AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

CONTRACT ID CODE | PAGE OF PAGES 1 | 16

2. AMENDMENT/MODIFICATION NO.	3. EFFECTIVE DATE	4. REQUISITION/PURCHASE REQ. NO.	5. PROJECT NO. (If applicable)
01	October 22,, 1992	N/A	

6. ISSUED BY — CODE

National Institute of
Environmental Health Sciences
Contracts & Procurement Management Branch, OM
P.O. Box 12874 (79 T.W. Alexander Dr.)
Research Triangle Park, NC 27709

7. ADMINISTERED BY (If other than Item 6) — CODE

OMB No.: 0990-0115

ATTN: Thomas M. Hardee

8. NAME AND ADDRESS OF CONTRACTOR (No., street, county, State and ZIP Code)

TO ALL POTENTIAL OFFERORS
RFP NIH-ES-92-31
"Toxicity of Lead in Children - Clinical Center"

(X) 9A. AMENDMENT OF SOLICITATION NO.: NIH-ES-92-31

X 9B. DATED (SEE ITEM 11): August 27, 1992

10A. MODIFICATION OF CONTRACT/ORDER NO.:

10B. DATED (SEE ITEM 13):

CODE | FACILITY CODE

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

[X] The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offers [ ] is extended, [X] is not extended.

Offers must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended, by one of the following methods: (a) By completing Items 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA (If required)

N/A

13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS, IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

(X) A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.

[ ] B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation data, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(b).

[ ] C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:

[ ] D. OTHER (Specify type of modification and authority)

E. IMPORTANT: Contractor [ ] is not, [ ] is required to sign this document and return _____ copies to the issuing office.

14. DESCRIPTION OF AMENDMENT/MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.)

The purpose of this amendment is to amend SECTIONS C, H and L of the RFP and to 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.

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER (Type or print)	16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print)
	Thomas M. Hardde Contracting Officer, CPMB, OM, NIEHS
15B. CONTRACTOR/OFFEROR — 15C. DATE SIGNED	16B. UNITED STATES OF AMERICA — 16C. DATE SIGNED
(Signature of person authorized to sign)	BY Thomas M. Hardee (Signature of Contracting Officer) — 10/22/92

NSN 7540-01-152-8070 — STANDARD FORM 30 (REV. 10-83)

REFERENCE NO.: Request for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

---

a. The solicitation is hereby amended as set forth below.

(1) SECTION C entitled "DESCRIPTION/SPECIFICATIONS/WORK STATEMENT", ARTICLE C.2. entitled "STATEMENT OF WORK".

At the end of the Statement of Work (page 24) add the following paragraph:

"Subsequent to the treatment year, each of the 345 children will require 4 blood leads and 2 urine leads in the second year post treatment, and 2 blood leads and 2 urine leads in the 3rd year post treatment. Thus, the grand total for budget purposes is 7,130 blood leads per center, 21,390 for the whole study, and 3,450 urine leads per center, 10,350 for the whole study."

(2) SECTION H entitled "SPECIAL CONTRACT REQUIREMENTS", ARTICLE H.6 entitled GOVERNMENT PROPERTY"

Under paragraph b. entitled Government Furnished Property - Schedule II.B., correct the schedule to read as follows:

"1. The drug, succimer, to be administered during trial

2. Placebo to be administered during trial

NOTE TO OFFERORS: Whether nutritional supplements will be provided has not yet been decided.

3. Laboratory determinations of blood lead levels

NOTE TO OFFERORS: If CDC functions as the central laboratory, the Government will provide the blood leads and urine leads designated in the final protocol to be performed by the central laboratory. If CDC does not function as the central laboratory, those determinations will be done by either one of the clinical centers or by a separate central laboratory. In any case, central laboratory costs should not be included in the clinical center proposals unless they are pursuing the option to be the central laboratory. If they do pursue that option, costs for the central laboratory function must be clearly separable in the proposal.

