Supporting Statement of the Request for
OMB Review and Approval of

Descriptive Epidemiology of Missed or Delayed Diagnoses for Conditions Detected by Newborn Screening

Request for Extension with Revisions

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A. Justification

ABSTRACT
(Changes in protocol)

The Centers for Disease Control and Prevention (CDC) is asking for an extension with revisions of the previously approved protocol for "Descriptive Epidemiology of Missed or Delayed Diagnose for Conditions Detected by Newborn Screening" (OCN: 0920-0641). The extension is needed because although initial OMB approval was received in October 2004, with an extension expiring December 2006, data collection could not begin until April 2006 due to extended Institutional Review Board (IRB) clearance processes.

Since data collection was initiated in April, about half of participants have provided data. The current request seeks approval to collect data from the remaining participants. Therefore, the current request for one year extension includes fewer participants and burden hours than originally requested in the initial application. Please also note that data collection has been slower than anticipated due to the broad window (20 years) of data requested and the inevitable turnover of key personnel in state newborn screening laboratories during this period. In addition there has not been a comprehensive and cumulative record of laboratory errors or records of follow-up of newborns diagnosed with genetic inborn errors of metabolism kept in the states. For these reasons, the estimated burden hours and the total cost burden have also been adjusted. Otherwise, there have been no substantive changes to the study methodology since the original clearance.

A.1 Circumstances Making the Collection of Information Necessary

CDC requests approval by the Office of Management and Budget (OMB) for extension with revision of a one-time study to investigate the causes of missed or delayed diagnosis of conditions detected during newborn screening. As described above, OMB approval was initially granted in October 2004. Initial delays of this process begun in 2003 were due to extensive IRB review and discussion regarding confidentiality protection issues which have all been resolved. However, due to these delays and the experience from the initial data already collected, finalizing the remaining data collection will take another year. Data collection has taken longer than anticipated due to the lack of a unified or comprehensive record keeping system within states and the turnover of key personnel in the 20 year data collection window from 1984-2004. However, these obstacles can be overcome and we are confident that data collection can be completed as proposed with this extension.

Every state in the United States, Washington, D.C., Puerto Rico, and the U.S. Virgin Islands has a public health program to test newborn babies for congenital metabolic and other disorders through laboratory testing of dried blood spots. These programs screen for between 4 and 30 different conditions including phenylketonuria (PKU) and congenital hypothroidism, with testing performed in both state laboratories and private

laboratories contracted by state health departments. The screening process or system is broader than the state public health newborn screening program, which is composed only of the laboratory and follow-up personnel. It involves the collection of blood from a newborn, analysis of the sample in a screening laboratory, follow-up of abnormal results, confirmatory testing and diagnostic work-up. Parents, hospitals, medical providers including primary care providers and specialists, state laboratory and follow-up personnel, advocates, as well as other partners such as local health departments, police, child protection workers and courts play important roles in this process.

In the absence of a federal newborn screening program, separate programs have been developed by each state. Although all programs share the same basic structure, i.e., specimen collection, testing and follow-up, there are many differences in procedure between them. Each state decides which disorders to include in their screens, the procedures for sample collection and sample quality, the protocols for testing, the methods of record keeping and the procedures for follow-up and notification. As programs become increasingly more complex, there are more opportunities for potential system failures that would allow children born with serious metabolic, endocrinologic, or hematologic disease to pass through the system undetected or untreated in a timely manner.

Most children born with metabolic disease are identified in a timely manner and within the parameters defined by the newborn screening system of each state. These children are referred for diagnosis and treatment. If treated within a week or two after birth with special diets, antibiotic or hormone therapy, these children avoid the potentially tragic effects of their diseases and live relatively normal and productive lives. However, some cases are not detected at all or the detection comes too late to prevent harm. These "missed cases" often result in severe morbidity such as mental retardation or death.

Our proposed study will update and expand the previous study by Holtzman et al. (1986) to include missed cases in the United States occurring from 1984 to 2001. We will also expand the number of diseases examined to include not only phenylketonuria and congenital hypothyroidism examined in the previous study, but also galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, congenital adrenal hyperplasia, and sickle cell disease. These diseases are conditions screened for by newborn screening programs in six or more states. We will assess the number of cases of each disorder missed, the reasons for the miss, the health outcome of the child if available and legal outcomes, if any. The reasons for the miss will be tabulated according to which step or steps of the screening process it occurred. Tentatively, these steps are: specimen collection, specimen transportation, screening lab procedure, follow-up, health provider practices, biologic variants and other. These steps can be further divided to more accurately represent the cause of the miss. Data will be collected by circulating a questionnaire asking state public health laboratory directors, newborn screening laboratory managers, follow up coordinators, metabolic clinics and parent groups with an interest in newborn screening for information regarding missed cases. This survey will be conducted only once. Each participant will only be asked to respond once. We also plan to search for missed cases using sources such as medical literature, metabolic clinics, follow-up coordinators and parent advocacy groups that were not used in the previous study.

