales of Intelligence – Revised (WPPSI-R), three years after initiation of treatment of children initially aged 12 to 32 months with baseline blood lead concentrations between 20 and 44 μg/dL. Residential lead clean-up and nutritional supplementation with multivitamins and minerals will be provided to all study children, irrespective of treatment group.

1.2.2. Secondary Objectives

To evaluate the effect of chelation on other measures of developmental status, including the verbal and performance scales of the WPPSI-R, the Child Development Inventory, Conners' Parent Rating Scale, the Woodcock-Johnson Memory for Names, the Stanford-Binet Bead Memory, Kaufman's Magic Window, Diamond's Modified Stroop Task, and the Tower of Hanoi.

To compare the effects of lead chelation and placebo therapy on change in height, weight, and head circumference during the three-year period of treatment and follow-up.

To compare the effects of lead chelation and placebo therapy on change in systolic and diastolic blood pressure levels during the three-year period of treatment and follow-up.

2. OVERVIEW OF THE TLC TRIAL

2.1. Study Design

The TLC Trial is designed to compare the effect of lead chelation with succimer to placebo therapy in boys and girls who are between 12 and 32 months of age and have blood lead concentrations (PbB) from 20 to 44 μg/dL at enrollment in the trial. Children who are referred to TLC-affiliated Clinical Centers with elevated blood lead concentrations will be enrolled in a screening and home evaluation program that includes a minimum of two clinic visits and one home visit. During the screening period, the blood lead levels of referred children will be remeasured by the TLC's central laboratory at the Centers for Disease Control and Prevention (CDC), other eligibility criteria will be checked, and their homes will be visited to determine whether they are amenable to environmental clean-up. Children whose blood lead is confirmed to be in the range of 20 to 44 μg/dL by the CDC laboratory and whose home environments meet TLC criteria will be eligible for enrollment in the randomized trial. Upon receipt of informed consent from a parent or legal guardian, eligible children will be randomized to chelation therapy with succimer or placebo. The trial will be conducted as a double-blind, placebo-controlled trial and will enroll both boys and girls equally as mandated by the NIH Revitalization Act. TLC participants will be enrolled without regard to race, but it is expected that the majority will be of African-American descent. Except for the Newark site, where many of the study participants will be Hispanic, enrollment of linguistic minorities will not be possible due to small or non-existent populations at each clinic and due to language capabilities of TLC staff.

Children enrolled in the succimer group will receive one to three rounds of chelation therapy as described subsequently. Blood lead levels will be measured two weeks after the completion of each round of chelation and reported to the Data Coordinating Center. If a child has been randomized to the succimer group and this blood lead measurement is greater than or equal to 15 μg/dL, the Clinical Center will be directed to schedule an additional round of succimer treatment. At most three rounds of treatment will be given. To preserve the double blind, the Data Coordinating Center will direct the Clinical Centers to schedule an equal number of rounds of retreatment in the placebo group. Clinical Centers will not have access to blood lead measurements during the treatment period except under special circumstances as described below. The two treatment groups will receive identical vitamin and mineral supplementation and a common lead dust management program which may be supplemented by various Clinical Centers within limitations of budget. Enrolled children will be followed for at least three years, with periodic assessment of their developmental status. The test of the trial's primary hypothesis will be based on developmental status as measured by the Wechsler Preschool and Primary Scale of Intelligence three years after enrollment. A number of additional measures of developmental status will also be considered, particularly measures of learning, short-term memory, attention, and executive function.

2.2. Administration

The TLC Trial is sponsored by the National Institute of Environmental Health Sciences (NIEHS) with support from the Office of Research on Minority Health of the National Institutes of Health (ORMH, NIH). The Trial will be conducted at four Clinical Centers: the Children's Hospital of Philadelphia (Philadelphia PA); the Kennedy Krieger Institute, in association with the Johns Hopkins University and the University of Maryland (Baltimore MD); the University of Cincinnati (Cincinnati OH) in conjunction with Columbus Children's Hospital (Columbus OH); and the University of Medicine and Dentistry of New Jersey (Newark NJ). These sites were selected on the basis of technical merit and cost from an open, nationwide competition. They serve inner city communities that are primarily African-American

and reflect well the national distribution of lead poisoning. The Harvard School of Public Health (Boston MA) will serve as the Data Coordinating Center, the Centers for Disease Control and Prevention (CDC, Atlanta GA), through its Nutritional Biochemistry Branch, will serve under an Intra-agency Agreement as the Central Laboratory for the Trial, and the Public Health Service Supply Service Center (Perry Point MD) will serve under an Intra-agency Agreement as the Drug Distribution Center.

Central policy for the Trial will be set by a Steering Committee composed of one representative from each of the above-mentioned organizations and the Project Officer (from NIEHS) who will serve *ex officio*, making a total of seven members. Each regular representative will have one vote. The NIEHS Project Officer will vote to resolve ties. The Committee will elect its own Chair. The Steering Committee will be ultimately responsible for the Trial protocol and manual of operations. It will review and approve all requests to undertake ancillary studies that involve TLC subjects or TLC data as well as all proposals for publications and presentations based on TLC subjects or TLC data. The power to control the budget of the Trial and of the individual contracts rests with NIEHS under the usual federal laws and regulations.

NIEHS has appointed a Data and Safety Monitoring Committee which will be advisory to the Institute. The Committee is composed of the following seven members:

Stephen Gehlbach, Amherst, MA (Chair)
Carol Angle, Omaha, NE
John Faison, Philadelphia, PA
Bernadette Gray-Little, Chapel Hill, NC
Sherman James, Ann Arbor, MI
Lemuel Moyé, Houston, TX
Herbert Needleman, Pittsburgh, PA

Membership was determined by the NIEHS and was limited to people without appointments at the Universities involved in implementing the Trial. Meetings of the Data and Safety Monitoring Committee will be arranged by the Data Coordinating Center. The Project Officer, the Principal Investigator from the Data Coordinating Center, and the Chair of the Steering Committee will commonly attend all or parts of these meetings, but the Data and Safety Monitoring Committee shall have the prerogative of working in executive session without these other individuals. The Data and Safety Monitoring Committee will review and approve the Trial protocol and will monitor the accumulating data and progress of the Trial at least annually. It is anticipated that ordinary recommendations from the Data and Safety Monitoring Committee will be made to the Project Officer, but unusually important findings or opinions of the Committee can be forwarded, at the Committee's discretion, to the Director of NIEHS or to other officials.

A Planning Committee composed of the Steering Committee members and other professional personnel at the various sites will meet as necessary and will be responsible, with assistance from the Data Coordinating Center staff, for writing the Trial protocol and for developing a manual of operations for the Trial. The planning committee will assist with arrangements for the comparable and coordinated implementation of the protocol at the various sites. Meetings of the entire or of partial membership of the Planning Committee may be called by the Steering Committee or by the Project Officer in consultation with the Principal Investigator from the Data Coordinating Center and the Chair of the Steering Committee. The Chair of the Steering Committee will also chair the Planning Committee. The protocol and manual of operations developed by the planning committee will be subject to amendment and approval by the Steering Committee and to approval by the Data and Safety Monitoring Committee.

The work of the Planning Committee will be facilitated by subcommittees with expertise in the several areas related to the Trial. These subcommittees may be established, altered, or abolished as

necessary by the Planning Committee. Their membership and responsibilities are subject to review by the Steering Committee. Subcommittees established at the outset of the Trial are: Clinical Issues, Psychometrics, Environmental Issues, Screening and Eligibility, Treatment and Toxicity Monitoring, Community Relations, and Drug Management.

See Appendix 1 for a list of TLC Centers and for committee and subcommittee membership.

2.3. Study Population

The planned sample size for the TLC Study is 1,332. Each of four Clinical Centers will enroll 333 children. The racial and ethnic composition of the study sample is expected to reflect the composition of the clinic population at each Clinical Center. However, linguistic minorities will be excluded in all centers except Newark, where Hispanic children make up a sizable portion of the population and will be included.

Table 1 provides estimates in percentages of the racial and ethnic makeup of each Clinical Center's population and of the overall Study population.

Table 1: Racial and Ethnic Makeup of Study Population by Clinical Center and Overall

Clinical Center	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic origin	Hispanic	White, not of Hispanic origin	Other or unknown	Total
Baltimore, MD	0%	< 1%	87%	< 1%	11%	1%	100%
Cincinnati & Columbus OH	0%	< 2%	79%	< 1%	19%	0%	100%
Newark, NJ	0%	0%	71%	23%	5%	1%	100%
Philadelphia, PA	0%	5%	85%	2%	8%	0%	100%
OVERALL	0%	< 2%	81%	6%	11%	0%	100%

Table 2 provides estimates in percentages of the racial and ethnic makeup of the proposed Study sample, given the planned exclusion of linguistic minorities.

Table 2: Racial and Ethnic Makeup of Proposed Study Sample by Clinical Center and Overall

Clinical Center	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic origin	Hispanic	White, not of Hispanic origin	Other or unknown	Total
Baltimore, MD	0%	0%	89%	0%	11%	0%	100%
Cincinnati & Columbus, OH	0%	0%	81%	0%	19%	0%	100%
Newark, NJ	0%	0%	72%	23%	5%	0%	100%

Philadelphia, PA	0%	0%	91%	0%	9%	0%	100%
OVERALL	0%	0%	83%	6%	11%	0%	100%

Overall, we estimate that 80 to 85% of TLC subjects will be African-American. Due to physical location and language capabilities at the Clinical Centers, only one Center (Newark, NJ) will have substantial Hispanic representation, at approximately 23% of the Center's population. The Hispanic population is small at the remaining Centers and none of these Centers has the linguistic capability to perform the proposed psychometric testing in Spanish. Asian, Pacific Islander, Alaskan Native and American Indian representation in the TLC population is small at all Clinical Centers and none of the Centers has the linguistic capability to deal with the wide range of languages possible in these racial groups. In addition, the psychometric instruments proposed as outcome measures in this Trial are not available in the appropriate languages and normed for the appropriate cultures. However, since the issue is one of language, not ethnic background, children from these racial groups will be recruited as TLC participants unless the family's primary language is not English.

2.4. Compliance with the NIH Revitalization Act of 1993

The TLC Trial must comply with the NIH Revitalization Act of 1993, which requires that any NIH-funded clinical research include women and minorities as research subjects. In addition, in any trials in which women and minorities are included as subjects, the trial must be designed in a way that will allow for valid sub-group analyses. NIH has completed a set of proposed guidelines for the implementation of the act and these guidelines were published in the Federal Register on March 28, 1994.

The study population will reflect the population known to be at greatest risk due to lead exposure, i.e., low income, urban, African-American children. Consequently, the TLC Trial is primarily a study of a minority population. There is currently no evidence suggesting that there are or are not differences in the effects of lead on cognitive development or of the efficacy of succimer by racial or ethnic group.

The TLC Trial will recruit boys and girls equally as Trial subjects. Research on gender differences in the effects of lead on cognitive development has yielded mixed results.[7] With the expected balanced enrollment by gender, we will be able to perform valid analysis on differences by gender.

We are committed to meeting the spirit as well as the letter of the law with respect to the inclusion of women and minorities in the TLC Trial. A number of leadership positions in the Trial administrative structure are held by women, including the Principal Investigator of the Philadelphia Center and the Chair of the Treatment and Toxicity Subcommittee. Membership on the various TLC committees is well-balanced by gender. With respect to minority representation, the administrative structure of the TLC Trial does not reflect the population to be recruited. However, we are aware of the need for sensitivity to this issue. The proportion of minority membership on the Data and Safety Monitoring Committee is greater than 50%. One of the criteria applied in selecting Clinical Centers was the level of experience of the site in working with inner city communities that are primarily African-American, reflecting the national distribution of lead poisoning. We intend to employ minorities whenever possible in this project, especially as case managers, psychometricians, and other key positions involving interaction with the community. For Spanish-speaking families in the Newark Center, all Informed Consent forms will be translated into Spanish and at least one of the

psychometricians will be bilingual to ensure that all neurobehavioral assessments are performed in the preferred language of the children. The Newark Center will also have bilingual members of the environmental assessment team and there will be a translator available for the study as needed.

Every effort will be made to provide courteous and culturally sensitive service to participating TLC families. The training of TLC personnel will cover issues surrounding the need for cultural sensitivity in working with patients, their families, and the larger community. The TLC staff will attempt to provide assistance to the family that goes beyond the confines of the TLC protocol, for example, assistance in obtaining benefits such as WIC and food stamps. In addition, the removal of barriers to participation, such as lack of transportation, is crucial to recruitment and retention. Accordingly, TLC will cover the costs of transportation to and from all study visits. Trial-related treatments will be provided free of charge, including drug or placebo, multivitamin and mineral supplements, blood lead tests, developmental assessments, and assessment and clean-up of homes. In addition, the subjects and their families will be given small gifts to establish a sense of camaraderie between TLC families and staff. Such gifts might include small toys for the children and food coupons, diaper coupons, cleaning supplies, and door mats for the families. Participating Centers have found these kinds of gifts to be very welcome to their Clinic families. Such an incentive strategy benefits not only the subjects and their families but is also crucial for a successful Trial, in that incentives tend to encourage long-term followup.

