Treatment Protocol

Treatment Endpoint. The TLC treatment goal of 15 µg/dL was based on an 0.82 power to detect a three-point IQ difference at 36 months, which TLC expected from a 10 mg/dL decrease in BLL from the mean baseline of 26 mg/dL.18 A 10 mg/dL separation appears to have occurred for only a few weeks at the beginning of treatment. The mean BLL of the succimer group was 4.5 mg/dL (95% CI, 3.7 to 5.3 mg/dL) lower than the placebo group at 6-months after treatment initiation and 2.7 mg/dL (95% CI, 1.9 to 3.5 mg/dL) lower at 12 months. BLLs slowly dropped in the control group, possibly a result of the household cleaning most participants received prior to beginning treatment, and dilution of serum levels due to rapid growth and lead deposition into bone. With our current understanding of childhood lead burden and IQ, it's unsurprising that TLC failed to detect an association between their chelation protocol and IQ, when concurrent BLLs in both groups were once again the same.

The TLC's treatment goal of 15 µg/dL is not supported by current evidence, which shows that BLLs well below 10 µg/dL are associated with measurable and clinically significant decreases in IQ27,28, and that the relationship between BLL and IQ is nonlinear27,29—the greatest IQ decrement per unit increase occurs at the lowest concentrations.

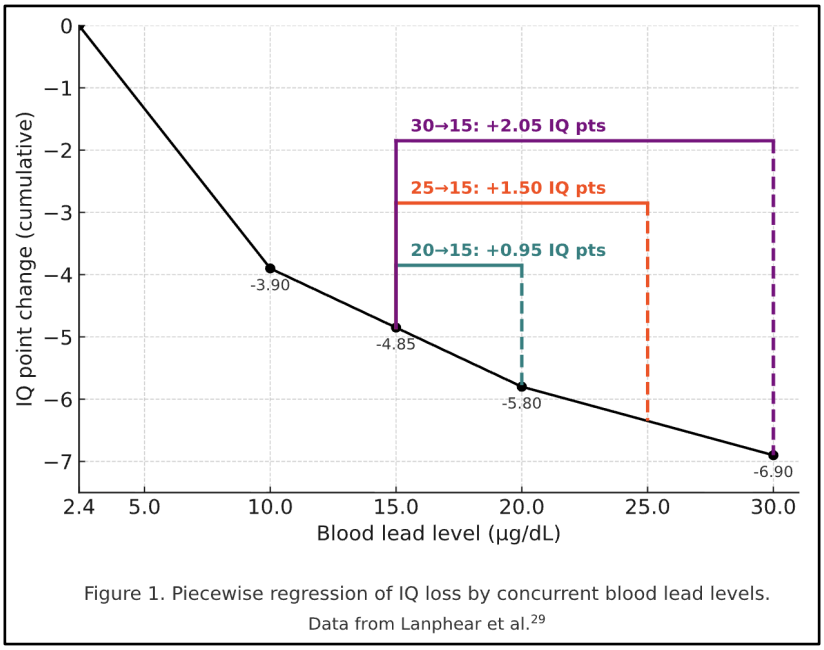

Figure 1. Piecewise regression of IQ loss by concurrent blood lead levels. Data from Lanphear et al.[29]

A pooled analysis by Lanphear et al., quantified the IQ decrements associated with incremental BLL increases after adjustment for confounders.29 Specifically, they showed an increase in concurrent BLL from 2.4 to 10 µg/dL was associated with a 3.9-point decrease in IQ; from 10 to 20 µg/dL: −1.9 points; and from 20 to 30 µg/dL: −1.1 points; indicating a much steeper slope at lower exposures. This non-linear pattern is confirmed by meta-analyses and systematic reviews, which show that BLLs below 5 µg/dL are associated with significant reductions in IQ in children.30,31 Jusko et al. found that children with average BLLs between 5 and 9.9 µg/dL scored 4.9 points lower on full-scale IQ compared to those with levels below 5 µg/dL, and that the association persisted down to as low as 2.1 µg/dL.32 This is further corroborated by Canfield et al., who reported a 7.4-point IQ decline as blood lead increased from 1 to 10 µg/dL, with a steeper decline at lower concentrations.27

In **Figure 1,** we applied the Lanphear et al. pooled analysis data as a rough estimate of the changes needed to elicit a 3-point difference in IQ.29 The average BLL at randomization was

around 26 µg/dL. If we assume an average of 25 µg/dL, and a sustained BLL difference of 10 µg/dL was maintained until follow-up, the estimated IQ difference would be ~1.50 points in favor of the treatment group— well below the 3-point difference the trial was powered to detect. A child with a BLL of 30ug/dL could be expected to be 3 IQ points lower than one with levels of 10ug/dL. This three-fold difference in BLL would just barely be detected by the TLC. In contrast, the child with BLLs of 10 mg/dL could be expected to test 3.9 IQ points lower than a child with 2.4 mg/dL.

Concurrent vs. Peak BLL. The treatment goal of 15 ug/dL was based on the best evidence available at the time: which suggested that peak BLL (often occurring around 24 months old) was the most accurate metric in determining IQ deficits later in life.[33] Peak childhood BLL almost always occurs around 24 months of age, due to pica related behaviors, and subsequent decreases in BLLs are common due to dilution and sequestration of serum lead into bone as rapid growth and bone formation occurs. The protocol was designed to lower the peak BLLs in children during a developmentally critical time to see whether it would have any benefit on IQ later in life.