Currently there is no mechanism to share information about missed cases across organizations and states. Further, there is no systematic assessment of missed cases on a population basis; this project will seek to identify procedures for routine surveillance of missed cases. Analysis of these data should highlight the areas of potential improvement of the screening system and may suggest ways to change the procedures that currently exist and possible ways to add new ones. The Association of State and Territorial Laboratory directors has a subcommittee on Newborn Screening which is charged with implementing improved data collection on newborn screening and will hold a session at the annual meeting 2007 highlighting the needs for ongoing review of missed cases and possible remedial actions for improvement. The current study will be highlighted in this session. The National Newborn Screening and Genetics Resource center is a collaborator and funded by HHS Maternal and Child Health Bureau to collect and distribute pertinent information on newborn screening. They also maintain a web based list serve bulletin board which will be used to solicit responses and distribute information upon completion of this study to the newborn screening community. Dr. Brad Therrell is a collaborator in this study.

Authority for CDC to collect this data is granted by Section 301 of the PHS Act (42 U.S.C. 241) (Attachment 1).

A.2. Purpose and Use of Information Collection

The public health system in each state, Washington, D.C., Puerto Rico, and the U.S. Virgin Islands is responsible for its own newborn screening program. Each state individually determines which disorders to screen, which tests to use, the protocols used for screening including the length of time allowed for each step and how to analyze the results. They are also responsible for contacting children with abnormal screening results and referring them for diagnosis and treatment (follow-up). Each of these steps has the potential for error that could result in a missed case that could cause injury or death to an affected child. Missed cases usually result in legal action against the public health system, hospitals, and doctors with settlements often in the millions of dollars. The reduction of missed cases will also decrease the costs of treating affected children and allow them to live normal, productive lives. It is therefore critical that states implement all possible steps and safeguards to avoid missed cases. The results of our study will provide examples of what has happened in other programs and provide suggestions for ways to prevent these events in the future. These results can be analyzed by the public health department of each state to determine what can be done in their newborn screening program to avoid circumstances that may lead to missed cases.

There has been much interest in the newborn screening community for a study of this type. Newborn screening laboratory directors, follow-up coordinators, and many others involved have been suggesting an update of the previous study to the Newborn Screening Branch, CDC (formally the Newborn Screening Quality Assurance Program) for many years. We believe that the information provided by this study will be both welcomed by and useful to this community.

It is our hope that the comprehensive study we plan to undertake will reveal opportunities for improvement by sharing information among states. These results may suggest ways in which policies and procedures may be changed to reduce the chance that an error can result in a missed case, thus protecting children from the consequences of these treatable conditions.

The Newborn Screening Branch of the CDC's Division of Laboratory Sciences is charged with improving the quality of newborn screening. The information gathered as part of this study will directly serve this goal by identifying the causes of missed cases and developing solutions to prevent them in the future.

A.3. Use of Improved Information Technology and Burden Reduction

The questionnaire used to collect data will be mailed by regular mail to newborn screening laboratory directors, follow-up coordinators, and metabolic clinics. They will return the questionnaire using a prepaid return envelope. Parent advocacy organizations will distribute the questionnaire electronically to their members. Parents who wish to respond will return the survey by regular mail.

The CDC IRB has requested that we not collect returned questionnaires electronically in order to preserve the anonymity of the respondents. The data will be entered into an electronic database upon receipt at the CDC.

A.4. Efforts to Identify Duplication and Use of Similar Information

A previous study (Holtzman et al, 1986) surveyed newborn screening laboratory directors about missed cases of two disorders, phenylketonuria and congenital hypothyroidism that occurred in their state. This study will look at missed cases that occurred since the last survey was conducted and will expand the list of disorders to include not only phenylketonuria and congenital hypothyroidism, but also galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, congenital adrenal hyperplasia, and sickle cell disease. We also intend to collect information from participants not included in the previous study such as follow-up coordinators, metabolic clinics, and parent advocacy groups.

