Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Presentation to SACGHS

March 12, 2009

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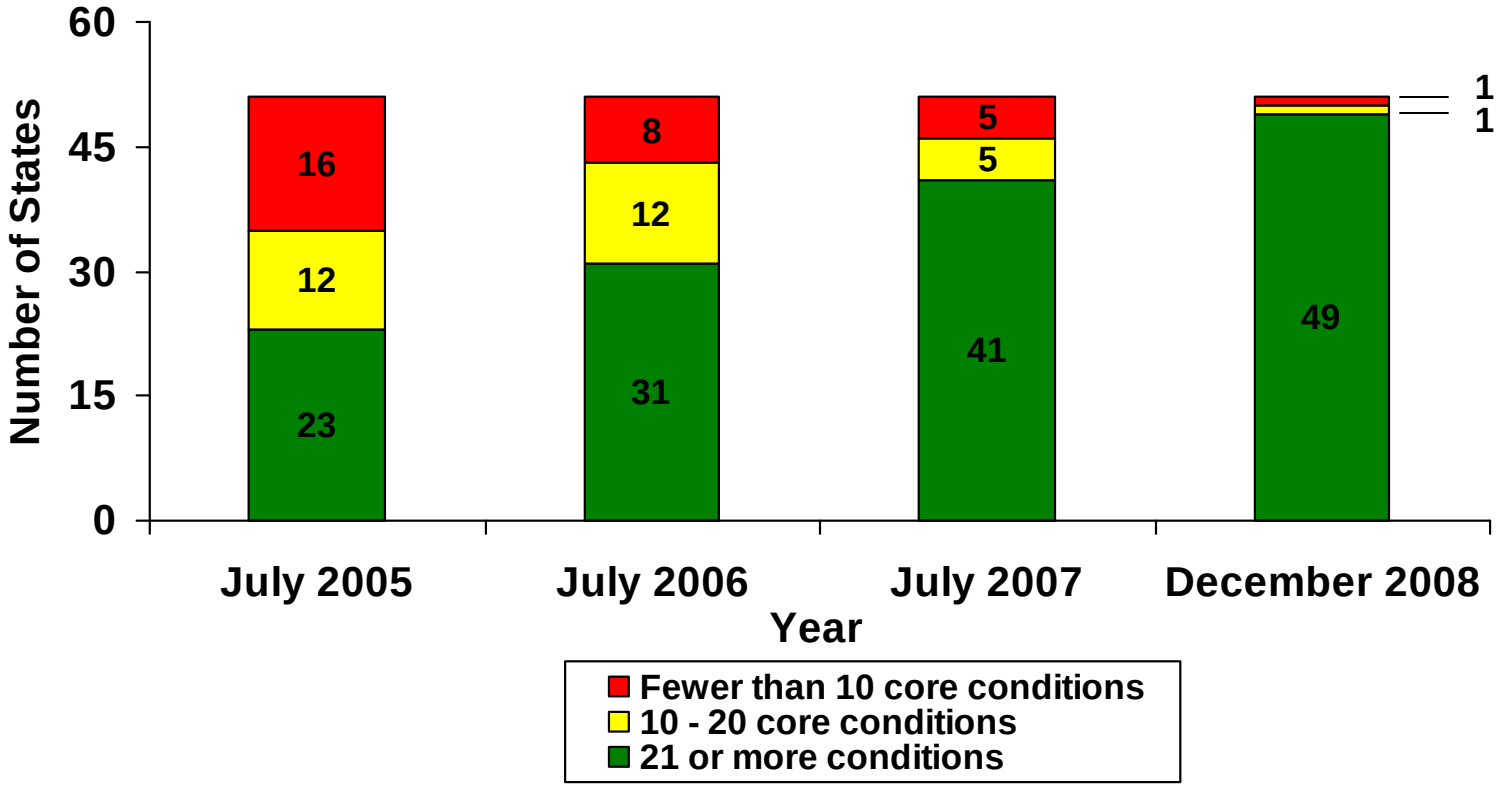
Authorizing Legislation

- **Title XXVI of the Children's Health Act of 2000 enacts three sections of the Public Health Service (PHS) Act:**
  - **two grant programs under Sections 1109 and 1110, and**
  - **Established the Advisory Committee on Heritable Disorders in Newborns and Children under Section 1111.**
  - **Committee first met on June 7-8, 2004**
  - **Although Committee charge is broad, to date committee has focused efforts on newborn screening**

Newborn Screening Tests



Source: March of Dimes. Data reported from NNSGRC.