In a secondary analysis of their data, TLC investigators found that concurrent (not peak) BLLs were most strongly correlated to IQ-deficits.[34] This suggests that the majority of IQ deficits seen in children when they are older may be caused by the lead currently in their bodies, and not only by lead they were exposed to during development. The pooled analysis by Lanphear et al., also found that the strongest correlation was between IQ-loss and *concurrent* BLL—measured at the same time as IQ. These findings contrast with the paradigm that peak childhood lead levels are the strongest indicator of IQ-loss measured later in childhood, and that lowering them transiently—as done in TLC—would result in a measurable increase in IQ [33]

The high dosages, long chelation courses, and insufficient control of ongoing environmental exposures reflect an approach aimed at aggressively lowering peak BLLs, with less attention towards keeping them lowered long-term. Investigators state the clean-up participants received was designed to reduce lead dust levels for the 6 months children were chelating,[35] and indeed, a BLL rebound in both the treatment and control group is seen around the 6-month mark. Analyses of lead-dust in their homes revealed many still had lead dust levels above federal standards.[36] TLC proved the efficacy of DMSA in lowering blood lead levels, and that their specific regimen was ineffective as implemented.

Mineral Status

Iron deficiency increases gastrointestinal lead absorption and independently impairs neurodevelopment in children. Within a causal framework, iron status functions both as a prognostic factor (affecting baseline blood lead levels) and a potential effect modifier (altering response to chelation). The TLC trial's inadequate assessment and management of iron status therefore threaten internal validity through unmeasured confounding.

Iron Status and Stratification

The TLC protocol's management of iron deficiency introduced systematic bias in both participant selection and baseline risk stratification. Children with hemoglobin <9 g/dL were excluded, but those with values between 9 and 10 g/dL were allowed to enroll after only minimal intervention. In these borderline cases, screening relied solely on red cell distribution width (RDW), a measure with less sensitivity and specificity than serum ferritin. Although ferritin was measured once pre-randomization, it's unclear how ferritin results were used to guide decision making. Participants with elevated RDW received just one month of therapeutic iron prior to enrollment—a duration insufficient to replete iron stores, even if hemoglobin normalized. Children achieving hemoglobin ≥10 g/dL after the multivitamin run-in were deemed iron-sufficient, yet hemoglobin recovery precedes iron repletion by weeks to months, and this threshold does not ensure adequate stores. Most concerning, the protocol mandated interruption of iron supplementation during active chelation, further hindering correction of deficiency. By substituting a hematologic proxy for direct measures of iron status and basing eligibility on hemoglobin change alone, the trial weakened its capacity to stratify baseline risk. As a result, many participants labeled "sufficient" may have remained iron-deficient at the start of chelation. Given that iron deficiency increases lead absorption and independently impairs neurodevelopment, these methodological flaws undermined internal validity and complicated attribution of outcomes.

Tracing the Origins of the TLC:
Walter Rogan, MD (AAP Liaison and Chair of the IRB at NIEHS)

Who came up with the idea for TLC? Why would NIEHS fund such an expensive trial? Was there pressure from a particular institution? Or did NIEHS feel, since they had funded the clinical trials used in succimer's FDA approval process, that they had a responsibility to investigate it now that it was being used at lower BLLs?

The Project Officer and primary author on most of TLC's publications, was Walter J. Rogan, MD. He was one of the first epidemiologists at NIEHS in the mid-70s, working there until his retirement in 2014.

From Rogan's own 2016 Oral History[1]:

> "The institute had supported the development of a drug that lowered blood lead called Succimer. **We proposed to Dr. Olden that we do a clinical trial,** because lowering blood lead might be a good thing, but it might not be a good thing in the sense of reversing any effect that lead had already had, and it exposed you to the side effects of drug, which you might or might not need. The only thing wrong with you from these low levels of lead that we were going to treat was you'd lost some IQ points, two or three per every 10 micrograms per deciliter of blood lead."

From the 1999 TLC NIEHS Archived Website[2]:

> **"NIEHS and its advisors, especially the American Academy of Pediatrics Committee on Environmental Health, believed that many children would be treated with this drug at blood leads below the labelled level**, despite the fact that there was relatively little evidence of safety and no evidence of efficacy for prevention of the latent effects of lead, including developmental delay. Lowering of blood lead per se at these levels is without known clinical benefit."

So, Walter Rogan himself frames the TLC as something he was involved in proposing to Ken Olden, to make happen. The emphasis "*especially the American Academy of Pediatrics Committee on Environmental Health"* is interesting.

The current NIEHS website's emeritus profile on Rogan[3]:

> "**Rogan was NIEHS Liaison to the Committee on Environmental Health at the American Academy of Pediatrics (AAP) for 36 years.** AAP has many technical committees that write policy statements guiding the thousands of pediatricians who are members of the Academy. Rogan was primary author on several such statements, and he participated in the drafting and editing of the many statements produced by the Committee on Environmental Health in his time there. He was also an Ex Officio member of the U.S. Department of Health and Human Services Advisory Committee on Childhood Lead Poisoning Prevention for 16 years. These two committees provided much of the influential policy about children's environmental health in the U.S."

The American Academy of Pediatrics (AAP)

Now, the AAP had apparently harbored some sentiment against universal screening since at least 1987, when the Committee on Environmental Health (of which Rogan was a member), published its guideline update.