Each Clinical Center will develop and implement a plan to educate key individuals and groups in its constituent community about the TLC Trial. The details of these efforts will vary among the Centers, but their general theme will be to inform key individuals about the need and rationale for the trial, about the opportunities that it creates to provide better care to local children with lead poisoning, and about more general issues regarding lead in the environment. Such education will serve to prevent misunderstanding about the randomized, placebo-controlled design of the TLC trial and may assist with recruitment. This educational effort will be carried out primarily through meetings with selected groups and individuals in the respective communities. Limited use of mass media is a possibility. Centers may establish Community Advisory Committees to guide these educational efforts.

3. ELIGIBILITY

3.1. Pre-randomization Visit 1 (V1)

3.1.1. Inclusion Criteria

a. Projected age at randomization (in approximately five weeks) of 12 to 32 months.
b. Elevated blood lead level per local laboratory.
c. English-speaking family or, in Newark, English or Spanish-speaking family.
d. Willingness of parent or legal guardian to participate as evidenced by first informed consent.

3.1.2. Exclusion Criteria

a. Exclusions based on pre-existing medical conditions by parental report and/or physical examination:
   (1) Pre-existing significant developmental deficit or disease or syndrome known to be associated with mental retardation, neuromuscular disorder, or sensory deficit, including, but not limited to, PKU, Down Syndrome, and Fetal Alcohol Syndrome.
   (2) Birth weight under 3 pounds by best available information.
   (3) Psychiatric or psychological disorder which would prohibit adequate evaluation, including, but not limited to, autism and reactive attachment disorder.
   (4) Known renal or hepatic disease.
   (5) Known chronic anemia which is not due to iron deficiency; including, but not limited to, sickle cell disease and thalassemia major.

(6) Cyanotic congenital heart disease.
(7) Known HIV positive.
(8) Allergy to sulfa or mercaptans as evidenced by hives or anaphylactic reaction.
(9) Prior chelation therapy for lead poisoning.
(10) Body surface area greater than 0.713 m^2.

b. Any child living in the same household with another child in the treatment phase of the TLC protocol. Housemates may be sequentially entered after six months.

c. Children currently enrolled in any other research drug protocols, other research protocols using psychometric assessments, or other research protocols conflicting with this protocol.

d. Exclusions based on residential history:
(1) The child's current address is outside the defined catchment area of the Center.
(2) The family has definite plans to move from the catchment area of the Center within the foreseeable future.
(3) Family plans for child to be away for three months or more during the first six months of participation.
(4) Child's current residence is too dangerous for TLC personnel to visit.

e. Exclusions based on abnormalities in laboratory values obtained at pre-randomization clinic visit 1 (V1):
(1) PbB < 20 μg/dL or PbB > 44 μg/dL.
(2) Iron status
(a) Hemoglobin level less than 9 g/dL from any cause.
(b) Hemoglobin level greater than or equal to 9 g/dL and less than 10 g/dL combined with an increased red cell distribution width. Such children will be prescribed three months of therapeutic iron and will return for repeat testing in one month. If the hemoglobin is greater than or equal to 10 g/dL at repeat testing, the child will be enrolled.
(3) Liver function studies
(a) Alkaline phosphatase greater than twice the upper limit of normal for the local laboratory.
(b) AST greater than twice the upper limit of normal for the local laboratory.
(c) ALT greater than twice the upper limit of normal for the local laboratory.
(d) Absolute neutrophil count below 800/mm^3.
(e) Platelet count below 150,000/mm^3.
Children with abnormalities in alkaline phosphatase, AST, ALT absolute neutrophil count, or platelet count will be scheduled for repeat testing of the abnormal laboratory value(s) in two to three weeks. Any further TLC activities will be deferred until the results of this repeat testing are known. If the results are normal, the child will be enrolled.
(4) Other laboratory values
(a) Serum creatinine greater than 1.0 mg/dL.
(b) Proteinuria greater than 2+ on dipstick.
(c) Glucosuria on dipstick.
Children whose serum creatinine is greater than 1.0 mg/dL or with glucosuria or proteinuria will be referred for further work-up of their condition and may be reconsidered for study eligibility if these abnormalities resolve. In such cases, repeat testing of the abnormal laboratory values will be required before any further TLC activities are carried out.

3.2. Pre-randomization Visit 2 (V2)

3.2.1. Inclusion Criteria

a. Projected age at randomization (in one week) of 12 to 32 months.
b. Venous blood lead level from CDC of 20 - 44 μg/dL.

c. Willingness of parent or legal guardian to participate as evidenced by second informed consent.

3.2.2. Exclusion Criteria

a. Inability of family or child to comply with the TLC protocol:
   (1) Children missing 50% or more of scheduled visits without extenuating circumstances during the pre-randomization period.
   (2) Children at the extremes of multivitamin compliance during the pre-randomization period, i.e., inability to give medication to TLC subject or dispensation of medication to other than TLC subject.
   (3) Children or families who, in the best judgment of the clinician, are unable to comply successfully with trial requirements.

b. Exclusions on the basis of the home visual assessment:
   (1) Child's current residence is too lead-hazardous to be adequately cleaned and child cannot be relocated in lead-safe housing. The child may be enrolled later if these conditions change.
   (2) Child's current residence is too dangerous for TLC personnel to visit.
   (3) The child spends significant amounts of time in two or more residences and the TLC Home Assessor is unable to assure that the child's total residential environment will be sufficiently clean to begin chelation therapy.

c. Body surface area less than 0.357 or greater than 0.713 m^2.

4. CLINICAL INTERVENTION

4.1. Pharmacology of Succimer

Succimer (2,3-meso-dimercaptosuccinic acid) is an orally active dithiol compound that is a relatively specific chelating agent for heavy metals, especially lead, arsenic and mercury. The drug undergoes limited absorption in the gastrointestinal tract and then is rapidly metabolized to mixed disulfides which are eliminated in the urine. Blood levels decline slowly with an apparent elimination half-life of about 48 hours in adults.

Succimer has several advantages over other available lead chelating agents. Urinary excretion of essential elements (Ca, Fe, Zn, Cu) is only minimally increased after succimer, in contrast to extensive metalluresis following $CaNa_2EDTA$. Plumburesis appears to be greater following administration of succimer compared to conventional doses of other lead chelating agents. Oral administration of succimer allows for outpatient therapy which is impractical with the parenterally administered $CaNa_2EDTA$. Finally, clinical experience to date has shown succimer to be well-tolerated with minimal toxicity during single or repeated courses of therapy.

To date, reversible adverse effects of succimer include hypersensitivity (incidence about 1-2%) and asymptomatic serum transaminase elevation. Neutropenia and asymptomatic, reversible alkaline phosphatase elevation occasionally have been reported. Other than drug hypersensitivity, these effects have not required discontinuation of succimer therapy.

Disadvantages of succimer relate to the drug's characteristics and pharmacologic information gaps. The "rotten-egg" odor and bad taste may affect compliance as well as produce occasional gastrointestinal upset in children taking the drug. Whether succimer enhances lead absorption is unknown, but it is an important consideration when a child taking the drug continues to reside where lead paint hazards are unabated. Data from animal studies suggest that succimer may produce a redistribution of internal lead stores.

Data from McNeil Laboratories on the stability of succimer in various liquids is presented in Table 3.

Table 3. Stability of Succimer in Liquid After 15 Minutes

Liquid	% Retention of original activity
Cranberry juice	96%
Apple juice	85%
Coca Cola	78%
7-Up	75%
Kool-Aid	66%

Food is a difficult matrix for analysis and background interference precluded analysis of chocolate-containing foods. However, McNeil chemists estimate that about 80% of active drug remained 15 minutes after it was mixed with applesauce. It is not believed that succimer bioavailability will be affected by the protein content of any food with which the drug might be mixed.

The optimal dosing regimen and duration of therapy with succimer have yet to be determined.

4.2. Treatment Regimen

The treatment dosing in this trial will be based on body surface area (BSA). BSA will be calculated using the following formula, developed by Du Bois and Du Bois.[8]

$$\text{BSA in mm}^2 = (\text{WEIGHT}^{0.425} \times \text{HEIGHT}^{0.725} \times 71.84) / 10{,}000$$

Children randomized to succimer will receive approximately 1050 mg/m^2 of succimer in three divided doses per day for seven days, followed by 700 mg/m^2 in two divided doses per day for 19 days for a total course of therapy of 26 days. Table 4 provides the exact succimer dose by body surface area.

Table 4. Succimer Dose by Body Surface Area

BSA CLASS	BSA RANGE (m^2)	DAYS 1 - 7		DAYS 8 - 26	
		DAILY DOSE in mg (# caps/dose)	DOSE DELIVERED (mg/m^2/day)	DAILY DOSE in mg (# caps/dose)	DOSE DELIVERED (mg/m^2/day)
A	0.357 - 0.428	400 (1-1-2)	1120 - 935	300 (1-2)	840 - 702
B	0.429 - 0.499	500 (2-1-2)	1167 - 1002	300 (1-2)	700 - 602
C	0.500 - 0.523	500 (2-1-2)	1000 - 956	400 (2-2)	800 - 765
D	0.524 - 0.618	600 (2-2-2)	1145 - 971	400 (2-2)	764 - 647

E	0.619 - 0.642	700 (2-2-3)	1131- 1091	400 (2-2)	646 - 624
F	0.643 - 0.713	700 (2-2-3)	1089 - 981	500 (2-3)	778 - 701

Children whose body surface area is less than 0.357 or greater than 0.713 will be excluded from the study. Children randomized to placebo will follow a similar BSA-specific regimen. During treatment, children will be seen on days 7, 28, and 42. At each visit, blood will be drawn to measure PbB, complete blood count (CBC), differential, platelet count, AST, ALT, and alkaline phosphatase.

Children whose PbB at day 42 is greater than 15 μg/dL will be retreated beginning on day 49. Each child on succimer requiring retreatment will be paired with a placebo child who will follow the same protocol as the retreated child. A maximum of three courses of drug therapy will be administered for up to six months in the treatment phase for children receiving three courses of drug. The protocol for retreatment will be the same as for the initial course of treatment.

In this trial, succimer will be administered using fruit juice or soda. Non-carbonated fruit-flavored beverages will be avoided. If a child refuses to take drug in one of these liquids, the drug will be mixed with approximately one teaspoonful of applesauce, jelly, or vanilla pudding for administration.

4.3. Toxicity Monitoring

If the PbB increases to 45 μg/dL or greater during the treatment period, the Data Coordinating Center will notify the Clinic to bring the subject in for a repeat blood test within three days. The repeat PbB will be processed by the central laboratory on an urgent basis. If the repeat PbB value from CDC remains above 44 μg/dL, the study treatment will be interrupted, and the child will be treated according to the Clinical Center's standards of care for children with lead levels above 44 μg/dL. This will include reassessment of the child's environment for potential lead exposure and coordination with the local health department for formal lead assessment as per local requirements. Blinding of treatment assignment will be maintained.

In the unlikely event that the PbB increases to 60 μg/dL or greater during the treatment period, the Data Coordinating Center will notify the Clinic immediately, and study treatment will be stopped immediately. The child will be treated according to the Clinical Center's standards of care for children with lead levels 60 μg/dL or greater. This will include a reassessment of the child's environment for continuing sources of lead exposure. Repeat blood testing by the CDC laboratory will not be required for treatment; however, a second blood sample will be obtained and sent to the CDC for evaluation. Blinding of treatment assignment will be maintained.

If a child's PbB increases to more than 15 μg/dL above her or his baseline (V2) PbB value within six months of randomization, a repeat PbB will be performed as soon as possible. Confirmation of the increase in PbB will trigger environmental reassessment and, where appropriate, further cleanup. Blinding of treatment assignment will be maintained.

Possible toxicities of succimer include elevation of liver function tests and decline in neutrophil counts. Elevations in liver function tests occur in about 5% of children. To maintain blinding, liver function levels will be blinded for both parents and clinic personnel until six months after randomization. Each Clinical Center will identify a physician not having direct subject or guardian contact who will review laboratory results during the period of blinding. The reviewing physician will notify the clinician if transaminase exceeds two times the upper limit of normal, alkaline phosphatase exceeds five times the upper limit of normal, the absolute neutrophil count decreases to less than 800/mm^3, the platelet count decreases to less than 150,000/mm^3, or the values change in a way which

the reviewing physician considers to be of concern. If a value is abnormal, the reviewing physician will order repeat testing. If a second abnormal value is obtained, the reviewing physician may recommend discontinuation of study drug. Blinding of treatment assignment will be maintained.

Suspected or known adverse drug reactions will be reported promptly to the manufacturer, to the Food and Drug Administration, and to the local human subjects committee.

4.4. Informed Consent

For all TLC participants, the consent of a parent or legal guardian will be required. The language of the informed consent documents will be that of the parent or legal guardian and will be geared to a 6th grade school educational level. Informed consent will be sought on two occasions. Stage I informed consent will cover the pre-enrollment period and will be obtained at pre-randomization clinic visit 1 (V1). Stage II informed consent will cover enrollment in the randomized protocol and will be obtained either during the visit immediately prior to the initiation of treatment (V2) or the visit at which treatment will be initiated (T0). See Appendix 2 for informed consent forms from each of the Clinical Centers.

4.5. Randomization

After Stage II informed consent has been obtained, subjects will be randomized in a 1:1 ratio to either the succimer or placebo treatment group. Treatment assignments will be determined by a permuted blocks randomization scheme with stratification by city (Baltimore, MD, Newark, NJ, Philadelphia, PA, Cincinnati, OH, and Columbus, OH), class of body surface area as defined in Table 4 above, and most recent CDC blood lead level (20 - 24 μg/dL and 25 - 44 μg/dL). Once a treatment assignment has been made, a child will be considered to be enrolled in the randomized trial for its duration, regardless of followup status. Children who are taken off the treatment protocol prematurely will continue to be followed according to the TLC schedule. Children will be followed according to study protocol irrespective of their level of compliance with study treatment, and all available outcome data will be included in the analyses according to the principle of "intent to treat" analysis.