Provisions of Public Law 110-204
Newborn Screening Saves Lives Act of 2008

- **This statute amends the Public Health Service Act to facilitate the creation of Federal guidelines on newborn screening**
  - **To assist State newborn screening programs in meeting federal guidelines**
  - **To establish grant programs to provide for education and outreach on newborn screening and follow-up care once newborn screening has been conducted**
  - **To reauthorize programs under Part A of Title XI of the Act**

Public Law 110-204
Newborn Screening Saves Lives Act of 2008

- **The Act reauthorizes and expands the role of the Advisory Committee on Heritable Disorders in Newborns and Children**
- **Establishes an Interagency Coordinating Committee on Newborn and Child Screening**
- **Creates an Internet-based information clearinghouse to provide information about newborn and child screening for heritable disorders**

Public Law 110-204
Newborn Screening Saves Lives Act of 2008

- **Bill requires the Secretary of HHS**
  - **To ensure the quality of laboratories involved in newborn screening activities**
  - **To develop a national contingency plan for newborn screening**

- **Gives the National Institutes of Health the authority to carry out research in newborn screening, including identifying new screening technologies and researching diseases management strategies for the conditions that can be detected through screening (NIH program to be known as the Hunter Kelly Newborn Screening Research Program)**

- **There are seven sections to the bill**

Nomination Process - concepts

- **Broad access to the process**
- **Considered review**
- **Streamlined process**
- **Transparency**
- **Consistent criteria throughout nomination process**
- **Structured Evidence-Based Review through ACHDGDNC external workgroup (Dr. Perrin)**
- **3 main areas for consideration:**

  <u>Condition, Test, Treatment</u>

Nomination Form (ftp://ftp.hrsa.gov/mchb/genetics/NominationForm.doc

NEWBORN SCREENING UNIFORM PANEL			
NOMINATION FORM FOR PROPOSED CONDITION			
Name of Proponent	*(Organization, if relevant)*	Date	
Condition			
Type of Disorder			
Screening Method			
Treatment strategy			

CONDITION	Comment

Gene		Locus		OMIM or other names for disorder	

*Note: Please reference each statement, listing references below (p.2)

Incidence	(Determined by what method(s): pilot screening or clinical identification?)
Timing of clinical onset	(Relevance of the timing of newborn screening to onset of clinical manifestations)
Severity of disease	(Morbidity, disability, mortality, what spectrum of severity)

TEST	Comment
Screening test(s) to be used	(High volume method, platform)
Modality of screening	(Dried blood spot, physical or physiologic assessment, other)
Clinical validation	(Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation)
Laboratory performance metrics	(Sensitivity, specificity, detection rate, positive predictive value, false positive rate)
Confirmatory testing	(Reliability, availability)
Risks	(False positives, carrier detection, invasiveness of method, other. Detection or suggestion of other disorders)

NOMINATION OF CONDITION (page 2)	
TREATMENT	Comment
Modality	(Drug(s), diet, replacement therapy, transplant, other)
Urgency	(How soon after birth treatment needs to be initiated to be effective)
Efficacy (Benefits)	(Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence.)
Availability	(Any limits of availability)
Risks	(Potential medical or other ill effects from treatment)