In a 1987 conference, Dr. Routt Reigart criticized the AAP's most recent guideline update[4]:

> *"My interpretation of what happened is that the AAP said, 'It is not our problem, it is the government's problem.' Rather than coming out for universal screening, it told pediatricians that if they made a prudent decision to not screen a child they did not have to."*
>
> *"What the AAP in effect told pediatricians is, 'This is an important problem but you don't have to be a leader and you don't really have to worry about it unless you are in a 'high risk environment.'"*
>
> *"The impression we are left with is that the AAP is saying, 'It's not our problem, it's the government's problem, let the government handle it.' Frankly, I find this to be an appalling position for a group that should be at the forefront of child health advocacy."*

In 1998, Dr. Herbert Needleman published an opinion paper titled: Childhood Lead Poisoning: The Promise and Abandonment of Primary Prevention.[5] In it, he writes, "*the attempt to achieve primary prevention of lead paint exposure is a clear failure, and it can claim at least 8 foster fathers. Some are the traditional enemies of lead poisoning control, but significant opposition also emerged from surprising quarters*". One of the "opponents" he describes, was the American Academy of Pediatrics:

> "The general decrease in blood lead levels that followed the removal of lead from gasoline was interpreted to mean that the threat had ended. Lead poisoning was once again portrayed as a disease of the ghetto. In fact, between 1988 and 1991 about 8.9% of White children from families above the poverty level had blood lead levels higher than 10 µg/dL, the value currently accepted as toxic. A long-standing tension between medical practice and public health theory became more pronounced. Pediatricians in many middle-class areas believed that testing children's blood for lead was an unnecessary bother and expense and were reluctant to screen children even when asked to do so by parents."

He goes on to write, that "while the organization's official 1993 statement took a "progressive position" supporting screening as part of routine health supervision, other forces within AAP were moving in the opposite direction. Resolutions against universal screening began appearing on local AAP chapter agendas and were "passed up the ladder." In March 1993, AAP's executive director publicly stated that '*there is a good deal of question about whether or not universal testing should be carried out throughout the country.*'"

"An organized campaign against universal screening emerged from California, with commentaries - acknowledging "editorial assistance of the medical editing department of the Kaiser Permanente Foundation Hospitals" - appearing in letters to journal editors, newspapers, and "throwaway" medical journals. These commentaries argued that the prevalence of elevated blood lead levels was questionable, that health effects at these levels were dubious, and that spending on screening and treatment would "'starve more worthy public health efforts.'"

The same arguments were circulated to AAP chapter heads and eventually picked up by a former AAP president, Dr. Birt Harvey, who wrote a lengthy attack in 1994,[6] questioning the value of identifying and treating children with BLLs under 20 µg/dL.

In 2002, Dr. Birt Harvey go on to would become the main editor of the ACCLPP's lengthy 200 page recommendation, *Managing Elevated Blood Lead Levels Among Young Children.*[7] Harvey served as AAP President 1989-1990, and was based in Palo Alto, California- the same state where Needleman

documented the "organized campaign against universal screening" occurred, with Kaiser Permanente's editorial assistance.

TLC's Planning

We can map the following timeline of TLC's approval, using exhibits from Featherstone v. KKI.

July 31, 1992	RFP NIH-ES-92-31 published in NIH Guide.	NIH Guide Vol. 21, No. 27[8]
October 8, 1992	Preproposal conference	Document 37-4; *Featherstone v KKI*, No. 1:07-CV-01120 (D. Md. 2007[8.5]
October 22, 1992	AMENDMENT OF SOLICITATION/MODIFICATION OF RFP	Document 37-4; *Featherstone v KKI*, No. 1:07-CV-01120 (D. Md. 2007[8.5]
November 23, 1992	KKI submits Technical Plan to NIEHS.	Exhibit List (2 & 4) [9]
February 9-10, 1993	Johns Hopkins IRB approves protocol, sends letter of approval to Chisolm.	Hendrix letter[10]
February – June 1993	NIEHS IRB rejects KKI consent form due to "too high of reading level"'; KKI resubmits to JHU IRB, NIEHS IRB approves revised forms.	Affidavits from Merrill Brophy and Cecilia Davoli.[11,12]
June 25, 1993	- Rogan appointed Project Officer (memo date). - NIEHS Award/Contract for TLC study to KKI.	HHS Memorandum[13]

Dr. Chisholm submitted KKI's technical plan in response to NIEHS's RFP[8] on November 23, 1992.[9]
Thomas Hendrix, JHU IRB Chair, writes him on December 9, 1992[14] to ask clarifying questions for approval. Chrisholm replies on January 25, 1993, [14] to answer his questions.

On February 10, 1993,[10] Hendrix writes back to Chisholm confirming protocol approved February 9, 1993, but stated it would not release the consent forms for use until receipt of the IND number for the experimental drug, and that the approval date would not change.

Dr. Chisholm submits it to NIEHS IRB and hears back from them that the 'reading level was too high on the consent forms',[11,12] so he must resubmit to JHU, and then send the edited version back to NIEHS.

On June 25, 1993,[13] the HHS Contracting Officer appointed Walter Rogan as Project Officer (and Beth Ragan as Alternate Project Officer) for Contract No. NO1-ES-35362 (RFP 92-31) and awarded the contract to the Kennedy Krieger Research Institute.