4.6. Maintenance of Double-blind

Treatment will be blinded to the fullest extent possible. Both parents and clinic personnel will be blinded to the child's PbB levels during treatment until six months after randomization.

Succimer emits a strong odor of sulfur, while the placebo for succimer emits a smell of alcohol. Therefore, it will not be possible to provide a fully comparable placebo. However, to provide a more sulfur-like smell to the placebo, a vented cylindrical plastic canister, 0.5 inches in diameter and 0.6 inches in length, will be filled with 100 mg. of succimer and added to all bottles of study drug (not just those containing succimer). The addition of the canister will change the odor of the placebo to one which is qualitatively similar to, but not as intense as, that of the active drug. Further, every effort will be made to avoid the need for any clinic personnel to open any subject's medication bottle or otherwise deal directly with the study drug. The subjects taking succimer may themselves give off a strong odor; therefore, it may not be possible to blind clinic personnel entirely. For example, parents or caregivers may comment on the smell. Clinic personnel responsible for psychometric assessment, however, will not have contact with subjects or their caregivers during the treatment period.

As discussed above, local laboratory results will be reviewed by a physician who does not have direct subject or guardian contact during the treatment period. If a value is abnormal, the physician will order repeat testing. If a second abnormal value is obtained, the physician may recommend discontinuation of study drug. Blinding of treatment assignment will be maintained.

4.7. Compliance Assessment

Because succimer emits a strong odor, the use of pill counts to assess compliance at each Clinic visit will unblind TLC personnel. Several other strategies will be used to quantify compliance with study drug. The parent or caregiver of all subjects will receive a specially designed medication diary. The diary will use pictorial directions in addition to text in English or Spanish. The caregiver will make an entry into the diary when each dose is administered. In addition, they will be instructed to bring the diary and the medication bottle to each treatment visit. At each treatment visit, a member of the clinic staff will review the medication diary and talk with the caregiver about their success in complying with treatment instructions. At the end of each round of treatment, the bottle will be returned to the Drug Distrubution Center for pill counting and destruction of left-over study drug. The results of study drug pill counts will be forwarded to the Data Coordinating Center.

Pill counts, while the standard measure of compliance currently in use in most drug trials, have been shown both to overestimate compliance[9, 10] and to be unreliable.[11] Medication diaries are helpful only when used in conjunction with an objective measure of compliance. Accurate compliance monitoring will help distinguish between the two known reasons for inadequate response to succimer therapy, i.e., continued environmental exposure to lead versus noncompliance with therapy. In the Ohio Center, the Medication Event Monitoring System (MEMS) will be used to provide a more accurate measure of compliance than can be provided by pill counts or medication diaries. The standard MEMS bottle cap contains a special electronic chip which records date and time whenever the bottle is opened. The data gathered in the Ohio Center using the MEMS caps will be used to assess the accuracy of pill counts and medication diaries as measures of compliance.

A relatively new and untested version of the MEMS caps is their "smart cap", which records the number of hours between bottle openings, as well as the date and time of each opening. The "smart" cap can also be programmed to beep when a dose is scheduled to be taken and to display the number of bottle openings that have occurred during each 24-hour interval. In addition to providing an accurate measure of compliance, this new "smart" MEMS cap is hypothesized to assist parents with compliance. The Ohio Center will test the hypothesis that the newer cap enhances compliance by using "smart" caps for half the children and the standard "track" cap for the remainder of the children.

5. DEVELOPMENTAL ASSESSMENT

5.1. Introduction

Longitudinal studies of the neurobehavioral sequelae of asymptomatic lead toxicity have consistently reported deficits in IQ in lead-exposed children.[12] Thus, the primary hypothesis to be tested in the TLC Trial is that treatment with succimer will lead to improved developmental outcome as evidenced by improved scores on standardized intelligence testing. IQ of study participants will be measured by the Bayley Scales of Infant Development-II (BSID2) at baseline and at the six-month followup visit, by the BSID2 or the Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R) (depending on the child's age) at the 18-month followup visit, and by the WPPSI-R at the 36-month followup visit.

Using IQ as the sole outcome measure in a study whose population is projected to be 85% African-American would be unacceptable. Controversy has surrounded the assessment of intellectual ability for over a century. Legitimate concerns were raised in the 1960s and 1970s concerning the appropriateness of existing psychological tests for the assessment of minorities, particularly African-Americans.[13] These concerns were focused on potential racial or ethnic bias in standardized measures of intellectual attainment and academic achievement. This has been one of the most emotionally and politically charged controversies in the psychological sciences.[14, 15] Until the last few decades, the instruments used to measure intellectual ability were not subjected to quantitative or qualitative

analyses aimed at evaluating racial, ethnic, or gender bias. The more recent psychometric instruments available from the major test publishers are less likely to suffer from these problems.

The assessment of intelligence using norm-referenced tests alone does not provide a complete description of developmental status. The underlying basis for poor intellectual performance (e.g., deficits in attention, organization, impulse control, ability to follow directions, or quality of motor activity) may not be captured by standardized tests of intellectual attainment. Primate and human neurodevelopmental research has provided evidence that the attention, learning, short-term memory, and executive function are the selectively deficient domains of cognition that may underlie IQ differences.[2, 3] Behavioral problems have been found to be associated with lead exposure in some observational studies.[16, 17, 18] In addition, deficits in the fine motor skills important for school work (e.g., the ability to use pencils, crayons, or scissors) have been associated with low to moderate exposure to lead.[19]

Several other measures of developmental status will be obtained. The Child Development Inventory (CDI) and Conners' Parent Rating Scale (CPRS) utilize parental reports as the principal source of data. Some studies have suggested that the diagnostic utility of standardized tests of cognitive and motor development is improved through the use of maternal reports.[20] Parents are also an important source of information about the child's behavior outside the clinical setting. The CDI will be administered to parents at all psychometric visits (baseline, six-, 18-, and 36-month followup visits) and the CPRS will be administered to parents at the 36-month followup visit. In addition, all children will be assessed at the 36-month followup visit with instruments sensitive to attention, learning, short term memory, and executive function. All children will be tested using Woodcock-Johnson Memory for Names, Stanford-Binet Bead Memory, Kaufman Assessment Battery for Children (K-ABC) Magic Window, and Diamond's Modified Stroop Task. The Tower of Hanoi will be administered to children who are 60 months of age or older at the 36-month followup visit.

Parental IQ will be obtained at the 12-month followup visit using the Wechsler Adult Intelligence Scale – Revised, Short Form. Maternal IQ is preferred; however, paternal or guardian IQ will be obtained if the biological mother is unavailable for testing.

The schedule for psychometric testing is summarized in Table 5.

Table 5. Schedule of Psychometric Testing

Instrument	Baseline	6 mos. post randomization	12 mos. post randomization	18 mos. post randomization	36 mos post randomization
Bayley Scales of Infant Development-II (BSID2)	✓	✓		✓	
Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R)				✓	✓
Child Development Inventory (CDI)	✓	✓		✓	✓
Conners' Parent Rating Scale (CPRS)					✓
Woodcock-Johnson Memory for Names					✓
Stanford-Binet Bead Memory					✓
K-ABC Magic Window					✓
Diamond's Modified Stroop Task					✓

Tower of Hanoi***					✓
Wechsler Adult Intelligence Scale – Revised, Short Form (WAISR-SF) (parental IQ)			✓		

* For subjects up to and including 42 months of age at this visit
** For subjects over 42 months of age at this visit
*** For subjects 60 months of age or older at this visit

5.2. Bayley Scales of Infant Development-II (BSID2)

The BSID2[21] is a revision and restandardization of the well-known Bayley Scales of Infant Development.[22] It is suitable for infants and young children from one to 42 months of age. The Bayley Scales of Infant Development are the most widely used and precisely constructed of all published infant intelligence tests.

The BSID2 yields a Mental Development Index (MDI) and Psychomotor Development Index (PDI) which are similar to a deviation IQ score with a mean of 100 and a standard deviation of 15. The MDI is designed to evaluate the development of sensory and perceptual acuities and discriminations, acquisition of object constancy, memory, learning, problem solving, vocalization, beginning of complex language, and mathematical concept formation. The PDI is designed to evaluate the development of postural control, coordination of the large muscles, postural imitation, and stereognosis.

The BSID2 includes a Behavior Rating Scale with which the examiner rates the infant's affective, attentional, and motivational behaviors. It consists of thirty separate 5-point items which assess qualitative aspects of the subject's attentional, emotional, and motor behaviors. Previous studies suggest that the regulation of attentional, motor, and emotional behaviors may be perturbed in children with blood PbB concentrations in excess of 20 μg/dL.

The BSID2 takes from 45 to 75 minutes to administer.

5.3. Wechsler Preschool and Primary Scales of Intelligence - Revised (WPPSI-R)

The WPPSI-R[23] is a revision of the original Wechsler Preschool and Primary Scale of Intelligence[24] and is suitable for children aged 35 to 87 months. The WPPSI and WPPSI-R possess the best psychometric properties of all published tests of preschool intelligence. Among all preschool IQ tests, the WPPSI-R has been used the most to establish the construct and criterion-based validity of other measures of preschool intellectual attainment.

The WPPSI-R consists of a collection of 12 subtests organized into two scales, a Verbal Scale and a Performance Scale. The Verbal Scales use language-based items while the Performance Scale test uses visual-motor items that are somewhat less dependent on language. The WPPSI-R yields scale scores for the 12 subtests as well as Verbal, Performance, and Full-Scale deviation IQs which have a mean of 100 and a standard deviation of 15.

The WPPSI-R takes from 60 to 75 minutes to administer.

5.4. Wechsler Adult Intelligence Scale - Revised, Short Form (WAISR-SF)

Parental intelligence is one of the most powerful predictors of child IQ. An assessment of parental IQ is included in this clinical trial to serve as a potent covariate as well as a check on the randomization.

Parental IQ will be assessed using the two-subtest short form of the Wechsler Adult Intelligence Scale - Revised[24]. Maternal IQ will be obtained whenever possible. When the maternal IQ cannot be obtained, the clinic will attempt to obtain the paternal IQ or the IQ of the child's primary caregiver. The two-subtest short-form includes the vocabulary and block design subscales. The scoring tables of Silverstein[25] will be used. The WAISR-SF will yield a full scale deviation IQ. This particular short form of the full WAIS-R has a higher correlation with full scale IQ based upon the total Wechsler battery than any other subtest dyad (corrected r = 0.90).

The WAISR-SF takes from 20 to 30 minutes to administer.

5.5. Child Development Inventory (CDI)

The CDI[26] is a revised version of the Minnesota Child Development Inventory (MCDI) and is administered to the parent or caregiver. The 270 items on the CDI are grouped to form several scales. TLC psychometricians will administer only those items which contribute to the scoring of the General Development Scale (GDS). The GDS has a correlation of 0.89 with age in the normative sample. Validity studies using the original MCDI showed that the General Development Scale correlated significantly with various outcome measures, including the Mental and Psychomotor Indices from the Bayley Scales of Infant Development and the General Cognitive Index from the McCarthy Scales of Children's Abilities.[27, 28, 29, 30]

The CDI scales were derived rationally, not through factor analysis, and were normed with reference to a sample of 568 children from South St. Paul, Minnesota, a primarily white, working class community. An earlier version of the CDI was shown to have good concurrent validity when applied to a population of minority, high-risk children.[31] The CDI is designed to require an eighth-grade reading level for parents to complete it independently. The mean years of parental education for the normative group was approximately 13 years. Interviewers will be available to guide and assist parents in filling out the CDI form. It is anticipated that there will be a significant number of TLC parents and caregivers who will need help filling out the form.

The GDS of the CDI takes approximately 20 minutes to administer.

5.6. Conners' Parent Rating Scale (CPRS)

The Conners' Parent Rating Scale[32] is a 48-item rating scale administered to the parent or caregiver and used to characterize patterns of child behavior. The items yield standard scores on five scales: Conduct Problem; Learning Problem; Psychosomatic; Impulsive-Hyperactive; and Anxiety. The scales were derived in factor analyses using normative data from 578 children aged 3 to 17 years. The CPRS has been used extensively in research, and considerable validation data are presented in the test manual[32].

The CPRS also includes a Hyperactivity Index, which is composed of the ten items most sensitive to drug (i.e., stimulant) effects. The Hyperactivity Index was developed to provide a practical, empirical assessment of the extent to which children display behaviors that are usually considered indicative of hyperactivity.

The CPRS takes approximately 10 minutes to administer.

5.7. Neurodevelopmental Battery

A small battery of supplemental neurodevelopmental measures will be administered on the final followup visit. At that time, all subjects will be between 48 and 66 months old. Cognitive areas assessed by the battery include attention, memory, learning, and executive function. Deficits in these cognitive areas have been associated with lead toxicity in various studies. The following tests will be included in the battery: Woodcock-Johnson Memory for Names, Stanford-Binet Bead Memory, Kaufman Assessment Battery for Children (K-ABC) Magic Window, Diamonds' Modified Stroop Task, and Tower of Hanoi (for children 60 months of age or older). For children under 60 months the battery will take approximately 45 to 60 minutes with an additional 25 to 30 minutes for children older than 60 months.