KEY REFERENCES (Specific citations – limit to 15)	
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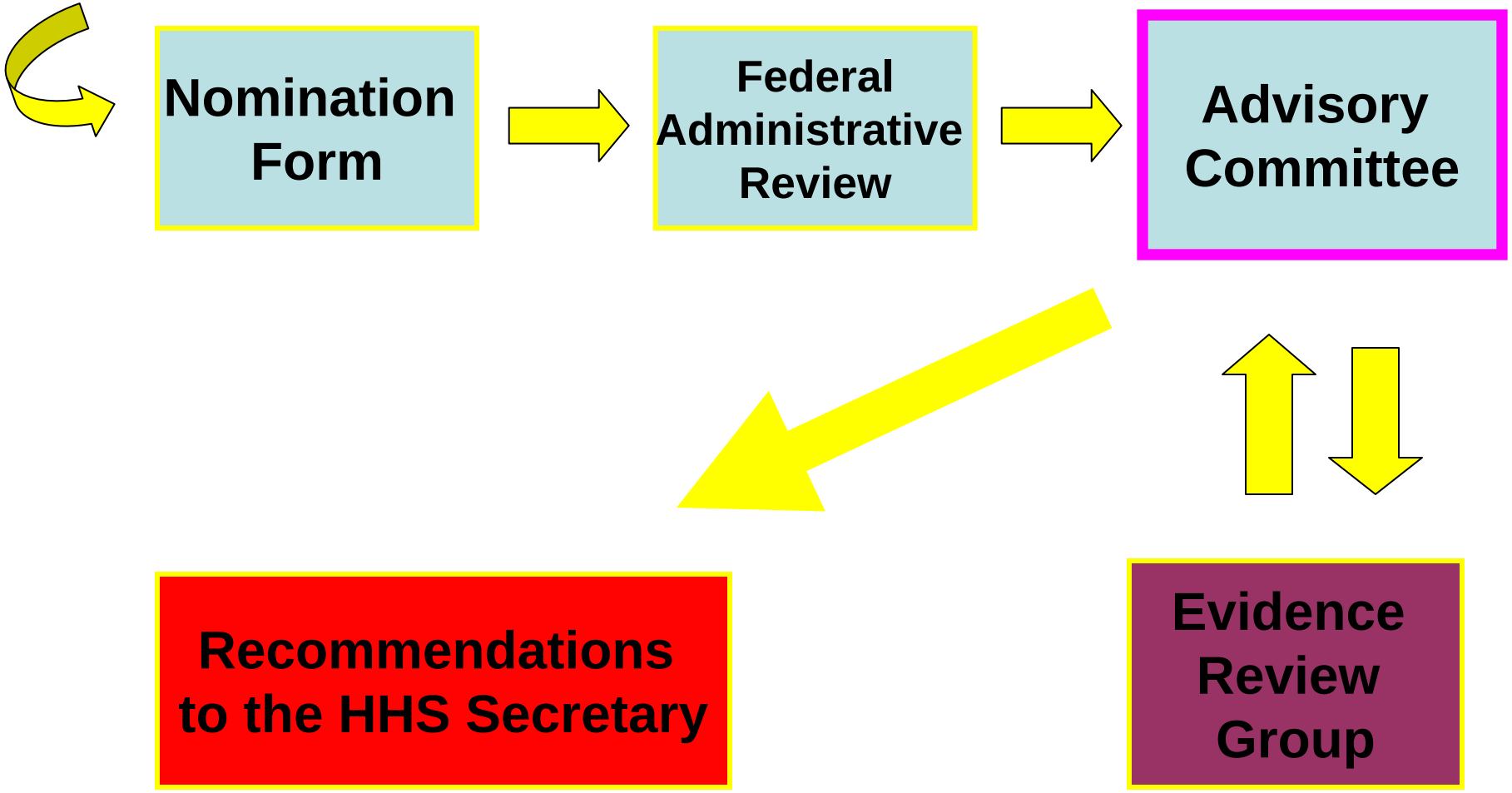
Submission Check list		Submit Nominations to:
	Cover letter by proponent	Michele A. Lloyd-Puryear, M.D., Ph.D. Chief, Genetics Services Branch Division of Services for Children with Special Health Needs Maternal and Child Health Bureau 5600 Fishers Lane, Room 18-A-19 Rockville, MD 20857 301-443-8604 –fax 301-443-1080 - phone
	Nomination form	
	Copy of references listed on this form	
	Formal conflict of interest statement by proponent	