Assuming the contract couldn't be awarded until IRB approval was complete, the back and forth between the NIEHS IRB and Chisholm occurred sometime between February and June 25, 1993.

According to his 1997 CV,[15] Rogan became Acting Clinical Director in 1993. His CV also lists him as the **founding chair of the NIEHS IRB** and **Chair from 1992–1993:**

1980-1993 – NIEHS Institute Clinical Review Subpanel (now Institutional Review Board)
1980-1983 – **founding chair**
1983-1993 – **member**
1992-1993 – **chair**
1993-1997 – **Acting Clinical Director,** Division of Intramural Research
1991-1993 – **Associate Director for Prevention**, Division of Biometry and Risk Assessment

This overlap of duties, during the planning phase of TLC, appears to have been a possible conflict of interest. This is concerning, given the numerous ethical lapses that occurred during the TLC, and alleged harms to participants, ultimately leading to being classified as nontherapeutic by the U.S. District Court for the District of Maryland.

Who oversaw the NIEHS IRB from 1992–1993, when TLC was being planned and proposals were being screened? Did Rogan know he would be appointed as Project Officer (PO) of the TLC, a project he takes credit for having proposed to Ken Olden? If he didn't know he'd be appointed as PO, what requirements would he have had to recuse himself from IRB proceedings discussing the TLC, given that the idea for the trial allegedly came from him? While we don't know the answers to these questions, we can look at what was addressed by NIEHS and what they communicated in their RFP.

AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT
EFFECTIVE DATE: OCTOBER 22, 1992

TO ALL POTENTIAL OFFERORS
RFP NIH-ES-92-31
"Toxicity of Lead in Children - Clinical Center"
The purpose of this amendment is to amend SECTIONS C, H, and L of the RFP and provide general information resulting from the preproposal conference held October 8, 1992 as indicated in ARTICLE L.1.1. of the RFP.

The due date for proposals is not extended. Proposals are due 4:00 p.m. local time on November 24, 1992.

GENERAL COMMENTS

This will be an interactive project with a shared protocol. Each offeror is encouraged to propose what they believe to be the best approach to this work, since a statement of simple willingness on the part of the offeror does not allow the technical review panel sufficient insight into the qualifications of the offerors. However, the final protocol will be the result of the deliberations of the steering committee, which will be composed inter alia of the PIs of the three clinical centers. It is thus unlikely that the study as performed will be exactly as any one of the offerors proposes. **The basic concept, including the ethics, for the study, which was reviewed and approved at NIEHS, is (among other things)** a randomized, blind or double blind, placebo controlled trial of succimer at lead levels below 45 µg/dl; open designs or studies of other drugs are not what was approved. Plausible designs include fully blinded ones, such that neither are aware the examining physician, the parents, nor the psychological testers are aware of whether the child was given active drug or not, and a fixed drug regimen (A responsible clinician monitors lab values in such a design). If an offeror believes that children in these ranges must receive drug under circumstances likely to arise in the trial, or that there are plausible final designs for the trial that they could not ethically participate in, then they should state so clearly. If all designs other than the one that they propose in detail are ethically unacceptable, then they should reconsider whether participation in an interactive study is appropriate for them. Offerors must not propose studies that they would be ethically unwilling to do; offerors must be willing to participate in an interactive research protocol and must be willing to participate in plausible designs that are arrived at by responsible investigators and cleared by the appropriate committees.

QUESTIONS
Ethics, placebos, etc.

Is a placebo arm ethical?
Although this issue has come up several times, it has not been seen as a major problem by any of the groups or individuals with whom we have discussed the concept of the trial. There is wide variability in the use of chelating agents in the US. This, however, probably represents the facts of practice rather than "standard of care." The current CDC document states:

> Blood lead level 25 to 44μg/dl: For this blood lead range, the effectiveness of chelation therapy in decreasing the adverse effects of lead on children's intelligence has not been shown. Treatment regimens vary from clinic to clinic. Some practitioners treat children with lead levels on this range pharmacologically.
>
> (CDC: Preventing Lead Poisoning in Young Children, 1991, p. 61).

The ethics of a placebo arm if the drug were to be effective, or the ethics of a treatment arm if the drug were to be ineffective or toxic or harmful, has come up but was considered to be a question that arises whenever a drug trial is proposed. The ethics of treating children parenterally at these levels provoked greater discussion and led to the decision not to have an EDTA arm. The issue of liability per se has not arisen.

For purposes of the proposal, ethical treatment of children is, of course, paramount, and offerors must only propose regimens that they believe to be ethical. The final protocol will have to be approved by the review boards at each clinical institution, at NIEHS, and possibly, under a recently proposed guideline, a special review board because of the involvement of children. Offerors must propose a regimen that they consider to be best. **Remember, the first sentence of the statement of work says "Independently, and not as an agent of the government". Offerors concerned about legal liability should discuss such matters with appropriate legal staff at their institutions.**

Is it legal to treat children with placebo in these ranges?
NIEHS its unaware of any state that requires children to be treated with chelating agents at any level of blood lead. If this trial would be illegal to pursue in its basic form, i.e., a placebo controlled (double) blind experiment, then institutions in such municipalities should consider such constraints before proposing. Some states may require continued monitoring of blood lead and further intervention depending on the persistence of the blood lead above a certain concentration.