5.7.1. Woodcock-Johnson Memory for Names

This test is a subtest of the Woodcock-Johnson Psycho-educational Battery – Revised.[33] The Woodcock-Johnson is used widely in the diagnosis of learning disabilities and instructional planning. This particular subtest measures how well a child is able to learn to associate unfamiliar, nonsense names with drawings of imaginary alien space creatures. It assesses the efficiency of verbal and visual processing as well as memory.

The Woodcock-Johnson Memory for Names takes approximately 10 minutes to administer.

5.7.2. Stanford-Binet Bead Memory

This test is a subtest of the Stanford-Binet-V Intelligence Test.[34] It measures visual short term memory for colors, shapes (ellipsoids, cones, and saucers), and sizes. The examinee is exposed to either the tester's example construction (base and stick on which beads are assembled) or a photographed construction for five seconds. The subject must then accurately reproduce the model or picture. Children with deficits in visual-spatial abilities or who are impulsive and/or easily distracted will experience difficulties with this task.

The Stanford-Binet Bead Memory test takes approximately 10 minutes to administer.

5.7.3. Kaufman Assessment Battery for Children (K-ABC) Magic Window

The K-ABC Magic Window[35] measures the child's ability to identify and name an object whose picture is rotated behind a narrow slit, so that the picture is only partly exposed at any point in time. The subtest consists of 15 readily recognizable items such as a car, girl, apple, hat, watch, and table.

The cognitive domains of this task are attention and temporal-spatial abilities. Children who are generally impulsive, easily distracted, or unable to respond under conditions of uncertainty will have difficulty with this test. For the preschooler, Magic Window involves a fairly complex integration of spatial information presented temporally, thereby assessing cerebral hemispheric integration. It is a relatively unbiased test, providing reliable results regardless of race, gender, or overall level of intelligence.[36]

The K-ABC Magic Window test takes approximately five minutes to administer.

5.7.4. Diamond's Modified Stroop Task

Diamond's Modified Stroop Task[37] is a simplified version of the Stroop color-word task.[38] In this version, the interviewer uses a deck of cards with two kinds of cards. Half of the cards show a bright sun against a white background; the other half show a moon and stars against a black

background. The child is instructed to say "night" when shown the white card with sun and to say "day" when shown the black card with moon. The task requires inhibitory control of a natural tendency to give a different verbal response than requested. In addition, unlike the original Stroop task, the modified version also requires working memory. The task has been used with children between the ages of 3½ and 7 years, with normative data available for each six-month interval in this age range.

Diamond's Modified Stroop Task takes approximately 15 minutes to administer.

5.7.5. Tower of Hanoi

The Tower of Hanoi puzzle[39] series is a test which has been used in clinical research to measure executive function, i.e, the ability to plan and execute a series of related actions. In the Tower of Hanoi, subjects are required to assemble rings of differing sizes and colors arranged on a peg to make a tower which duplicates the examiner's disk configuration. Factor analytic studies have shown that this task loads most highly on a cognitive planning factor when used with children. Efficient performance also requires the ability to inhibit irrelevant responses.

The examiner provides subjects with an age-appropriate explanation of the task objectives and rules. For young children, the abstractness of the task is reduced by a cover story describing the test as a game concerning a family of monkeys jumping among trees (pegs) in a forest. Practice trials are administered to be certain the child is aware of the demands of the game. The scoring system yields a "planning efficiency score" which ranges from 0 to 6.

This test will be administered to children 60 months and older only. A reliability coefficient of 0.74 has been established for test-retest.[40]

The Tower of Hanoi takes approximately 25 minutes to administer.

5.8. Quality Control Procedures

The supervising TLC psychologist at each Clinical Center will train the psychometricians at that Center in all psychometric instruments. In particular, each psychometrician will obtain pilot experience in the assessment of children between the ages of 12 and 72 months using the instruments selected for the trial. On a pilot basis, each trainee will administer the BSID2 to two or three children and the CDI to their parent at ages 12, 18, 24, and 30 months. Training on the WPPSI-R, CPRS, Woodcock-Johnson Memory for Names, Stanford-Binet Bead Memory, K-ABC Magic Window, and Diamond's Modified Stroop Task will focus on the assessment of preschool children between three and five years of age. Training on the Tower of Hanoi will be performed on children five years of age or older. Pilot children will be sampled from a population similar to that expected to be recruited into the trial at that Center.

Intertester reliability in scoring will be well established prior to formal data collection through the use of video-tape or other means of observation. The performance of psychometricians will be periodically evaluated throughout the study with the use of reliability studies.

Each Center will provide a clean, quiet, and comfortable room large enough to administer all components of the psychometric examinations. To assure optimum performance and standardization among the Centers, children will be scheduled for psychometric examinations during daytime hours, avoiding the child's usual nap time. Care will be taken to ensure that the child is not tired, ill, hungry, or taking any medications which may affect performance when the exam takes place. Children who are ill will be rescheduled for psychometric evaluation.

TLC psychometricians will be required to score each test twice to prevent error resulting from the misreading of raw to scale-score conversion tables. Supervising psychologists will review each test prior to data coding on TLC forms and submission to the Data Coordinating Center.

6. ENVIRONMENTAL ASSESSMENT AND CONTROL

6.1. Introduction

The environmental intervention in this trial is designed to reduce substantially the subject's exposure to lead attributable to lead-based paint in poor condition and/or to lead-contaminated house-dust. This reduction in exposure is particularly important during the treatment phase, a period of up to six months, and during the period of greatest hand-to-mouth activity for each child, up to approximately 36 months of age. A secondary goal is to reduce exposure to lead for the duration of the trial, a period of up to three years from enrollment. In order to be able to detect any long-term impact of succimer, it is necessary that at least the primary goals be accomplished. Optimally, a child with lead toxicity should be relocated to lead-safe housing; however, this is usually not possible. Lead paint abatement is the next best option but is often difficult and prohibitively expensive, taking many months to complete. The final option, and the one adopted by this trial, is to provide interim control measures aimed at reducing exposure to lead in deteriorating paint and lead dust through in-place management of sources.

This protocol establishes standards of environmental assessment and intervention to be followed by all Clinical Centers. Each Center will meet or exceed applicable local, state, and federal guidelines for the clinical management of children with lead toxicity. See Appendix 3 for copies of the relevant laws, regulations, and guidelines. As resources permit, individual Centers may elect to provide environmental management beyond the common core. TLC efforts are not meant to substitute for lead paint abatement that would be required or encouraged by local health departments. See Appendix 4 for supplemental environmental protocols from the TLC Clinical Centers.

The TLC clean-up protocol does not, and is not intended to, substitute for the legally mandated activities carried out by local or state agencies in each city. TLC activities will be carried out independently of and in addition to municipal or state activities. TLC participation will not relieve anyone of the responsibility to abate. All participants in the Trial will have more clean-up activities done to their homes than they would otherwise have.

6.2. Environmental Assessment and Monitoring

6.2.1. Initial Home Assessment

At the first clinic visit (V1), environmental assessment will begin with a residential questionnaire designed to help determine eligibility for the trial. Children may be excluded because of the reported quality of current housing, high frequency of changing residences, or extended periods of time spent by the child at two or more secondary residences. In addition, the parent or guardian will be asked several questions related to any lead paint problems in their current dwelling. This information will be of value to the Assessor at the time of the first home visit (H1).

At the first home visit (H1), trained TLC personnel will determine whether the child will be excluded from the Trial based on the condition of the housing, will estimate the amount of work required to clean the residence, and will assess the likelihood that efforts at lead dust suppression will fail within an unacceptably short interval. An assessment will be made of the likely risks of lead exposure based on

(1) condition of painted surfaces
(2) accessibility of non-intact painted surfaces

(3) condition of painted substrates
(4) ease with which surfaces can be cleaned
(5) overall structural integrity of the dwelling, both interior and exterior.

Standardized assessment forms will be used in all Clinical Centers to assess the residential dwelling unit, common areas (such as hallways and stairwells), and porches. Frequency of access by the child to each area will be considered in the environmental assessment and clean-up plan. If the housing unit meets eligibility criteria, the TLC Assessor will sketch a floor plan, record room sizes and number of windows, note the type of flooring with particular attention to carpeting, estimate the amount of time required to prepare and clean the unit, and determine if it will be necessary to contact the building owner or manager prior to any planned clean-up activities.

During the first home visit, the family will be informed as to what will be done, when the cleaning and paint stabilization will be conducted, how long it will take, what they should do in preparation, and what they should do during cleaning and other work. In some cases, a child with an elevated blood lead may be found to live in relatively lead-free housing or to have moved to relatively lead-free housing after the detection of the blood lead elevation and prior to study enrollment. In such cases, the TLC Assessor may elect to implement a less aggressive clean-up plan, if the age and condition of the housing so warrant.

6.2.2. Collection of Environmental Lead Monitoring Data

There are several needs for measuring the amount of lead in the child's environment. These data are needed to describe the average level of dust lead exposure across cities. This can be accomplished, for a minimal expenditure of resources, by measuring dust lead levels in a random subset of all study residences in each city. Monitoring data are also needed to assure that the residence has been appropriately cleaned and is relatively lead-safe. This monitoring should be performed as soon as possible following clean-up. Finally, lead measurements may serve as covariates in analyses which attempt to characterize the effectiveness of succimer in reducing blood lead levels. Such data could also be used to explain anomalous responses to succimer therapy and to quantify the extent of residential lead reduction.

Evaluation of contractor performance with respect to the clean-up protocol will be based on post-clean-up visual inspection and a "white glove" test. Since we do not know if our clean-up protocol is adequate to attain Housing and Urban Development (HUD) clearance levels, these guidelines should not be used to monitor clean-up. Similarly, we have no basis for specifying a particular percent reduction in lead loading of dust samples.

To determine and document the effectiveness of the clean-up strategy, pre- and post-clean-up dust wipe samples will be collected from approximately 50 homes in each site. Half of these homes will be evaluated during the first two months of recruitment, analyzed quickly, and reviewed by the Environmental Subcommittee. If the lead loadings increase following clean-up activities, this information will be used to evaluate the clean-up protocol and the performance of the cleaning crew. The remaining homes will be evaluated over the rest of the year.

A single composite wipe from the floor areas will be collected from each residence approximately three to six months after clean-up. This sample will document the exposure of each study participant following clean-up and treatment. These samples will be archived pending availability of funds to analyze the samples.

The measures of lead loading will be obtained by using the HUD wipe method. This is a standard measure which is relatively inexpensive to collect and analyze. It cannot be used on carpets and provides only a measure of loading; however, these constraints are not seen as serious limitations in the context of the TLC Trial.

6.3. Lead Dust Suppression Procedures

A TLC cleaning crew will return to the home of each eligible child before randomization to clean that child's house according to a standardized protocol. As resources permit, the family will be provided with plastic bags or cardboard boxes several days prior to cleaning, so that they can pick up items on the floor for easy removal by the cleaning crew.

A strict series of contamination control procedures will be in force throughout the dust suppression process to ensure that contaminated furnishings, cleaning water, and dust are handled appropriately on-site and transported to the designated disposal site as appropriate without loss or spread of material. Vacuum cleaners equipped with high-efficiency particulate accumulator (HEPA) filters will be used to abate interior dust. If the vacuum cleaner bag breaks while a vacuum cleaner is operating or if the vacuum cleaner is operated without a bag, the second stage filter must be changed prior to any further use of the vacuum cleaner.

Each cleaning crew will consist of two or three individuals. This crew will be responsible for the temporary removal of the furnishings and carpeting to other locations within the housing or to a lockable van brought to the housing site for this purpose. Moving the furniture will permit more efficient use of time in cleaning. Removal of all furniture is not necessary; however, furniture remaining in a room during cleaning will be covered in plastic. The crew is also responsible for vacuuming and washing household surfaces including the floors and ledges (e.g., window wells and sills) and restoring the furniture and personal belongings to their original locations.

The first step in cleaning will be the preparation of an area for temporary storage of household belongings from other rooms. This preparation will include an initial one-pass vacuuming. After the temporary storage area has been prepared, the rooms will be cleaned in a sequence which begins with rooms located furthest from the entrance. All ledges (e.g., sills, tops of baseboards) will be washed with a detergent solution. Window wells, if accessible, will be vacuumed to remove paint chips and dust and then wiped clean with a damp sponge. Other dust traps (e.g., venetian blinds, cold air return registers, baseboards) will be inspected and cleaned as appropriate. The family will be encouraged to wash curtains and dispose of old carpets and blinds.

Carpeting will be vacuumed as follows. The carpet will be folded in half and the bottom side of the carpet will be vacuumed and the exposed floor will be vacuumed and damp mopped with the detergent solution. The carpet will then be folded to the opposite side of the room and the same procedures will be carried out on the other half of the carpet and exposed floor. If there is padding beneath the carpet, it will be cleaned in a manner similar to the carpets, if possible. The last step in the cleaning process will be a final vacuuming of the carpet. The carpet will be vacuumed three times at the rate of one minute per square yard each time. Workers will be required to time this vacuuming with a watch. All carpets will be vacuumed with an approved HEPA equipped vacuum and an approved beater bar. In rooms where the carpeting is permanently installed (e.g., wall to wall carpeting), the carpeting will not be folded back and the floor beneath the carpeting will not be cleaned. The carpet will be vacuumed at the rate indicated above. At the completion of the vacuuming, the furniture and personal belongings will be replaced in their original positions.