We are unaware of any other study being conducted presently or in the past that collected similar information. Literature searches have failed to identify any other similar studies. Authors and collaborators of this study (Drs. Harry Hannon, Brad Therrell, and Ken Pass) are recognized worldwide as experts in this field. They attend national and international meetings, are familiar with the newborn screening literature, and have extensive contacts in the newborn screening community. We are confident, therefore, that this study will be unique.

A.5. Impact on Small Business or Other Small Entities

Most of the data collected from this study will be from laboratory directors and follow-up coordinators who are workers in the state public health system and are not considered small businesses. Workers in metabolic clinics will also be contacted as will parent advocates. These participants may be considered to be employed by small businesses. The questionnaire is the same for all participants. However, if the participants have no data to report, they are simply instructed to return the form with just the name of the state indicated. The length of the questionnaire has been kept to the absolute minimum required to obtain the intended data and will only impose a minimal burden on respondents.

A.6. Consequences of Collecting the Information Less Frequently

We feel that this study is necessary in order to improve the quality of newborn screening. This study will provide information necessary to implement new programs and procedures that will reduce the number of missed cases. These improvements may help affected children avoid disability or death related to their conditions and may allow them to lead normal, productive lives. In addition to the health benefits to the children, these improvements will also reduce health care costs associated with their care and protect newborn screening programs and the associated hospitals, doctors, and other health care workers from potentially expensive litigation.

Data collection will be performed one time only. We feel that this collection will provide us with enough data to accomplish our goals.

There are no legal obstacles to reduce the burden.

A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

Our participants are asked to submit a separate copy of the questionnaire for each missed case that they are reporting. This is necessary to keep the data from each case separate, as some may have occurred in different states, at different times and may be due to different conditions and circumstances. We anticipate that most respondents will have only one or a few cases to report. However, some respondents may have many.

This request fully complies with the other guidelines of 5 CFR 1320.5.

A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A. A 60-day notice was published in the *Federal Register* on September 13, 2006, Volume 71, Number 177, Page 54086 (Attachment 2). No public comments were received.

B. Consultation Outside the Agency

On January 15, 2002, this proposed study was presented to the Association of Public Health Laboratories (APHL) Advisory Committee meeting in Atlanta, Georgia. The committee members, including the chairman, Dr. Ken Pass, reviewed the proposed research and provided scientific input regarding our planned approach. CDC has consulted extensively with Dr. Brad Therrell of the National Newborn Screening Genetics Resource Center as well as Dr. M. Ramachandran of the Georgia Public Health Laboratory.

Person contacted	**Title**	**Agency**	**Date**	**Phone Number/E-mail**
Dr. M. Ramachandran	Clinical Laboratory service Director	Georgia Public Health Laboratory	7/23/2002	(404) 327-7937
Dr. Brad Therrell	Director	National Newborn Screening Genetic Resource Center	5/8/2002	(512) 454-6419
Dr. Ken Pass	Chairman	APHL Newborn Screening Advisory Committee, Director, New York Department of Public Health	5/23/2002	Kap03@health.state.ny.us

A.9. Explanation of Any Payment or Gift to Respondents

No payments or gifts will be given to respondents.

A.10. Assurance of Confidentiality Provided to Respondents

The CDC Privacy Act Officer has reviewed this application and it has been determined that the Privacy Act does not apply. While sensitive information will be collected concerning missed diagnoses, the survey will not request personal information about the respondent or identifiable information about the patient whose case is reported.

Data obtained from State's public health departments including follow-up programs within these departments is public information. However the names or other personal identifiers will not be given on report forms. The names of States on forms sent to State Public Health Directors will be used to clarify information on patients reported in a given state where the patient may have been born in another state and then moved to the reporting state and subsequently enrolled in a follow-up program in that state and also to verify which states have submitted data. Information of the state of submission will not be encoded in the database as a separate field. Information solicited from parents contacted through Parent Advocacy groups will be submitted by mail anonymously, again, with no personal identifiers and all reporting forms are uniform and not distinguishable by origin. Case reports will be sequentially numbered but not contain any personally identifiable information. Duplicate case reports will be rare and will be reconciled with official state health department records and follow-up program records if similar report submissions occur. We have also taken many other steps, as requested by the CDC IRB, to further protect the identity of reported cases. These steps include sending and receiving completed questionnaires by regular mail to eliminate the connection of the respondents name or email address with the data and destroying the return envelope upon receipt. We will also not collect any personal identifiers.