Contact information (proponent)

ACHDNC Review and Decision Process

- Condition is nominated for review
- The Advisory Committee receives advice on this nomination from a formal internal workgroup that assesses, based on the nomination package for the condition and its own expertise, whether there is likely to be sufficient information on each of the three major components of a review:
    - the aspects of the condition (incidence, prevalence, significance),
    - the screening test, and
    - treatment.
- Advisory Committee evaluates and votes on whether a nominated condition should move forward for a full evidence review.
- The Decision Criteria and Process to be used in reviewing all nominations was presented by this workgroup at the February 26-27, 2009 meeting, approved and adopted by the Committee

Paradigm for Committee Consideration for Adding Disorders to the NBS Panel



Evidence Review Main Questions I

- **Questions for Review**
  - **Natural history, including variations in phenotype**
  - **Prevalence, including genotype, phenotype and phenotypic variations**
  - **Impact and severity**
  - **Methods of screening and diagnosis (in screen positive individuals)**
    - **Screening test utilities (sensitivity, specificity, predictive values)**
    - **Feasibility and acceptability of screening**

Evidence Review Main Questions II

- **Benefits of treatment**
  - **in screen positive individuals**
  - **In otherwise diagnoses individuals**
- **Harms or risks of**
  - **Screening**
  - **Diagnosis**
  - **Treatment**
- **Costs (screening, diagnosis, treatment, late treatment; failure to diagnose in newborn period)**

Evidence Review Model and Methods

- Decision model and development of evidence questions

- Search methods (time frame and search engines used)

Systematic Review and Additional Data Collection and Review

- **Study selection and data abstraction and review**
  - **Inclusion/exclusion criteria**
    - **Peer-reviewed published literature**
    - **English only**
    - **Gray literature – limited to pharmaceutical companies, unpublished studies (and related data)**
    - **Exclude case reports**
    - **Review consensus statements as guides, not for abstraction**

Systematic Review and Additional Data Collection and Review

- **Data abstraction and quality assessment**
  - **Standard quality assessment methods**
  - **Analyses of (any) additional raw data from unpublished sources**
    - **Special issues of data format and constraints on use (data sharing agreement template in process)**
- **Focus groups of experts (investigators and families) re impact and severity estimates**
- **Data synthesis**

Evidence Review Rationale and Objective

- **Rationale (for review at this time)**
  - **Nomination form and consideration by the AC**
  - **Recent changes in treatments and/or screening**
- **Objectives of Review**
  - **Provide timely information to the Advisory Committee to guide recommendation decisions for a specific screening protocol**

Evidence Review Results and Summary

- **Results**
  - **Follow order and content of main questions**
  - **Decision analyses/decision model findings (outcomes tables)**