If there is no carpeting on the floor, the floor will be vacuumed at the rate of one minute per square yard. After the first vacuuming, the floor will be damp mopped with a detergent solution and then vacuumed a second time at the specified rate. This second vacuuming may only be needed in the worst situations where the floor surface is in very poor condition and is therefore likely to retain large quantities of dust.

Badly deteriorated carpets or padding will be permanently removed, if possible. Disposal of the carpet or padding is left to the discretion of the TLC Home Assessor. When disposal or

replacement of carpets or padding is indicated, the existing carpet or padding should be rolled into a tight roll and wrapped with 4 mil polyethylene plastic and taped securely with duct tape or a similarly durable strapping tape prior to removal from the room. If new carpet or padding is to be installed, it should not be installed until all cleaning and paint stabilization in the housing unit has been completed.

Common areas (e.g., hallways, stairs) will be included in the cleaning effort to increase the effectiveness of the dust suppression efforts. Similarly, porches and other exterior entryways will be included in the clean-up program. The limited paint stabilization effort will also be applied to the common areas, porches, and entryways. Particular attention will be given to deteriorated painted surfaces on porches, including ceilings. All surfaces will be vacuumed to remove loose paint.

Door mats at the interior entry to the residential unit will be used to minimize the amount of dust which enters the living space. These mats will be periodically cleaned or replaced to prevent them from becoming a reservoir of lead dust that can contaminate the house. Outdoor mats or indoor-outdoor carpet are recommended. The thickness of indoor mats and their placement must not interfere with the normal opening of the entry door; otherwise, they are likely to be removed by the resident.

A two-bucket system will be used for washing floors. The cleaning solution will be mixed in one bucket; the second bucket will contain rinse water for cleaning the mop head. The water in both buckets will be changed after cleaning approximately every 75 to 100 square feet of floor and after each room is completed. Wash water will be disposed of in the toilet. It will not be disposed of in other places such as sinks, bath tubs, street gutters, or back yards.

6.4. Paint Stabilization

It is not the objective of this trial to carry out or oversee comprehensive lead paint abatement activities. However, the interim dust control procedures will be rapidly negated if no attention is given to deteriorated paint surfaces. If the deterioration is extensive and proper paint abatement is not an immediate possibility, then relocation must be sought or the child will be excluded from participation in the trial. If the deterioration is localized to one or two surfaces (e.g., window sills or frames), then in-place management is an appropriate interim option to be carried out under this trial. Loose, peeling paint will be gently brushed with a damp towel or damp sponge to remove the flakes or these can be removed with a vacuum cleaner with an appropriate attachment. Contact paper or a coat of paint may be applied over the deteriorated surface to provide a short term stabilization of the surface. All loose chips must be vacuumed and the surrounding surfaces washed. It is important that the family and landlord understand that this is an emergency measure only. Without adequate preparation of the painted surface, any form of encapsulant will have a short life expectancy. Constant reinspection by the family is required. The family will be instructed to keep children away from the repaired area until more complete abatement can be provided by the owner.

The parent or guardian will be instructed to contact the TLC representative if the surface deteriorates further or if the landlord performs her or his own repairs or repainting. In the latter case, the parent will be instructed to request that the workers clean the area thoroughly by damp mopping and wiping up any dust. The parent should further remove any dust left behind by repair workers.

6.5. Followup

Each family will be provided with educational materials and information on lead poisoning and how to minimize its occurrence. As needed and within the constraints of available funds, families will be supplied with cleaning materials, such as a bucket, mop, sponges, and detergent.

Cleaning by TLC personnel beyond the baseline clean-up will occur at a minimum when a subject changes residence. Frequency of recleaning beyond this minimum will be within the constraints of available funds and proportional to the perceived rate of lead dust reaccumulation and rate of deterioration of painted surfaces. The condition of painted surfaces should be assessed periodically. If the temporary stabilization does not appear to be satisfactory, other measures, such as owner-provided abatement or relocation, should be considered.

6.6. Quality Control Procedures

To standardize the home visual assessment process, assessors from each city will undergo common training and will use a common assessment form. Photographs of various painted surface conditions with varying degrees of surface degradation will be used.

Training for cleaning and paint-stabilization personnel will include relevant parts of the four-day EPA-approved *Lead Abatement Course for Workers, Supervisors, and Contractors* or its equivalent as developed specifically for this trial. Prior to the enrollment of the first subject, pilot cleaning will occur in each community in housing selected specifically for this purpose. Workers will be supplied with uniforms to wear during working hours and a facility for changing clothes and cleaning up at the end of the day to eliminate the potential for carrying lead dust into their cars or homes. Work crews will not engage in any paint removal activities unless they have received appropriate training in lead paint abatement procedures and are provided with respirators and other safety equipment and supplies in accordance with local requirements.

7. STUDY PROCEDURES

7.1. Pre-Randomization Evaluation

7.1.1. Introduction

The pre-randomization evaluation schedule includes two pre-randomization clinic visits (V1 and V2) and two home visits (H1 and H2), for a total of four pre-randomization visits. Table 6 summarizes the activities during the pre-randomization period.

Table 6. Visit Schedule for Pre-Randomization Evaluation

VISIT	V1		H1	V2	H2	T0
WEEK	-6 → -5	-6 → -5	-6 → -2	-2 → -1	-4 → -1	0
DAY	-42 → -35	-41 → -34	-28 → -8	-14 → -7	-27 → 0	0
Eligibility Checklist	✓		✓	✓		
Informed Consent	✓			✓		
PbB	✓			✓		✓*
CBC, Differential, Platelet Count	✓					
Serum Chemistries	✓					
Creatinine	✓					
Urine Dip (protein, glucose)	✓					
Ferritin	✓			✓**		
Physical Examination	✓					
Multivitamin + Minerals + Iron	✓**					Stop

3 mg/kg/day Fe		✓****				Stop
Assess Compliance				✓		✓
Dispense Drug						✓
Psychometric Testing						✓
Home Visual Assessment			✓			
Home Clean-up					✓	

* If V2 > 14 days prior, repeat CDC PbB and reschedule T0.
** Repeat if V1 ferritin < 12 ng/dL.
*** Prescribed for all children.
**** Prescribed for children with hemoglobin between 9 and 10 with increased RDW.

7.1.2. Management of Iron Status

Because iron deficiency increases lead absorption and is independently associated with poor developmental outcomes,[41] careful management of the child's iron status is required. Children whose hemoglobin at V1 is less than 9 g/dL from any cause will be excluded from further participation. Children whose hemoglobin at V1 is greater than or equal to 9 g/dL but less than 10 g/dL will be checked for iron deficiency on the basis of the red cell distribution width (RDW). If the RDW is normal, the child will be enrolled. If the RDW is increased, the child will be treated with a therapeutic iron supplement of 3 mg/kg/day and their hemoglobin rechecked in one month. Further TLC activities, such as home visits, will be deferred until the results from the repeat testing are known. If the repeat hemoglobin is 10 g/dL or greater, the child will be enrolled, otherwise, excluded. If a three-month course of therapeutic iron is not completed before study treatment begins, iron supplementation will be interrupted and resumed after the completion of study treatment until a full three months of iron supplementation have been completed. Children whose hemoglobin at V1 is 10 g/dL or greater will be considered to be iron sufficient by virtue of a month or longer course of multivitamin plus iron supplement prior to randomization.

7.1.3. Pre-randomization Visit 1 (V1)

Each Clinic will identify potential subjects with elevated blood lead levels whose projected age at enrollment is 12 to 32 months and whose family's language is English (English or Spanish in the Newark Center). At Pre-randomization Visit 1 (V1) or over the phone prior to V1, the Clinic Coordinator will explain the trial to the family and assess initial eligibility. At V1, informed consent for the pre-randomization evaluation will be sought from the parent or legal guardian of children who satisfy the initial eligibility requirements. See Appendix 2 for Stage I Informed Consent Forms from each of the Clinical Centers. If informed consent is given, a medical history will be obtained and a physical examination performed. Height, weight and head circumference will be measured by standardized procedures. Blood pressure will be obtained. A TLC physician will review and verify the child's eligibility.

Blood will be drawn for determination of blood lead concentration and ferritin by the central laboratory and for local laboratory determination of hemoglobin, red cell distribution width, absolute neutrophil count, platelet count, alkaline phosphatase, ALT, AST, and serum creatinine. A urine dip stick test will be performed in the clinic for proteinuria and glucosuria.

All children will be given a multivitamin with minerals including iron and the caregivers will be instructed as to their administration. A vitamin diary will be provided for parents to record vitamins taken each day. The diary will assist TLC staff in the assessment of compliance. Appointments will be

scheduled for the home visual assessment visit (H1) in one to two weeks and for Pre-Randomization Visit 2 (V2) in approximately one month.

Local laboratory results will be available shortly after V1. Children whose hemoglobin is less than 9 g/dL will be excluded from the study. Children whose hemoglobin is equal to or greater than 9 g/dL and less than 10 g/dL and whose red cell distribution width is increased will be provided with three months of supplemental iron therapy and will undergo repeat testing at their next visit (approximately one month). Children who are not iron deficient on the basis of the RDW or whose hemoglobin is greater than or equal to 10 g/dL will be enrolled. Children who show abnormalities on their liver function studies will be brought back to the Clinic for repeat testing of the abnormal values in approximately two to three weeks. If the repeat values are normal, the child may be enrolled. Children whose serum creatinine is greater than 1.0, who show proteinuria of 2+ or greater, or who show glucosuria will be referred for evaluation. If these conditions resolve and the child is otherwise eligible, she or he may be entered in the study at a later time but will be required to repeat the appropriate laboratory tests. In all cases, further TLC activities, such as H1 or V2, will be deferred until the abnormality resolves.

CDC PbB results will be available approximately one week following V1. Children whose PbB from V1 is 45 μg/dL or greater will be referred for immediate treatment according to the local standards of care and excluded from the study. Children whose PbB from V1 is less than 20 μg/dL will be excluded from the study.

Families of excluded children will be appropriately notified, any scheduled study visits will be cancelled, and they will be provided with appropriate followup based on their lead status.

7.1.4. Home Visit 1 (H1): Home Visual Assessment

The Home Visit 1 (H1) will take place as soon as possible after V1 for eligible children. This initial visual assessment will be used to determine whether the child should be excluded from the trial based on poor condition of the housing and to estimate the amount of work required to clean the residence. An assessment will be made of the likely risks of exposure to lead in paint and dust based on the following criteria:

(1) condition of painted surfaces
(2) accessibility of non-intact painted surfaces
(3) condition of painted substrates
(4) ease with which surfaces can be cleaned
(5) overall structural integrity of the dwelling, both interior and exterior.

Attention will be given to the immediate dwelling unit, common areas such as hallways and stairwells, and porches. Frequency of access to the hazardous areas by the child will be considered in the environmental assessment and clean-up plan. An attempt will be made to do visual assessments of secondary residences so that the condition of supplemental residences can be taken into account in determining eligibility.

The assessor will sketch a floor plan, record room sizes and number of windows, note presence and condition of carpeting and other flooring, estimate the amount of time required to prepare the unit for cleaning and determine if it will be necessary to contact the building owner or management prior to any planned clean-up activities.

A Home Visual Assessment Report will be issued and the child's eligibility on the basis of residence reassessed. Families of children who are excluded on the basis of the home visual assessment will be appropriately notified, any scheduled study visits will be cancelled, and they will be provided with appropriate followup based on the child's lead status.

If the child is still eligible, an appointment will be scheduled before the projected date of randomization for Home Visit 2 (H2) for home cleaning.

7.1.5. Home Visit 2 (H2): Home Cleanup

If the child's residence(s) meets eligibility criteria, a second home visit will be made for lead dust suppression. This visit will ordinarily take place sometime between H1 and T0. If H2 has not occurred before T0, randomization may proceed with home clean-up to take place as soon as possible after T0. If it is not possible to clean the child's home within one week of initiation of treatment, the child will be excluded.

7.1.6. Pre-Randomization Visit 2 (V2)

At Pre-Randomization Visit 2 (V2), eligibility will be reviewed. Ability of the family to attend scheduled study visits and to give study medications will be assessed through compliance with the TLC schedule and with multivitamin supplementation. Families whose children are excluded from the TLC Trial on the basis of compliance will be provided with appropriate followup based on the child's lead status.

If the child remains eligible for the Trial, informed consent for participation in the Trial will be sought. See Appendix 2 for Stage II Informed Consent Forms from each of the Clinical Centers. Demographic information on the subject's family will be obtained. An interim medical history will be obtained and a brief physical examination performed. Height, weight, and blood pressure will be measured by standardized procedures. Blood will again be drawn for central laboratory determination of blood lead level. Children whose ferritin level at V1 was less than 12 ng/dL or who required iron supplementation will also have their ferritin rechecked by the Central Laboratory. If the child's home has not yet been cleaned, an appointment for the home clean-up will be scheduled at the earliest possible date. All eligible children will be scheduled for Treatment Visit 0 (T0) in one week.

7.2. Randomization

A few days before T0, eligibility will be reviewed and randomization to treatment group made. Children whose PbB from V1 is 45 μg/dL or greater will be referred for immediate treatment according to the local standards of care and excluded from the study. Children whose PbB from V1 is less than 20 μg/dL will be excluded from the study. Families will be notified before T0 and provided with appropriate followup.