CDC Protocol # 3618 "Descriptive Epidemiology of Missed or Delayed Diagnoses for Conditions Detected by Newborn Screening was approved by the Human Subjects IRB through 5/4/2007 (Attachment 3). The CDC IRB granted a waiver of documentation of informed consent. In the original submission we described our plans to seek a Certificate of Confidentiality. However, subsequent changes to the methodology rendered the response data unidentifiable and the application for the Certificate of Confidentiality was withdrawn.

A.11. Justification for Sensitive Questions

The information collected in this survey may be considered sensitive because it may expose the participant to potential liability if not held in strict confidence. Liability for an incorrect laboratory test result is a concern but no cases will be documented that are currently under judicial review or the judicial outcome has not been documented. Judicial review is not a data element. The sensitive information collection is necessary to categorize the individual disorder or family of disorders that were not detected initially by laboratory testing or presented with clinical symptoms after the routine newborn screening chronology specified within the state of birth. The value of results is enhanced if the disorder is documented and may lead to remedial responses by States for a given disorder or family of disorders which are identified as problem areas from data collected.

We will not be collecting race/ethnicity data for this project since it is not relevant or necessary to our study.

A.12. Estimates of Annualized Burden Hour and Costs

A. Burden Hours

The Burden estimates were derived by asking 3 people (non-federal employees) with knowledge of missed cases to fill out the forms and report the length of time required. The number of respondents is based on an estimated 80% response rate. The total estimated remaining burden hours are 28.1.

Respondents	**Form Name**	**Number of Respondents**	**Number of Responses per Respondent**	**Average Burden (hours) per Response**	**Total Burden (hours)**
Director, State Newborn Screening Laboratory	State Form	25	1	3/60	1.3
	Case Report Form	25	1	10/60	4.2
Follow-up State Coordinator	State Form	25	1	3/60	1.3
	Case Report Form	25	1	10/60	4.2
Metabolic Clinic Employee	State Form	60	1	3/60	3
	Case Report Form	60	1	10/60	10
Parent Advocate	Case Report Form	5	1	10/60	0.8
Parent	Case Report Form	20	1	10/60	3.3
Total					28.1

B. Annualized Cost to Respondents

Type of Respondents	Number of Respondents	Frequency of Response	Estimated Hourly Wage	Hours per Response	Respondent Cost
Lab Director	25	1	$45.00	13/60	$244
Follow-up Coordinator	25	1	$35.00	13/60	$190
Metabolic Clinic employee	60	1	$25.00	13/60	$325
Parent Advocate	5	1	$15.00	10/60	$13
Parent	20	1	$15.00	10/60	$50
Total	135				$822

Cost for Parent Advocates and Parents are based on the average hourly wage rate according to the U.S. Census Bureau, Bureau of Labor Statistics, 2005.

A.13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

The data collection entails no additional costs to respondents or record keepers.

A.14. Annualized Cost to the Federal Government

Clerical costs = $5.00/ survey
$5.00 x 135 = $675.00

0.25 FTE (L. Omar Henderson)/year = $25,000

Total cost = $25,675.00

A.15. Explanation for Program Changes or Adjustments

This is a request for extension to complete a one time data collection. Data collection began in April 2006 and approximately one-third to one-half of anticipated total data has been collected.

A.16. Plans for Tabulation and Publication and Project Time Schedule

We plan to collect information about cases of phenylketonuria, congenital hypothyroidism, galactosemia, maple syrup urine disease, homocystinuria, biotinidase deficiency, congenital adrenal hyperplasia and sickle cell disease that were not detected by the newborn screening system or whose detection came too late to prevent harm. Data on missed cases will be collected from public health laboratory directors and follow-up coordinators from each state, metabolic clinics, and parent advocacy groups. Information about missed cases can also be derived from published medical literature. We plan to solicit information from our sources by asking for information that they are aware of related to a missed case of any of the diseases listed above between 1984 and 2004. We will ask that they provide us only with information pertaining to the disease, the circumstances surrounding the miss and the medical and legal outcomes. We will request that the information be provided to us without any personal identifiers such as names or addresses. After collecting data the data, we will organize it based on disease, reason for miss and outcomes.

The time schedule for the project is shown in the table below.

Project Time Schedule*

Activity	**Time Schedule**
Letters sent to respondents	1 month after OMB approval
Second mailing to non-responders	2-5 months after OMB approval
Telephone follow-up	6-9 months after OMB approval
Complete data collection	12 months after OMB approval
Analysis	12-18 months after OMB approval
Write, review, clear paper	30 months after OMB approval
Publish manuscript	

* Initial letters have been sent (April 2006) to State Laboratory Directors and second letters sent June 2006. Telephone follow-ups have not been conducted yet (December 2006) Parent advocacy groups have been notified (April 2006) but response from advocacy groups and parents has been slow. Parent advocacy groups will be recontacted and urged to increase participation.