Again, NIEHS is unaware of any state with regulations detailed at that level, but if state regulations proscribe methods that are plausible for the trial, such as uniform levels of clean-up and efforts at abatement that depend on the initial blood lead, then institutions in those municipalities should give due consideration to the impact of such-regulations before offering proposals.

(...)

Should compliance be monitored?
The RFP said that putting an easily monitored substance, such as riboflavin, in the vitamin supplement could be done. It will be technically more difficult to alter the succimer-placebo. **NIEHS believes that compliance is an issue, and a means to monitor it should be proposed.**

Can continued monitoring and clean-up of house dust etc. be proposed? Can inspection of a new home be proposed?
Yes.

How frequently should blood lead be monitored?
Offerors are free to propose whatever monitoring scheme they believe to be best. As is true for many aspects of the trial, the approach that the offerors take to the problems posed by this trial will allow the technical review group to evaluate the insight and expertise of the offerors. The actual monitoring scheme will be part of the final protocol, decided upon as noted above. The blood lead and urine lead monitoring scheme in the RFP is designed to allow simple budgeting for those proposing to be the central labs, and should be viewed as a budget device rather than a scientific recommendation.

Clean-up, abatement, etc.
Clean-up short of full abatement is a moving target. Offerors should propose means of clean-up that they believe to be ethical and clinically justified, that can be generalized to most or many of the 3 million children in this lead range, and that do not constitute an emolument of such great value that consent to be in the trial is coerced or appears to be coerced. HUD has recently proposed guidelines for in place management; CDC offers tactics for temporary management. NIEHS does not discourage abatement, and offerors should expect to pursue their usual avenues of attempting to have housing fully abated; however, the trial is not an abatement trial.

Once a child is eligible for the trial, the aggressiveness with which abatement is pursued should be independent of the blood lead level. Neither CDC nor HUD guidelines state that abatement can be pursued less vigorously if the child's blood lead falls. If drug treatment does alter blood lead levels more than clean-up, and abatement does lower blood lead levels, and abatement is pursued more vigorously in the placebo group, then that will diminish the effect of treatment. Therefor, abatement should be pursued because a child initially had an elevated blood lead and not because the elevated blood lead level persists after initial treatment and clean-up.

Are there cost constraints on clean-up?
The paramount considerations are the ethical treatment of children and the generalizability of the trial. NIEHS hopes that the regimen tested will reflect "real world" conditions, which unfortunately do not include immediate full remediation for all children.
CDC has proposed guidelines for children with blood levels of 20-44 μg/dl that include environmental investigations within 10 working days, emergency measures to reduce lead exposures, and some "preventive maintenance" practices until abatement is done. In general, abatement is the responsibility of the landlord, housing agency, or owner. Offerors should propose inspection and clean-up practices that reflect the realities of their catchment districts, such that if the intervention succeeds, it can be expected to succeed in practice, and if net, then due diligence on the part of the pediatric care giver has been exercised. Coordination of the trial with other local agencies is encouraged, While no fixed dollar amount has been devoted specifically to clean up, the question reflects the fact that abatement of all dwellings of children in the trial would be extremely expensive and would likely make the conduct of the trial non-feasible. The final protocol will include an inspection and clean-up protocol; this will result from the deliberations of the steering committee.

What if performing clean-ups result in children still needing environmental intervention, and are eligibility levels realistic?
These topics have been subjects of considerable discussion; there are clearly dilemmas and no easy answers. There is nothing in the RFP that says that children should not have their sources of lead abated, and the trial comparison is unaffected by abatement if treated and placebo children have their sources

abated similarly. In general, the design of the trial assumes that abatement efforts would proceed as if the trial were not taking place.

Whatever efforts those responsible for treating the child would make in any case should still be made, but if the results of the trial are to be applicable to the real world for the next generation or so until abatement is complete, then including immediate abatement for children in the trial when it is not generally available poses problems in generalizability of results. In addition, an emolument worth in some cases thousands of dollars could prevent true informed consent on the part of the parents.

The question does pose a specific difficulty that does affect trial validity; if the signal for more aggressive efforts at abatement is the child's lead level, and drug affects lead level more than placebo, then the extent to which children with higher levels do in fact receive greater abatement and the extent to which that actually translates into lower levels biases the comparisons between groups. If the offerors believe that this will be a frequent chain of events, then they should discuss means of dealing with it. In general, though, the CDC guidelines do not appear to say that continued efforts at abatement can be relaxed if the child's lead level falls. Once a source is identified, then abatement of that source is pursued, and if immediate abatement is not possible, then whatever temporary measures appear appropriate are taken.

Can trial funds be used for legally required abatement?
Trial funds may not be used for legally required abatement. If someone is legally required to abate, then their responsibility to do so is not removed by the child's participation in the trial.

Are limited abatements - 1.e., scraping and repainting deteriorated surfaces - permitted as a prerequisite to starting succimer?
The final decision will be based on the final protocol. There may not be as much hazard associated with giving succimer to a child who might have further exposure, but it is clearly not desirable.