7.3. Treatment

7.3.1. Treatment Visit 0 (T0): Initiation of Treatment

Treatment Visit 0 (T0) will be scheduled for approximately one week after V2. If the Data Coordinating Center notifies the Clinical Center that the child is ineligible, then this visit will be cancelled, the parent will be told the blood lead result, and appropriate follow-up will be provided based on the child's lead status. Table 7 shows the activities during the treatment phase.

Table 7. Activities During Treatment Phase

	CLINIC VISITS					
All Rounds	T0 / T4 / T8		T1 / T5 / T9		T2 / T6 / T10	T3 / T7 / T11

DAY OF DRUG (within course)	0	1	7	26	28	42
PbB			✓		✓	✓
CBC			✓		✓	✓
Chemistries			✓		✓	✓
Dispense Study Drug	✓					
Treatment		start		stop		
Brief Physical Exam			✓		✓	✓
Psychometric Testing	✓*					

* Psychometric testing will take place at T0 only (initial round of treatment).

If not already signed, the second informed consent for randomization and treatment will be obtained at this time. If V2 was more than 14 days earlier, blood will be drawn and shipped to CDC for an additional PbB and the T0 visit will be rescheduled for the following week, when the more recent PbB results become available.

Baseline psychometric testing using the Bayley Scales of Infant Development II and the Minnesota Child Development Index will be performed at T0.

Study drug will be dispensed and dosage reviewed with parent(s). Training in drug administration will be provided to the parent or appropriate caregiver. Using placebo capsules, the TLC nurse will demonstrate how to open the capsule and mix the drug beads with a small amount of fruit juice or soda. After briefly mixing the beads with the liquid, the child will be given the liquid to drink. The parent will be instructed to rinse the medicine cup with additional liquid twice and give to the child to ensure that all beads are administered. If the child refuses to take the drug in a liquid, the beads can be mixed with about one teaspoonful of applesauce or jelly and then given to the child. Before leaving the clinic, the parent will be asked to demonstrate this procedure for the TLC nurse. Parents will be shown how to record doses and any adverse events or problems in the medication diary. Problems in administration and use of diary will be identified and solutions proposed. The parent will be instructed to administer the study drug on an empty stomach. Subjects will begin taking drug on the following morning so that 3 doses can be given that day. Caregivers will be instructed to return with the pill bottle and the medicine diary at each visit.

Parents will be told to stop giving multivitamins and/or iron therapy to the child for the duration of the treatment period. They will also receive an emergency card with a 24-hour phone number to call should emergency unblinding be necessary. A subject and/or family incentive will be provided. These incentives will be determined by each Clinical Center. Appointments will be made, if possible, for all three Treatment Visits. The parent or guardian will be given a calendar showing scheduled appointments through the end of the treatment course (T1, T2, T3).

7.3.2. Treatment Visit 1 (T1)

Treatment Visit 1 (T1) will be scheduled on day 7 of study drug administration. A brief history and physical examination will be performed by the TLC nurse or physician. Any abnormalities will be

reviewed by a physician. The TLC nurse will review the medication diary and record study data. Dosing and administration of study drug will be reviewed, problems identified and solutions proposed. In addition, the caregiver will be reminded to reduce the dose starting the following day. Blood will be drawn and sent to the local laboratory for safety monitoring and to CDC for PbB. Monitoring will consist of absolute neutrophil count, platelet count, AST, ALT, and alkaline phosphatase. The appointment for the next visit, in three weeks, will be reviewed. A subject and/or family incentive will be provided.

7.3.3. Treatment Visit 2 (T2)

Treatment Visit 2 (T2) will be scheduled on day 28 of the treatment phase. The TLC nurse will review the medication diary and record study data. All pill bottles will be collected and returned to the Drug Distribution Center for pill counts and appropriate disposal. Blood will be drawn and sent to the local laboratory for safety monitoring and to CDC for PbB. Monitoring will consist of absolute neutrophil count, platelet count, AST, ALT, and alkaline phosphatase. The results of the T2 venipuncture are necessary to assess how well the child has tolerated the study drug in anticipation of further courses of treatment, should these be necessary on the basis of the PbB. The appointment for the next visit, in two weeks, will be reviewed. A subject and/or family incentive will be provided.

7.3.4. Treatment Visit 3 (T3)

Treatment Visit 3 (T3) will be scheduled for 2 weeks after the end of the treatment period, on day 42 of the treatment phase. A brief history and physical examination will be performed by the TLC nurse or physician. Any abnormalities will be reviewed by a physician. Blood will be drawn and sent to the local laboratory for safety monitoring and to CDC for PbB. Monitoring will consist of absolute neutrophil count, platelet count, AST, ALT, and alkaline phosphatase. The results of the T3 venipuncture are necessary to assess how well the child has tolerated the study drug in anticipation of further courses of treatment, should these be necessary on the basis of the PbB. Results of the PbB measurement obtained at T3 will determine whether a child is retreated or enters follow-up. The appointment for the next visit, in one week, will be reviewed. A subject and/or family incentive will be provided.

The appointment for T4 in one week will be scheduled before the PbB result is available, in anticipation that most children will need more than one course of study drug. If the Data Coordinating Center notifies the clinic that additional therapy is not indicated, the parent will be notified and the appointment will be rescheduled for the first follow-up visit. The family will be instructed to resume multivitamin plus mineral supplements and iron therapy, if prescribed.

7.3.5. Subsequent Treatment Visits

If the PbB measurement obtained at T3 or T7 is 15 μg/dL or greater, drug treatment will be readministered. Subsequent treatment visits (T4, T5, T6 and T7 for the second course of treatment, and T8, T9, T10 and T11 for the third course of treatment) will follow the schedule of the initial treatment phase, excluding psychometric testing. Except for psychometric testing, which will be administered at T0 only, the protocol for retreatment will be the same as for the initial course of treatment. No more than three courses of treatment will be given to any child.

7.3.6. Off Protocol

Children may be taken off the TLC treatment protocol for a number of different reasons, as discussed above. Such children will remain enrolled in the TLC Trial. In particular, followup and psychometric visits will occur on the originally projected schedule.

7.4. Followup Schedule

Once treatment has been completed, children will resume taking nutritional supplementation for the duration of the trial. Children who were found to be iron deficient during the enrollment phase will resume iron therapy, for a total of three months of supplementation.

The followup schedule will be timed with reference to randomization, rather than to end of treatment. This will keep the followup schedule in synch with the timing of psychometric followup. All children will be seen every three months through the 24-month post-randomization visit. After that visit, followup visits will occur every four months. In cases where the six-month post-randomization date occurs later than three months following the end of treatment, an additional followup visit will be scheduled between the end of treatment and the six-month post-randomization date. In particular, children who require only one round of treatment will have their first followup visit scheduled for one month after day 42 (T3). Any children who, for whatever reason, do not follow the standard TLC treatment schedule will still follow this schedule for followup, i.e., they will be seen at six months post-randomization regardless of their treatment status.

Children will be followed until the age of 72 months or the end of the study. A reminder call will be made or a card mailed to the family one week prior to each scheduled visit.

At each followup visit, a brief history and physical examination will be performed by the TLC nurse or physician. Any abnormalities will be reviewed by a physician. The subject will be given an adequate supply of multivitamins and the parent will be instructed to continue their administration. Blood will be drawn and sent to CDC for determination of PbB. A subject and/or family incentive will be provided. An appointment will be made for the next visit.

8. LABORATORY PROCEDURES

8.1. Introduction

Blood samples for blood lead and serum ferritin determination will be shipped to the Nutritional Biochemistry Branch, CDC, in Atlanta, which will serve as the Central Laboratory for the trial. All other blood work will be done locally, following local protocols. Samples for blood lead and ferritin analysis will be collected by venipuncture by personnel trained and experienced in pediatric venipuncture using proper sterile technique and following universal precautions and CDC guidelines.

Samples will be shipped to the CDC the same day they are collected. During the treatment phase of the trial, blood sample will be shipped via overnight delivery. During the followup phase of the trial, shipping need not be shipped overnight. Routine turn-around time, i.e., the time from the receipt of the sample at CDC to the reporting of results to the Data Coordinating Center, will be five working days (i.e., one week). The shipping and reporting system will include a means of identifying and expediting samples requiring analysis on an urgent or STAT basis. Urgent samples will be processed so that results are available no less than two days before the next visit; these will include PbB samples at V1, V2, and T3. STAT samples will be processed so that results are available within 24 hours of receipt of sample; these will include confirmation of PbBs greater than 44 μg/dL or confirmation of increase in PbB greater than 15 μg/dL.

All analytical results will be reviewed by both the study analyst and the study laboratory supervisor at the central laboratory. All quality control materials will be reviewed by the laboratory supervisor. Data will be transmitted to the Data Coordinating Center via Internet on a daily basis as needed. Data will also be recorded onto floppy disks and optical disks for archiving.

Residual TLC blood samples will be stored at CDC for a minimum of one year following publication of trial results.

8.2. Blood Lead Analysis

Lead will be measured in blood by atomic absorption spectrometry based on the method described by Miller *et al.*[42] The lead content will be determined by using a Perkin-Elmer Model 4100-ZL graphite furnace atomic absorption spectrophotometer with Zeeman-effect background correction. Lead contamination must be carefully avoided throughout all procedures. All materials used for collecting and processing specimens will be pre-screened for possible lead contamination. All laboratory processing work will be performed under clean conditions, including laminar flow hoods.

8.3. Ferritin Analysis

Ferritin, like hemoglobin, is a major iron storage protein. Circulating plasma ferritin is most like the L-isoferritin. Serum ferritin provides a much more sensitive indicator of iron body stores than a traditional serum iron assay. Serum ferritin is increased in iron overload, aging, infection, inflammation, liver disease, juvenile rheumatoid arthritis, leukemia, and Hodgkin's disease. Serum ferritin is reduced in iron deficiency.

Ferritin will be measured by using the Bio-Rad Laboratories "Quantimmune Ferritin IRMA" kit which is a single-incubation two-site ^{125}I-immunoradiometric assay (IRMA) based on the general principles of assays as described by Addison *et al.*[43] and Miles[44] and modified by Jeong *et al*[45].

8.4. Quality Control Procedures

8.4.1. Lot Testing of Supplies for Lead Contamination

Lot testing for lead contamination is a critical part of the accurate evaluation of lead in whole blood. Lead may contaminate most commercial blood collection devices (e.g., "Vacutainers") from a variety of sources, including the container materials themselves (glass, stainless steel, rubber, or plastic) and the anticoagulants used. EDTA is a particularly common source. To assure that blood lead values obtained are accurate and not falsely elevated from contamination, CDC will undertake a screening program to evaluate the lead levels in Vacutainer tubes for the TLC Trial and any and all devices that contact the TLC blood specimens, including disposable syringes, stainless steel needles, skin cleaning devices or solvents (such as isopropanol in alcohol pads).

8.4.2. Laboratory Analyses

Estimates of imprecision will be generated from long-term quality control pool results. A quality control system of "bench" quality control specimens will be inserted by the analyst in each analytical run (a set of consecutive assays performed without interruption) so that judgements may be made on the day of analysis. All levels of blood lead concentration are assessed by taking these samples through the complete analytical process. The data from these materials will then be used in estimating methodological imprecision and in assessing the magnitude of any time-associated trends.

The "bench" quality control pools are prepared in sufficient quantity to last the duration of the trial. The levels chosen are in the low range (approximately 20 µg/dL) as well as elevated range (approximately 40-44 µg/dL) so as not to be obvious to the analyst. In every batch of 20 specimens analyzed, either one low or high concentration quality control pool will be randomly inserted. Limits will be established for new pools after 20 runs.

If, after reviewing the analytical and quality control data, the system is declared "out of control" by the supervisor, the entire run will be repeated. If the "out-of-control" condition still exists for ferritin, a new kit will be used and the autodiluter evaluated for pipetting precision and accuracy. If the "out-of-control" condition exists for blood lead, all instrumental parameters will be reverified, and matrix modifier and all other reagents will be checked for possible contamination. National Institute of Standards and Technologies (NIST) Standard Reference Material (SRM) 955a "Lead In Blood" materials[46] will be analyzed in addition to normal bench quality control pools in order to confirm accuracy and precision has been reestablished. Specimens for any analytical run held in question will be reassayed after the system has been reverified to be "in control."

8.4.2.1. Blood Lead Analysis

The blood lead analysis method to be used in the TLC Trial has been used for several years in the Nutritional Biochemistry Branch, CDC, for environmental and occupational health studies, as well as for the Third National Health and Nutrition Examination Survey (NHANES III). The method has proven to be accurate, precise, and reliable. The primary standard used is a NIST SRM lead nitrate, and the NIST SRM 955a "Lead In Blood" materials will also be used as external standards. Bench quality control materials are prepared by CDC as EDTA-whole blood from lead-dosed cows.

8.4.2.2. Serum Ferritin Analysis

The serum ferritin method has also been used in the Nutritional Biochemistry Branch for a number of years, including the NHANES III Study. The method has been proven to be highly comparable to the International Committee for Standardization in Hematology (ICSH) reference enzyme immunoassay method. The ICSH International Reference Ferritin Standard from the National Institute of Biologicals, Standards, and Chemicals, U.K., is used as the external validation material for accuracy and precision.

Because of reliability and availability, four levels of Bio-Rad Laboratories ECS Division "Lyphochek" lyophilized human serum controls will be used as bench quality control materials for ferritin analysis. Approximate values will be 5, 50, 150, and 400 ng/mL. Bench quality control pools as well as blind quality control pools may also be made from filter-sterilized fasting human serum.