REFERENCE NO.: Request for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

---

(3) SECTION L entitled "INSTRUCTIONS, CONDITIONS, AND NOTICES TO OFFERORS", 1. entitled "GENERAL INFORMATION", paragraph h. entitled "SELECTION OF OFFERORS":

Under subparagraph (10), add the following clarification:

"For the purposes of this solicitation, an offeror is considered to be a separate physical and/or organizational entity which is not influenced by or involved with another entity within the same general institution in such a manner that a potential conflict of interest, either real or apparent, may arise. For example, different departments, schools, etc. within the same institutions of higher learning, hospitals, etc. could be considered as separate offerors, and may receive separate awards. In such cases where different entities within the same institution choose to submit proposals under NIH-ES-92-31 and NIH-ES-92-32, the proposal(s) shall include organization charts and an explanation of how the entities will act completely autonomously of each other."

b. The following information is provided for general information and clarification purposes only. It is not intended to constitute a change to the RFP unless so stated above. The comments were derived from consideration to questions which have been posed, either prior to, during, or resulting from the pre-proposal conference conducted October 8, 1992 at NIEHS as indicated in Article L.1.1. of the RFP.

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 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.

REFERENCE NO.: Request for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

Is it legal to treat children with placebo in these ranges?

NIEHS is 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.

Drug Regimen

The suggestion in the RFP was meant only to indicate that regimens other than the labelled one could be proposed, since the drug was being used for a non-label indication anyway. Offerors are free to propose what they think is the best regimen. The regimen actually used in the trial will be the result of the deliberations of the steering committee and approved by the human subjects committees and the Data and Safety Monitoring Committee.

Monitoring

Are McCarthy and Bayley scales required? What about quality control for the psychometricians?

Yes, for reasons of comparability with the majority of the literature in the area. Offerors are free to propose additional testing and justify it. Testing the testers is a customary part of studies using these instruments; offerors should propose a means of doing so.

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.

REFERENCE NO.: Request for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

How long should the children be monitored?

Children are followed until age 4 to 5; a scheme for monitoring their homes should be proposed.

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 not, 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.

REFERENCE NO.: Request for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

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 - i.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 that they believe preclude 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 NIEHS 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 is 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 relabelling. 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.

Miscellaneous

Are crossover designs allowed?

A cross-over design has not been discussed for this trial. As noted above, a parenteral drug would be problematic; penicillamine, has had no constituency in the various persons and groups with whom the trial has been discussed. If an offeror believes that such an approach is the best, or that it is the only ethical approach, then they are free to propose it. However, if the final protocol is succimer, placebo, and no crossover, and the offeror is unwilling to participate in a study so configured, then they should so state clearly in their proposal.

REFERENCE NO.: Request for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

Can children come from different institutions?

Offerors are free to propose any reasonable method for enrolling children. Technically, there must be one responsible investigator.

Is there a formal protocol?

The final protocol will result from the deliberations of the steering committee during the planning phase of the trial.

Budget:

a) *Guidelines*: See pages 91-99, and 104-108 of the RFP.

b) *Is there money committed to this project?* NIEHS anticipates that funds will be available to support this project.

c) *Third party payers*: We are not sure we understood this question, even after the meeting. If, for example, in those cases where a "patient" being treated for a separate disorder would otherwise have certain costs covered under an insurance plan, then those costs would continue to be appropriately covered under the plan. Otherwise, in terms of how NIEHS proposes to pay for the project, the information is not considered relevant to constructing a proposal.

Start date:

This depends on a number of variables influencing the length of negotiations. The anticipated start date should be no later than mid to late June, 1993 for the award of the contracts.

Sample size.

The assumptions for the sample size calculations are that the GCI of the McCarthy is the outcome variable of interest, that we wish to be able to detect a difference of 3 points between the drug and placebo groups with 80% power, that the two groups are statistically independent, and that the standard deviation of the GCI is 15 points. There is no analysis involved; the sample size was calculated with a program called POWER, but any method should give the same results.

REFERENCE NO.: Request for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

Format. Page 100 of the RFP provides a format.

Breakdown of hours.

The estimated number of hours per general classification and in total set forth in the RFP are primarily provided to give potential offerors an indication of the general magnitude of the effort contemplated. In developing proposals, as indicated in the instructions for preparation of technical and business proposal, offerors are expected to provide sufficient detail, including breakdown of specific labor categories, job titles, hours, rates, etc. to permit reasonable review. Offerors must propose what they think the work will take to do.

Why doesn't this study coordinate with other programs run by CDC and HUD?