What is the goal of the dust clean-up? Please express it in terms of blood-lead, and, if possible, in terms of dust lead. If there is no such goal, then why is it being done?
The goal of dust clean-up is to reduce the exposure of the child to lead. Since, at the very least, age and the child's behavior would affect the relationship between dust lead and blood lead, it is impossible to state a goal of blood lead by dust lead. The permissible values for dust lead vary. Maryland's 1988 interim numbers were about 2 mg/m^2 for floor dust and 5 mg/m^2 for window sills. The fact that a blood lead level can not be predicted from a dust lead is not a reason not to prevent exposure by cleaning up dust. Prevention of exposure by some degree of clean-up and abatement (with admittedly weak data on exactly what kind, how much, etc) is an explicit part of public health practice, HUD guidelines, and clinical practice, and proposing chelation therapy without some effort at prevention of further exposure would be very unlikely to be approved by an IRB.

What happens if blood lead of a kid rises to the pre-Rx level?
Will additional or more frequent clean-up be allowable?
What happens of if there is a pattern of such increases across clinical centers?
What happens if the levels still don't go down?
This trial is based on the idea that we do not know whether drug treatment of children at these levels confers a net benefit to the child. Clean-up may or may not be effective, but if done properly should be risk-free. The fact that a child's blood lead does not go down does not mean that we know that the child needs drug; it may mean that the child is spending time someplace other than where we thought, or that clean-up was not performed, etc. Offerors must propose what they think is the best way to handle variations in blood lead; however, they must be willing to accommodate to trial protocol, and a fundamental

assumption of the trial is that we do not know whether drug treatment at these levels is net good or bad. Thus, the (idea that children will "need" drug because clean-up does not work appears to be an unlikely aspect of the final design.

What is the basis for the premise that most houses will not need major remediation?
Perhaps this could have been better stated by saying that a child might achieve blood lead levels in this range without living in seriously deteriorated housing.

Can one use isotopic analysis for environmental Pb Survey?
One can propose it.

Will variation in efforts at abatement in different states affect trial validity?
Differences in abatement practices that are unrelated to active drug treatment do not affect validity; a series of assumptions are necessary to predict whether there would be an effect on power.

ELIGIBILITY

Are the age limits for the children set?
No, but if the age range is younger, say one year, then fewer children will be found in any given population who are eligible for the trial... Offerors should take into account the overall lower blood lead levels of one year olds and be sure that their accrual estimates are reasonable for this age if they propose to begin young. Also, recall that the relationship between blood lead and subsequent development is stronger for blood lead at 2 years than it is for blood lead at 1 year.

When is iron deficiency to be identified and treated?
Children should be known to be iron replete or at least being treated for any iron deficiency by the time they are randomized.

Are there conditions or illnesses that preclude a child's participation in the trial?
Probably yes. Offerors should list any conditions they believe participation and how they are to be diagnosed or recognized.

Does NIEHS want children enrolled that had never had evidence of iron deficiency?
Offerors should propose what they believe to be reasonable eligibility criteria. It seems likely that, in the children eligible for the trial on the basis of their blood lead, that **removing iron deficient kids would make the sample size extremely hard to get and would hamper the generalizability of the trial.**

Does NIERS want children enrolled that had never been chelated?
Offerors should propose what they believe to be reasonable eligibility criteria. Children with a history of chelation should be rare at this age. Does NIEHS want children enrolled that have no risk factors for developmental delay (i.e., premature, multiple gestation, chronic otitis media)? Offerors should propose what they believe to be reasonable eligibility criteria. Children so impaired that they are "bottoming" on testing are likely to have no effect from treatment even if it works, and thus such children use up trial slots but gain nothing and contribute nothing. Testable children who were premature, or not singletons, or who have otitis might well benefit from treatment, and they are part of the community to which the trial wishes to generalize.

BLINDING

What justifies loss of blinding? What level of blinding 1s required?
Offerors must propose what they believe to be the best study design. Designs consistent with the basic trial include fully blinded designs with an escape, in which the study physician, the parent and child, and the psychometrician are all blind, to single blind designs, in which treatment assignment is random and the psychometrician is blinded but the child's blood lead is managed openly. In general, the more open the design, the more likely it is that questions of bias

will be raised about the results. Proposals that do not offer truly random treatment assignment and blind psychometric assessment are proposing in essence a different study than what was approved at NIEHS. The degree of blinding proposed by the offeror will be considered, among other things, in the evaluation of proposals, but the final decision will be made by the Steering Committee.

Can parents be made blind to treatment, if children given active drug smell like mercaptan?
Possibly not. Offerors could consider proposing to query parents about whether they knew if the child was getting active drug, and see if they get it right. NIEHS knows of no agent that smells like a mercaptan and could serve as a placebo.

Do parents get the blood lead information?
Yes, if they want it.

Who knows lead levels?
Lead levels done prior to randomization are open. Those who must evaluate (McCarthy testers) the children cannot know lead levels after randomization. Ideally, no one knows post treatment lead levels; however, offerors may not find this degree of blinding acceptable. If the proposed treatment regimen requires succimer to be given until the blood lead reaches a certain level, then the person administering the drug must know lead level. Offerors are reminded of a fundamental premise of this trial: We do not know if treating lead levels in this range with a drug confers a net benefit to the child. If the drug regimen is fixed, then no one need know except an a safety monitor.