9. DRUG DISTRIBUTION

9.1. Trial Medications

As described in Section 4.2, children will be randomly assigned to active drug or placebo. The dosing regimen will be based on six categories of body surface area. The total number of bottles needed is projected to be 1,332 bottles of active drug and 1,332 bottles of placebo, based on the assumption that each participant will need an average of two treatments (two bottles per participant). An additional 30 bottles each of succimer and placebo will be retained by the Drug Distribution Center for quality assurance samples. Study drug, both active and placebo, will be packaged in bottles of 95 and 130.

All trial medication, both active and placebo, will be provided by the manufacturer, McNeil Consumer Products Company, to the Drug Distribution Center. The Drug Distribution Center will receive, inspect, store, repackage and ship all trial medications.

9.1.1. Repackaging of Trial Medications

The Drug Distribution Center will repackage the medications in amber color glass unit-of-use containers, with child-resistant safety caps and a tamper-evident seal. The Drug Distribution Center will prepare two-thirds of the projected drug requirements before enrollment begins. When half of the

projected total has been dispensed, the Drug Distribution Center will repackage the remaining one-third of the drug in proportions to be specified by the Data Coordinating Center based on actual trial experience.

In order to provide placebo with an odor comparable to that of succimer, the Drug Distribution Center will place a two cm^2 piece of filter paper which has been soaked with Mucomyst 20% solution into each bottle of placebo drug. An unsoaked piece of filter paper will be placed inside each bottle of succimer so that all bottles will appear the same.

Each bottle of drug will be assigned a unique number in random sequence at the Drug Distribution Center. Equal numbers of active and placebo drug will be placed in sequential order in shipping cartons. Each shipping carton will be assigned a unique identifying number. The Drug Distribution Center will provide to the Data Coordinating Center a database containing the bottle number, the carton number, and a code indicating whether active or placebo. This database will be used with a randomization algorithm different from that which was used at the Drug Distribution Center to further randomize drug assignments for trial participants.

9.1.2. Labelling of Trial Medications

The Drug Distribution Center will label all repackaged bottles of trial medications according to a double-blinded design. Neither the clinic nor the patient will know the contents of any bottle. The primary label affixed by the Drug Distribution Center will state that the bottle may contain succimer or placebo; will include a detachable, tamper-evident sealed packet containing identification of the drug in the bottle which can be used in cases of emergencies which require unblinding of the patient; and will include a standard, detachable bar-code with the unique Control Number of the bottle of drug. This bar code will be transferred to the patient record after the bottle of drug is assigned.

The Drug Distribution Center will provide each clinic with secondary labels that conform to local regulations. Clinic personnel will complete the label with the requisite dosing information when dispensing the drug. The secondary label will provide space for the date dispensed, dosing directions, Principal Investigator's name, address and emergency phone number. Secondary labels will be available in Spanish as required for individual patients. Clinical Centers will be responsible for providing the information on local regulations for the secondary label.

9.2. Vitamins and Mineral Supplements

Each child will receive a supply of multivitamins plus mineral supplements to be taken throughout the study except during treatment. Estimated total multivitamins plus mineral supplements is 1,391,366 tablets. This total assumes a 7% attrition rate each year of followup to treatment.

The Drug Distribution Center will purchase in bulk 1.5 million daily doses of multivitamins plus mineral supplements for the Trial. The Drug Distribution Center will receive, inspect, store, and ship containers of multivitamins plus mineral supplements to the Clinics. The Data Coordinating Center will recommend which vitamins to purchase.

Multivitamins plus mineral supplements will be repackaged in unit-of-use bottles.

9.3. Storage, Shipping and Inventory Control

The Drug Distribution Center will store all containers of trial medication and multivitamins plus mineral supplements for shipment and will maintain computerized inventory records of all available quantities of trial medication. The Data Coordinating Center will also maintain records of available drug in all clinics and at the Drug Distribution Center.

The Drug Distribution Center will ship the study drug and multivitamins plus mineral supplements to the clinics as needed. Copies of shipping invoices will be given to the Data Coordinating Center.

The Drug Distribution Center will distribute all orders for trial medication and multivitamins plus mineral supplements to the clinical sites using a delivery service that tracks shipments. Trial medication will be shipped to the Clinical Centers on an as-needed basis, upon request from the Coordinating Center, within two business days of request. Shipments of multivitamins plus mineral supplements will be sent to the Clinical Centers when requested by Clinical Centers and within five business days of request.

Trial drug and multivitamins plus mineral supplements will be dispensed at six clinics in four Clinical Centers: Baltimore (2 clinics), Newark (1 clinic), Ohio (2 clinics), and Philadelphia (1 clinic).

9.4. Documentation

The Drug Distribution Center will provide the Data Coordinating Center with:

- A statement of methods to be used for maintaining accurate and complete records of drugs dispensed.
- Assurance of proper storage and inventory control of drugs.
- A statement that dispensing and labelling of drugs and multivitamins plus mineral supplements are handled in accordance with local regulatory requirement for each Clinical Center.
- A listing on paper and 3½" disk in ASCII format, specifying for each bottle of drug or placebo:
  - Control Number
  - whether drug is active or placebo
  - carton number.
- Invoices and packing slips for each study medication shipment specifying the Control Numbers of all bottles shipped.
- Invoices and packing slips for multivitamins plus mineral supplements shipped.
- Specification of method used for generating Control Numbers, e.g. the name of the software used to randomly assign numbers and copies of relevant pages from the software manual describing the random sequence generator.
- The name and telephone number of a contact person with whom the Data Coordinating Center can work.

9.5. Return and Disposal of Unused Medication

The Clinical Centers will return all used and unused bottles of study drug to the Drug Distribution Center. Unused capsules will be counted and the counts reported to the Data Coordinating Center. The Drug Distribution Center will account for and dispose of all unused active drug and placebo capsules and bottles.

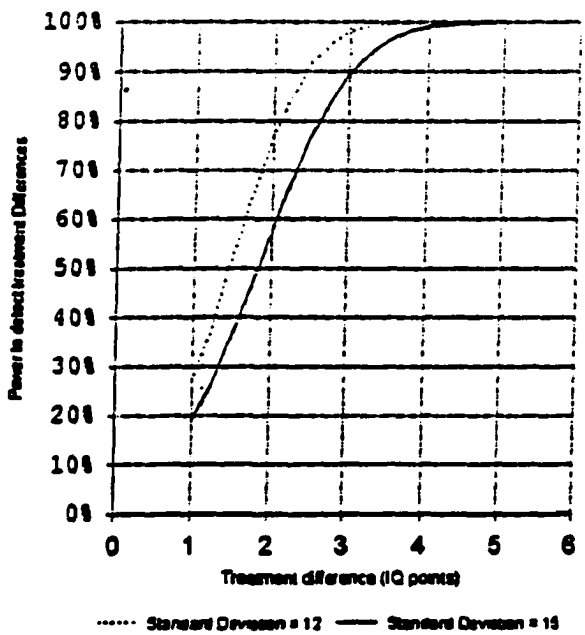
10. STATISTICAL METHODS

10.1. Power Calculations

The primary hypothesis of the TLC trial is that succimer treatment of children with elevated levels of blood lead will improve developmental status three years after treatment begins. Although the primary hypothesis will be tested by an analysis of covariance (see below), we assume for the purposes of the sample size calculation that the hypothesis will be tested by an unadjusted comparison of the mean developmental status at the three-year followup visit in the succimer and placebo groups. We assume that the standard deviation of the standardized WPPSI-R test scores in the study sample will be 15 and that 1,040 randomized children (78% of those enrolled) will complete the three-year followup visit successfully. The variance assumption should be conservative, both because test scores in the study sample may have lower variance than that in the normative population and because adjustment for baseline developmental status through analysis of covariance will reduce the error variance.

Study power with respect to the WPPSI-R can be calculated as a function of the difference in mean test scores between treatment groups. Assuming a Type I Error rate of 0.05 (two-sided) and a sample size of 1,040 evaluable children, Figure 1 shows the power of the study as a function of the difference. In particular, a difference of three IQ points implies a power of 90% for a standard deviation of test scores of 15 (solid line). This power improves to 98% if we assume a standard deviation of 12 (dashed line).

Figure 1. Power as a function of achieved difference in mean IQ score



Relatively little is known about the potential effects of chelation on other measures of developmental status (CDI, CPRS, Neuropsychological Battery), height and weight. The power of the study to detect differences in mean values of these outcome variables between treatment groups can,

however, be described in a generic way. Table 8 presents the smallest detectable difference for a standardized test score for a fixed sample size of 1,040 as a function of power and standard deviation of the test score. For example, for a score with a standard deviation of 10, the study will detect a mean difference in score of 1.7 with a power of 80%.

Table 8. Smallest detectable difference for standardized test scores.

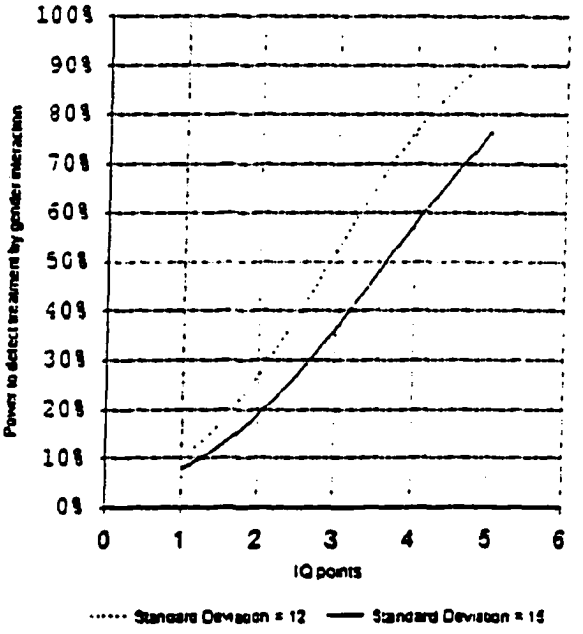
	Standard Deviation						
Power	4	6	8	10	12	14	16
20%	0.3	0.4	0.6	0.7	0.8	1.0	1.1
30%	0.4	0.5	0.7	0.9	1.1	1.2	1.4
40%	0.4	0.6	0.8	1.1	1.3	1.5	1.7
50%	0.5	0.7	1.0	1.2	1.5	1.7	1.9
60%	0.5	0.8	1.1	1.4	1.6	1.9	2.2
70%	0.6	0.9	1.2	1.5	1.8	2.2	2.5
80%	0.7	1.0	1.4	1.7	2.1	2.4	2.8
90%	0.8	1.2	1.6	2.0	2.4	2.8	3.2

Although the primary hypothesis of this study concerns the effects of chelation therapy in the study sample as a whole, questions about differential effects of chelation by race and gender are of scientific interest. Because approximately 85% or more of study participants are expected to be African American heritage, the study will provide little information about differential effects by race. The study will, however, provide some information about differential effects by gender. This question will be investigated by first testing for an interaction between gender and treatment in the analysis of covariance model. If a statistically significant interaction is detected, it will be necessary to estimate the treatment effect separately for boys and girls. If the test for interaction does not achieve statistical significance, the effect in each subgroup should be estimated by the overall estimate of the effect.

Because the sample must be divided into four subgroups for a test for interaction, the variance of the estimated difference in effect between boys and girls will have variance four times larger than the estimate of the overall effect. Figure 2 presents the power of the study to detect a gender by treatment interaction as a function of the size of that difference.

If we assume that test scores have a between-child standard deviation of 15 points, a test for interaction at the 0.05 level of significance will have power of approximately 76% to detect a difference in effect sizes between boys and girls of 5 points. With a standard deviation of 12, approximately the same power is achieved for differences of 4 IQ points. Given that the study is designed to detect an overall difference of 3 IQ points between treatment groups, it seems implausible that chelation therapy would have differential effects of that magnitude in boys and girls. The study will have power of 50% or less to detect interactions of 3 points or less.

Figure 2. Power to detect a gender by treatment interaction as a function of achieved difference in mean IQ score



10.2. Baseline Comparisons

Following standard practice in the analysis of parallel group randomized clinical trials, the analysis will begin with an assessment of the comparability of the two treatment groups at baseline. The Bayley scales of Infant Development II (BSID II) and the Child Development Inventory (CDI) will provide baseline measures of developmental status. Although randomization will ensure that any differences in the distribution of baseline characteristics are due to chance, exact and Student's t-tests will be used to compute p-values testing the equality of distributions and mean values for categorical and continuous variables, respectively. These p-values will be helpful in screening the baseline distributions for comparability.

10.3. Evaluation of Efficacy

10.3.1. Test of Primary Hypothesis

The primary hypothesis of the TLC Trial is that chelation with succimer will result in an increase in the mean IQ at three-year followup, as measured by the WPPSI-R full-scale deviation IQ. This hypothesis will be tested by an analysis of covariance. The dependent variable for this analysis will be WPPSI-R score at the three-year followup visit when that measurement is obtained, and WPPSI-R score at the 18-month followup visit when it is available and the three-year assessment is not. Independent variables will include indicator variables for clinic, treatment group, body surface area group, baseline blood lead level group, and baseline scores on the BSID II. Irrespective of compliance, each study participant for whom a WPPSI-R score is available will be included in the analysis according to their treatment assignment (an "intent-to-treat" analysis).