Requiring that this trial be performed at sites already participating in CDC or HUD programs would severely and, in our view, unnecessarily restrict competition. This topic has not arisen in our conversations with CDC, nor in our admittedly restricted conversations with HUD.

Do the clinical centers need to submit a data analysis plan?

No. The coordinating center submits a data analysis plan.

Can a clinical center also be a coordinating center?

Yes, subject to some constraints. (See paragraph a. to amendment)

Can the planning period be decreased in order to increase the enrollment period?

NIEHS believes that at least 9 months will be required to plan this study, get necessary clearances, get an IND, etc.

Will animal studies be supported under this RFP?

No.

REFERENCE NO. [redacted]uest for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

Elaborate on the pilot study.

Whether or not a pilot phase is needed will arise in the deliberations of the Steering Committee. It appears likely that some aspects of this trial will not have been tried before anywhere, and many will not have been done at any of the successful institutions. Having one institution try out data entry, or recruitment, or clean-up methods etc., may be wise before committing the whole trial to an untried method. The RFP asks whether a given institution wishes to be considered in that role, perhaps because it may already have in place recruitment, or clean-up. or other practices that could be incorporated into the trial.

Apply for the lab option alone?

Since the conduct of the lab work is uncertain at this point, and since the active clinical centers will have to do some lab work, it appeared unreasonable to solicit independent lab proposals for work that, in fact, may not be done by an independent lab. As outlined in the proposal, we think it more sensible to look for an independent lab only if CDC chooses not to do the lab work and none of the clinical centers have capable labs. Making an isolated award to a lab at this point would require solicitation of lab proposals, which we would rather not do until the other options are not open.

Lease equipment? Yes.

Page 102 under additional personnel: With the short time frame involved, it will be very difficult to identify all new additional personnel for the project, and to have their commitment letters included for the RFP submission. Can you extend the time to before the study section review?

From a technical point of view, adequate judgement of the merit of the proposals requires that the PI be committed and that there is sufficient assurance that personnel necessary to carry out the lab work will be available. The time for proposals will not be extended.

Is urine Pb performed on spot sample?

Yes.

REFERENCE NO.: Request for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

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 contribute 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.

c. The following documents which may be of interest to offerors are available through the means indicated below.

(1) Attachments:

TLC Laboratory Analyses

(2) Documents available through the public domain:

(a) Notice entitled "NOFA for Lead-Based Paint (LBP) Risk Assessments", Federal Register, June 29, 1992, Part II. Department of Housing and Urban Development

(b) Article entitled "Determination of Lead in blood Using Electrothermal Atomization Atomic Absorption Spectrometry with a L'vov Platform and Matrix Modifier", Analyst, December 1987, Vol 112

(c) Article entitled "Selected Methods for the Small Clinical Chemistry Laboratory", Selected Methods of Clinical Chemistry", Volume 9, 1982, American Association for Clinical Chemistry

(d) Article entitled "Three City Urban Soil-Lead Demonstration Project, EPA, May 1981, US Environmental Protection Agency, Solid Waste and Emergency Response (OS-240) 21S-2001

(3) Documents available from New York State Department of Health, Wadsworth Center Lead Poisoning Laboratory, Empire State Plaza, Albany, New York 12201-0509:

(a) Article entitled "Blood Lead Determination by Electrothermal Atomization Atomic Absorption spectrometry with Perkin-Elmer 4100ZL AAS", DOH, New York State Department of Health, December 18, 1991

REFERENCE NO.: Request for Proposal (RFP) NIH-ES-92-31

PROJECT: "Toxicity of Lead in Children Trial -- Clinical Center"

---

(4) Documents available from Centers for Disease Control (CDC):

(a) Article entitled "Spring 1992 Blood Lead Survey Results", Blood Lead Laboratory Reference System, CDC

(b) Article entitled "Quality Assurance of Chemical Measurements", John Keenan Taylor, Lewis Publishers, Inc., 1987

(c) Documents referenced in (2) and (3) not available otherwise

References identified in (2) may be available from libraries and the original source of publication. Offerors interested in obtaining reprints directly from CDC should contact:

Dayton T. Miller, Ph.D.
Chief, Nutritional Biochemistry Branch
Division of Environmental Health Laboratory Sciences
Center for Environmental Health
Centers for Disease Control
Atlanta, Georgia 30333

\\\ END OF AMENDMENT ///