What happens for repeat treatments if, over course of study, succimer is approved for use in this range? i.e., child placebo treated at age 18 months, has lead level of 39 at age 30 months and now succimer is on label? Do you deny treatment or assume randomization covers confounding between groups?
The fact that a drug is labelled for an indication, in this case the lowering of blood lead, does not mean that it provides a therapeutic benefit other than changing a number, FDA did not require evidence that succimer did anything other than lower blood. lead with an acceptable degree of safety and efficacy before labelling it for treating blood leads above 45 μg/dl, and they will likely not require. any other kind of data in support of relabeling. An analogy might be drugs used to lower blood pressure or cholesterol; the fact that the' drugs changed the numbers did not mean that they were known to- prevent stroke or heart attack, or that they did so with an acceptable degree of safety.

There is no evidence that chelation changes blood lead long term, i.e., years. Thus, children in either arm should be equally likely to experience higher blood leads later. There would still be no evidence that treating such elevations with drug conferred a net benefit, but treating such children should not affect the validity of the trial.

(...)

Why monitor urinary metals? How should peripheral issues such as XRF, chelation challenge, renal function, and other cations be handled?
These are options. If investigators believe that the issue of cation diuresis with succimer is sufficiently settled that no information with the trial is necessary, then they need propose no monitoring. If they believe that clinically relevant information can be gathered by monitoring of urinary cations, then they should propose to do it. If an offeror believes that any of the options are clinically or scientifically necessary, then they should so state. It is not obvious that chelation challenge is a necessary or desirable part of the trial, but it is a practice at some centers. If offerors believe that the options would contributes data of interest or relevance, but that such data are not crucial, then they are free to propose the use of such options, with the realization that they may or may not be fundable. The following documents which may be of interest to offerors are available through the means indicated below.

(...)

TO: United States District Court for the District of Maryland:

Pursuant to 28 U.S.C. § 1442 (a)(1), Defendants Kennedy Krieger Institute, Inc. ("Kennedy Kreiger"), and Cecilia Davoli, M.D. (collectively referred to as the "Kennedy Krieger Defendants"), hereby remove this action, *Shayonna Featherstone, et al. v. Kennedy Krieger Institute, Inc., et al.*, case number 24-C-07-002027, from the Circuit Court for Baltimore City, Maryland (hereinafter "State Court Action"), to the United States District Court for the District of Maryland (Northern Division), and allege as follows:

1. In 1992, the federal government, through the National Institute of Environmental Health Sciences ("NIEHS")[1], issued a Request for Proposals ("RFP") seeking clinical centers for a study entitled "Toxicity of Lead in Children." The purpose of the study was to determine whether succimer, a drug approved by the United States Food and Drug Administration ("FDA") for use in treating individuals with blood lead levels greater than 45 micrograms per deciliter, could prevent cognitive delay in young children with blood lead levels less than 45 micrograms per deciliter. This action is brought by Shayonna Featherstone, a minor, and Keona Featherstone, a minor, by their mother and next

[1] NIEHS is a subsidiary of the National Institutes of Health ("NIH") itself a branch of the United States Department of Health and Human Services.

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Plaintiffs' Allegations	Conduct of Kennedy Krieger Taken Pursuant to Federal Authority
"The parents of TLC research subjects, including the Plaintiffs, were not informed by KKI or Davoli that drugs like succimer should not be used as a substitute for the complete abatement of lead hazards to which a child is exposed nor were they informed that succimer should not be used on a child who continues to be exposed to lead hazards." *See* Complaint, Exhibit A at ¶ 8.	The process for enrolling Study participants and the information provided to Study participants was directly controlled by NIEHS in the Contract. *See* Contract, Exhibit D at 11 and the Steering Committee, *Id.* at 10. The Informed Consent provided to Study participants was governed by NIEHS, and through the Contract. *See* Contract, Exhibit D at § H; Exhibit C at ¶ 10; Exhibit I at ¶ 12.
"Via ~~the~~ Informed Consent Form ("IC") Parents and guardians of the children used in the TLC Study were promised that during the "treatment phase another doctor would know the results of blood-lead tests (in case their [was] a problem" and that the childrens' blood-lead levels would also be reported to the Baltimore City Health Department." *See* Complaint, Exhibit A at ¶ 9.	Measures taken to insure the safety of the Study participants was covered by the protocol created under the direct supervision of the NIEHS Project Officer (*See* Protocol, Exhibit H) and is further governed by Federal Regulation. ***See* ¶¶ *23-25.*** Obtaining of informed consent in the Study was governed by the NIEHS by the Contract and by Federal Regulation. Furthermore, the researcher/subject relationship Kennedy Krieger entered into was based solely on the NIEHS Contract, NIEHS approved trial protocol, and the NIEHS approved Informed Consent form; Exhibit C at ¶ 10, Exhibit I at ¶ 12.
"Via the IC Parents and the guardians of the children used in the TLC Study were promised that KKI and Davoli and/or their agents such as Lady "H" would clean up the lead in the homes of the study subjects." *See* Complaint, Exhibit A, ¶ 12.	Kennedy Krieger monitored and "cleaned" Plaintiffs' residences to the extent that it was required to pursuant to its Contract with NIEHS and the NIEHS approved trial protocol. *See* Contract, Exhibit D at 10, 13; Protocol, Exhibit H at 18-20; Exhibit C at ¶ 10, Exhibit I at ¶ 12.
"Pursuant to 45 C.F.R. § 46.101 (2005) approval and oversight by an Institutional Review Board (IRB) is required whenever research on human beings is conducted, supported, or is subject to federal regulation." Md. Code Health Gen. Art. § 13-201, *et seq.* (2005) requires that all research conducted in Maryland on human subjects to be conducted in compliance with federal regulations, regardless of the source of funding and/or support for the research." *See* Complaint, Exhibit A at ¶ 16.	The measures taken to insure the safety of Study participants was covered by the protocol created under the direct supervision of the NIEHS Project Officer. *See* Protocol, Exhibit H. It is further governed by federal regulation. *See* ¶¶ 23-25, *infra.*; Exhibit C at ¶ 10, Exhibit I at ¶ 12.
"There was no direct benefit to the child research subjects from participating in the TLC Study and the monitoring procedure employed in the TLC Study, including but not limited to "blinding" the results of Plaintiffs' blood-lead tests, was less beneficial to the child research subjects' well-being than the monitoring regime already in place." *See* Complaint, Exhibit A at ¶ 21.	The use of "blinding" blood-lead tests results was approved and required by the NIEHS Protocol. *See* Protocol, Exhibit H at 2.