10.3.2. Tests of Secondary Hypotheses

Secondary outcome variables to be assessed in the TLC Trial include the other developmental measures described in Section 5, as well as height, weight, head circumference, systolic blood pressure, and diastolic blood pressure, as measured at the three-year followup examination. The hypotheses that chelation has a beneficial effect on these outcome variables will also be tested by analyses of covariance. Each ANCOVA will included clinic, treatment group, body surface area group, baseline blood lead level group, and baseline measures of developmental status, height, or weight most appropriate for and highly correlated with the dependent variable. These analyses will also employ the intent-to-treat principle.

10.3.3. Analysis of Repeated Measures

Height, weight, and the CDI will be measured at each regular examination, and IQ (using either the BSID II or the WPPSI-R) will be measured at baseline, six, 18, and 36 months. Longitudinal methods will be used to compare the rates of change in these outcome variables during the three-year followup period. Specifically, linear models with unrestricted covariance structures[47] will be used to test the hypothesis of equality of rates of change in the two treatment groups. These hypotheses will be tested by fitting models of the form

$$y_{ij} = a + b_1 * t_{ij} + b_2 * group_i + e_{ij}$$

where y_{ij} is the developmental score for the ith child at the jth followup visit, t_{ij} is the elapsed time from baseline at this visit, "$group_i$" represents the child's treatment group, and e_{ij} is the error term. Two considerations lead to the decision to use longitudinal analyses as secondary rather than primary analyses. First, two different measures of IQ will be obtained in this study, the BSID II and the WPPSI-R, raising concerns about changes in measure in a repeated measures analysis. The second and most important consideration, however, is that the comparison of greatest interest in this trial is that at the three-year followup examination. Previous studies suggest that the beneficial effect of chelation may be largest at this examination, and developmental status at this examination is also most relevant to the long-term effect of chelation on development. The analysis of covariance of the WPPSI-R at the three-year examination, adjusting for baseline BSID II score, will retrieve most of the information about trend that would be available from longitudinal analysis of the three followup examinations.

10.3.4. Other Analyses

Additional analyses will be performed to compare blood lead levels during and after treatment in the two treatment groups, investigate the relation between blood lead level and developmental status at the three-year followup examination, investigate the relation between change in blood lead level and development status at the three-year followup examination, and evaluate the association between compliance-adjusted measures of treatment and developmental outcome.

10.4. Monitoring for Efficacy and Safety

All TLC participants will complete the treatment phase of the TLC trial before participants begin the three-year follow-up visits at which the primary outcome variable, the full-scale IQ will be measured by the WPPSI - R. Thus, it will not be necessary to develop formal sequential monitoring procedures for early termination of the enrollment and treatment phase of the trial on the basis of demonstrated efficacy. The investigators, the NIEHS Project Office, and the Data and Safety Monitoring Committee (DSMC) will nevertheless be responsible for monitoring the progress of the study closely for evidence of both efficacy and possible adverse effects of treatment.

FDA regulations for investigational new drugs include specific requirements for reporting of adverse drug experiences (ADEs). All serious ADEs will require an immediate telephone call by the TLC physician to the Data Coordinating Center (DCC), the FDA, the Project Office, and other TLC physicians. FDA notification must occur within three days of recognition of a possible serious ADE. Any death or hospitalization will be considered a serious ADE. In addition, the DCC will routinely gather data on all possible ADEs for regular reporting to the DSMC and the FDA.

All available information on efficacy and safety will be presented to the DSMC as part of the DCC report prepared for each Committee meeting, and annual reports will be prepared for submission to the FDA as required by the Investigational New Drug authorization. Because no single endpoint will be specified in advance as a primary endpoint for assessment of toxicity, no formal statistical stopping rules will be established for monitoring toxicity. The DCC will prepare, as part of its regular statistical report to the DSMC, an interpretation of any statistically significant finding regarding possible side effects of active treatment.

11. REFERENCES

1. Bellinger, D., Sloman, J., Leviton, A., *et al.* (1991). Low-level lead exposure and children's cognitive function in the pre-school years. *Pediatrics* 8, 219-227.

2. Baghurst, P. A., McMichael, A. J., Wigg, N. R., *et al.* (1992). Environmental exposure to lead and children's intelligence at the age of seven years: The Port Pirie Cohort Study. *New England Journal of Medicine* 327, 1279-1284.

3. Rice, D. C. (1992). Behavioral impairment produced by developmental lead exposure: Evidence from primate research. *Human Lead Exposure* (H. L. Needleman, Ed.). CRC Press, Boca Raton, FL.

4. U.S. Environmental Protection Agency. (1990). *Air Quality Criteria for Lead. EPA Report No. EPA-600/8-83/0281.* Environmental Criteria and Assessment Office, Research Triangle Park, N.C.

5. U.S. Centers for Disease Control. (1991). *Statement on Preventing Lead Poisoning in Young Children.* U.S. Centers for Disease Control, Atlanta, GA, U.S. Dept of Health and Human Services.

6. U.S. Agency for Toxic Substances and Disease Registry. (1988). *The Nature and Extent of Lead Poisoning in the United States: A Report to Congress.* U.S. Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA.

7. Bellinger, D., Dietrich, K. N. (in press). Recent studies of lead and neurobehavioral development in children. *Occupational Medicine: State of the Art Reviews.*

8. Du Bois, D., Du Bois, E. (1917). A formula to estimate the approximate surface area if height and weight be known. *Archives of Internal Medicine* 17, 863-871.

9. Cramer, J. A., Mattson, R. H., Prevey, M. L., Scheyer, R. D., Ouellette, V. L. (1989). How often is medication taken as prescribed? A novel assessment technique. *Journal of the American Medical Association* 261, 3273-3277.

10. Pullar, T., Kumar, S., Tindall, H., Feely, M. (1989). Time to stop counting the tablets? *Clinical Pharmacology and Therapeutics* 46, 163-168.

11. Rudd, P., Byyny, R. L., Zachary, V., *et al.* (1989). The natural history of medication compliance in a drug trial: Limitations of pill counts. *Clinical Pharmacology and Therapeutics* 46, 169-176.

12. Hammond, P. B., Dietrich, K. N. (1990). Lead exposure in early life: Health Consequences. *Reviews of Environmental Contamination and Toxicology* 115: 91-124.

13. Samuda, R. J. (1975). *Psychological Testing of American Minorities.* New York: Harper and Row Publishers.

14. Jensen, A. R. (1980). *Bias in Mental Testing.* New York: Free Press.

15. Grover, S. C. (1981). *The Cognitive Basis of the Intellect: A Response to Jensen's "Bias in Mental Testing."* Washington, DC: University Press of America.

16. Needleman, H. L., Gunnoe, C., Leviton, A. *et al.* (1979). Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *New England Journal of Medicine* 300, 689-695.

17. Yule, W. *et al.* (1984). Teachers' ratings of children's behavior in relation to blood lead levels. *British Journal of Developmental Psychology* 2, 295-305.

18. Fergusson, D. M., Fergusson, J. E., Horwood, L. J., Kinzett, N. G. (1988). A longitudinal study of lead levels, intelligence, school performance, and behavior. Part III. Dentine lead levels and attention/activity. *Journal of Child Psychology and Psychiatry* 29, 811-824.

19. Dietrich, K. N., Berger, O. G., Succop, P. A. (1993). Lead exposure and the motor development status of urban six-year old children in the Cincinnati Prospective Study. *Pediatrics* 91, 301-307.

20. Honzik, M. (1983). Measuring mental abilities in infancy: The values and limitations. *Origins of Intelligence: Infancy and Early Childhood* (2nd edition) (M. Lewis, Ed.). New York: Plenum Press.

21. Psychological Corporation. (1993). *Bayley Scales of Infant Development, Second Edition.* San Antonio, TX: Psychological Corporation, Harcourt Brace and Company.

22. Bayley, N. (1969). *Bayley Scales of Infant Development.* San Antonio, TX: Psychological Corporation.

23. Wechsler, D. (1989). *Wechsler Preschool and Primary Scale of Intelligence - Revised.* San Antonio, TX: Psychological Corporation, Harcourt Brace and Company.

24. Wechsler, D. (1974). *Wechsler Adult Intelligence Scale - Revised.* San Antonio, TX: Psychological Corporation, Harcourt Brace and Company.

25. Silverstein, A. B. (1982). Two- and four-subtest short forms of the Wechsler Adult Intelligence Scale-Revised. *Journal of Consulting and Clinical Psychology* 50, 415-418.

26. Ireton, H. (1992). *Child Development Inventory.* Minneapolis: Behavior Science Systems.

27. Chaffee, C. A., Cunningham, C. E., Secord-Gilbert, M. (1990). Screening effectiveness of the Minnesota Child Development Inventory Expressive and Receptive Language Scales: Sensitivity, specificity, and predictive value. Psychological Assessment. *Journal of Consulting and Clinical Psychology* 2, 80-85.

28. Guerin, D., Gottfried, A. W. (1987). Minnesota Child Development Inventories: Predictors of intelligence, achievement, and adaptability. *Journal of Pediatric Psychology* 12, 595-609.

29. Kopparthi, R., McDermott, C., Sheftel, D., Lenke, M. C., Getz, M., Frey, M. (1991). The Minnesota Child Development Inventory: Validity and reliability for assessing development in infancy. *Journal of Developmental and Behavioral Pediatrics* 12, 217-222.

30. Saylor, C., Brandt, B. (1987). The Minnesota Child Development Inventory: A valid maternal report form for assessing development in infancy. *Journal of Developmental and Behavioral Pediatrics* 7, 308-311.

31. Shoemaker, O. S., Saylor, C., Erickson, M. T. (1993). Concurrent validity of the Minnesota Child Development Inventory with high-risk infants. *Journal of Pediatric Psychology* 18, 377-388.

32. Conners, C. K. (1990). *Conners' Rating Scales Manual.* North Tonowanda, NY: Mental Health Systems.

33. Woodcock, R. W., Johnson, M. B. (1989). *Woodcock-Johnson Tests of Cognitive Abilities.* Allen, TX: DLM Teaching Resources, Subtest #1.

34. Thorndike, T. L., Kagen, E. P., Sattler, J. M. (1986). Stanford-Binet Intelligence Scale, Fourth Edition. Chicago, IL: Riverside Publishing Corporation, Subtest #2.

35. Kaufman, A. S., Kaufman, N. L. (1983). *Kaufman Assessment Battery for Children.* Circle Pines, MN: American Guidance Service, Subtest #1.

36. Nolan, R. F., Watlington, D. E., Wilson, V. L. (1989). Gifted and nongifted race and gender effects on item functioning on the Kaufman Assessment Battery for Children. *Journal of Clincal Psychology.* 45, 645-650.

37. Gerstadt, C. L., Hong, Y. J., Diamond, A. The relationship between cognition and action: Performance of 3-7 year old children on a Stroop-like Day-Night test. (Revised manuscript under review, *Cognition*).

38. Stroop, J. R. (1935). Studies of inference in serial verbal reactions. *Journal of Experimental Psychology* 18, 643-662.

39. Welch, M. C., Pennington, B. S., Groisser, D. B. (1991). A normative developmental study of executive function: An understanding of prefrontal function in children. *Developmental Neuropsychology* 7, 131-149.

40. Gnys, J. A., Willis, W. G. (1991). Validation of executive function tasks with young children. *Developmental Neuropsychology* 7, 487-501.

41. Lozoff, B., Brittenham, G. M., Viteri, F. E., Wolf, A. W., Urruita, J. L. (1982). Developmental deficits in iron deficient anemic infants: Effect of age and severity of iron lack. *Journal of Pediatrics* 1101, 948-951.

42. Miller, D. T., Paschal, D. C., Gunter, E. W., Stroud, P., D'Angelo, J. (1987). Determination of blood lead with electrothermal atomic absorption using a L'vov platform and matrix modifier. *Analyst* 112, 1701-1704.

43. Addison, G., Beamish, M., Hales, C., *et al.* (1972) *Journal of Clinical Pathology* 25, 326.

44. Miles, L. (1977). Chapter 4. *Handbook of Radioimmunoassay.* (G. Abraham, Ed.). New York: Marcel Dekker, Inc.

45. Jeong, H., Blakemore, J., Lewin, N. U.S. Patent No. 4,244,940.

46. *Methods for Measuring Lead Concentrations in Paint Films.* (1989). National Institutes of Standards and Technology. U.S. Department of Commerce. Gaithersburg, MD.

47. Liang, K-Y., Zeger, S. L. (1986) Longitudinal data analysis using generalized linear models. *Biometrika* 73, 13-22.

VITA

Lih-Ming Yiin

1985 – 1989	B.S. in Chemistry, National Taiwan University, Taiwan, Republic of China (R.O.C.).
1989 – 1991	Second Lieutenant in Military Service, Taiwan, R.O.C.
1991 – 1993	Research Assistant, Department of Chemistry, National Taiwan University, Taiwan, R.O.C.
1993 – 1995	M.S. in Environmental Sciences, Rutgers University, New Jersey.
1997	Yiin LM, Rhoads G, Lioy PJ. Seasonal Variation of Lead Exposure. 1997 International Society of Exposure Analysis Annual Conference, North Carolina.
1998	Lioy PJ, Yiin LM, Adgate J, Weisel C, Rhoads GG. The effectiveness of a home cleaning intervention strategy in reducing potential dust and lead exposure. Journal of Exposure Analysis & Environmental Epidemiology, 8(1):17-35 (1998).
1999	Ph.D. in Environmental Sciences, Rutgers University, New Jersey.