A.17. Reason(s) Display of OMB Expiration Date Is Inappropriate

No exemption from display of expiration date is requested.

A.18. Exceptions to Certification for Paperwork reduction Act Submissions

No exceptions to certification are sought.

B. Collections of Information Employing Statistical Methods

B.1. Respondent Universe and Sampling Methods

Statistical methods will not be used to select respondents. It is preferable to survey all persons with the potential for knowledge rather than a sample because this should allow us to obtain information on all known missed cases, rather than just a subset.

Since data collection was initiated in April, 2006, approximately one half of all respondents have sent in data (n=150). However, we seek to continue data collection for the remaining participants in order to obtain information about the cases of missed or delayed diagnoses that have not yet been reported. Participants in the study are recruited from all states as well as Washington, D.C., Puerto Rico, and the U.S. Virgin Islands.

We anticipate that there will be an 80% response rate from the remaining potential respondents with a total of approximately 135 participants sending responses back to us. The response rate is estimated based on our experience since data collection initiated in April 2006 and on past experience of Dr. Brad Therrell with surveys administered to the same type of respondent groups.

As of December 2006, we anticipate collecting data from the remaining state newborn screening laboratory directors in each state or territory (25 persons), the follow-up coordinators for each state or territory (25 persons), representatives of metabolic clinics in each state or territory (60 persons) as well as representatives from parent advocacy groups (5 persons) and parents (20 persons) who are familiar with missed cases that have not yet participated or responded to this data collection.

Respondent numbers have been modified for our request for an extension (see Table of Estimated Burden Hours in A12.) to reflect the burden hours of the remaining participants only. Additional information about the study methodology is presented in Attachment 8.

B2. Procedures for the Collection of Information

Information for our study will be obtained by mailing our introductory letters (Attachment 4) and State and Case Report Forms (Attachment 5 and 6) to respondents with potential knowledge of missed cases (newborn screening laboratory directors, follow-up coordinators, and representatives of metabolic clinics). The respondents are requested to return the completed questionnaire with the prepaid return envelope that is provided. Another version of the letter in simplified language (Attachment 7) with the same Case Report Form will be distributed by parent advocacy organizations to their members including parents of children with known or suspected genetic inborn errors of metabolism. The Introductory letter and Case Report Form may be distributed electronically per IRB approval, but responses will be delivered on paper forms through the mail.

Members with knowledge of missed cases are asked to send the completed questionnaire back to the CDC by regular mail. After a period of 2 months, the cover letter and data collection form will be mailed again to representatives in states who have not yet responded. We may also call some potential respondents to ask them whether they wish to participate if they do not respond to our mailings (see timetable and current status).

Once received, the data will be examined for clarity. We will contact the state newborn screening laboratory to clarify responses if necessary. We will not attempt to contact the individual who responded to our survey in order to protect their privacy. The completed data collection forms will be stored in a locked file cabinet. The data will be entered into a secure electronic database.

We presented short talks at national meetings related to newborn screening, including the APHL Newborn Screening and Genetic Testing Symposium (Phoenix, Arizona, November 4-7, 2002) and the World Conference on Disabilities (Orlando, Florida, October, 2002) in order to introduce our proposed study to our intended respondents and to familiarize them with our goals and to ask their assistance. The Association of Public Health Laboratories will also publish an announcement of this study in several of their newsletters.

B.3. Methods to Maximize Response Rates and Deal with Nonresponse

We estimate that our response rate will be at least 80% based on previous data collections by one of our collaborators, Brad Therrell, who has surveyed the same respondents.

Public Health Laboratory Directors will be contacted by telephone in the extension period. To date approximately 1/3 of Directors have responded, and the remainder will be a priority effort to solicit state laboratory information

B.4. Tests of Procedures or Methods to Be Undertaken

We have pilot tested our questionnaire with three of our potential respondents to determine whether the forms are clear and to determine the amount of time required for a response.

B.5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

The data collection form was designed jointly by Lisa Kalman, Ph.D. (CDC), Harry Hannon, Ph.D. (CDC), Scott Grosse, Ph.D. (CDC), Ken Pass, Ph.D. and Brad Therrell, Ph.D. (National Newborn Screening and Genetics Testing Resource Center), all of whom are collaborators on this study. The data will be collected by L. Omar Henderson Newborn Screening Quality Assurance Program, (770) 488-7972 will also analyze the data, with input from the other collaborators listed above.

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