"The IRB assisted the TLC study investigators in concealing the fact that the child research subjects would be placed in serious risk of permanent harm as a result of participating in the study, and concealing that recognize and approved therapies already existed for children with similar lead levels, to wit, the removal from the leaded environment." *See* Complaint, Exhibit A at ¶ 23.	Information provided to the TLC participants and their guardians were governed by the trial protocol. *See* Protocol, Exhibit H; Exhibit C at ¶ 10, Exhibit I at ¶ 12.
"The Defendants knew, or should have known, that the properties identified in paragraphs 4 (a) and 4 (b), contained numerous surfaces covered in lead-based paint. However, KKI, Davoli and/or their agents nonetheless represented to the Plaintiffs' family, the Plaintiffs' treating physician, and to the Baltimore City Health Department, hereinafter BCHD, that the homes were free of lead hazards." *See* Complaint, Exhibit A at ¶ 30.	Provision of information and obtaining of informed consent in the Study, was governed by the NIEHS and. and through the Contract and by Federal Regulation. *See* Exhibit C at ¶ 10, Exhibit I at ¶ 12.
"Prior to the lease of the premises to the property set forth in paragraphs 4 (a) and 4 (b), Baltimore, Maryland, the Defendants herein negligently made, and/or negligently permitted to be made misrepresentations to the Plaintiffs and their families regarding the condition of the premises." *See* Complaint, Exhibit A at ¶ 43.	The process of enrolling Study participants was directly controlled by the NIEHS Contract (*See* Contract, Exhibit D at 11) and by the Steering Committee (*See Id.* at 10). Moreover, the informed consent provided to the study participants was governed by NIEHS in and through the Contract as well as by federal regulation. *See* Contract, Exhibit D at Attachment 8; Exhibit C at ¶ 10 and Exhibit I at ¶ 12.
"The Defendants, KKI, JHU, the IRB and Davoli, by virtue of the IC form, entered into an agreement with the Plaintiffs, that in exchange of the Plaintiffs' participation in the TLC Study, the Defendants herein assumed a duty to: ensure that all children in the TLC Study, including the Plaintiffs, had their homes repaired and/or cleaned to get rid of lead dust and chipped paint, to carefully inspect the properties identified in paragraphs 4(a) and 4(b) to see if they could be repaired and/or cleaned to eliminate lead hazards, if the home did not qualify, the Defendants would assist with relocation to housing that was known to be free from lead-hazards, the Defendants would eliminate any lead hazards in the home, ensure that a doctor would monitor the blood-lead levels of the Plaintiffs and promptly and accurately report those test results to the family of the minor Plaintiffs and to the Baltimore City Health Department, and the Defendants also assumed a duty to provide ongoing medical care of the Plaintiffs' lead paint poisoning and lead toxicity." *See* Complaint, Exhibit A at ¶ 61.	The process for enrolling Study participants was directly controlled by NIEHS and the Contract. *See* Contract, Exhibit D at 11, and by the Steering Committee, *See Id.* at 10. Moreover, the informed consent provided to study participants was governed by NIEHS in and through the Contract as well as by federal regulation. *See* Contract, Exhibit D at Attachment 8; Exhibit C at ¶ 10 and Exhibit I at ¶ 12.
"The Defendants KKI and JHU warranted and agreed to the United States Department of	The TLC Study was conducted pursuant to the Contract with NIEHS (*See* Contract, Exhibit D)

Health and Human Services, hereinafter referred to as DHHS, prior to the constitution of, and during the administration of the TLC Study, that all human research at KKI would be conducted in accordance with the terms of the Belmont Report. *See* Ethical Principles and Guidelines for the Protection of Human Subjects of Research, promulgated by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979. The Defendants agreed to abide by the ethical duties and obligations set forth within the Belmont Report in furtherance of the Defendants' KKI and JHU Agreement with DHHS under a Multiple Project Assurance Agreement, hereinunder MPAA. This agreement existed prior to the tortuous acts alleged herein." *See* Complaint, Exhibit A at ¶ 67.	and by the Steering Committee (*See Id.*).
"The minor Plaintiffs allege that the Defendants herein, and each of them, by agreement or understanding agreed to materially breach their duties set forth within the IC to the child research subjects used in the TLC Study, including the minor Plaintiffs. *See* Complaint, Exhibit A at ¶ 78."	KKI's actions and relationship with the study participants was governed by the trial protocol and the Contract with the NIEHS. *See* Contract, Exhibit D; see trial protocol, Exhibit H.

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