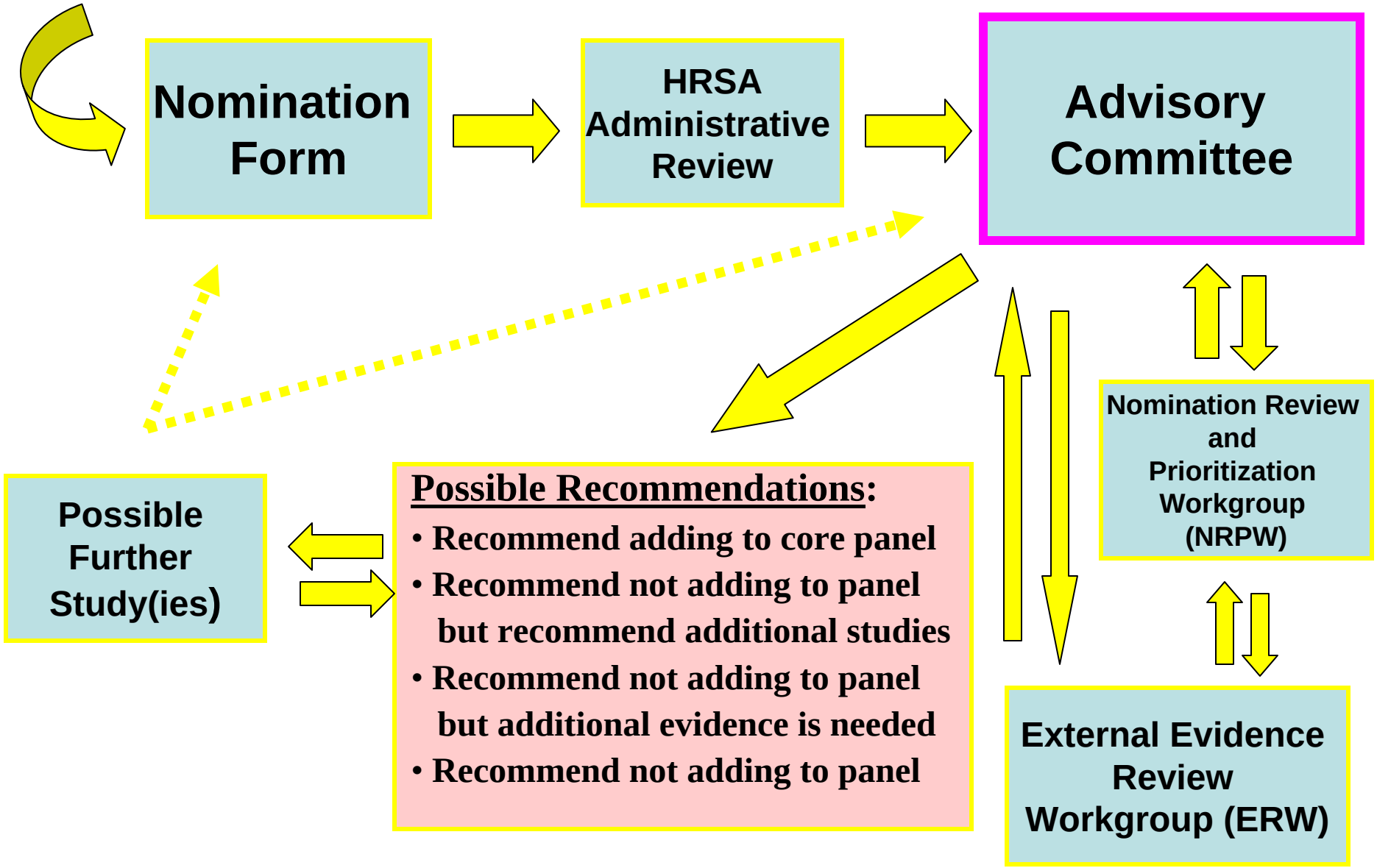
- **Summary**
  - **Key findings in summary and table form**
  - **Indicate where evidence is absent and what information would be most critical**
    - **What do we not know and level of uncertainty**
    - **What new information/studies would most help AC decisions**

Evidence Review Results and Summary

- **All decisions by AC – evidence group makes no recommendations**
- **Publication of evidence review and Committee recommendations:**

  As a Committee Report to be published on the Committee website as well as in a journal, from the workgroup, the Committee or as some combination

ACHDNC Evidence Review Process: Overview



Committee Discussions on Translational Research and Residual Blood Spot Policies

Two sessions on February 27, 2009

The goal of the sessions was to provide a broad overview of the issues, the current policies and model approaches to facilitate multi-center/site long-term follow-up in service delivery and translational research

1. **Translational Research Policies: Introduction to institutional review boards, informed decision-making and consent**

2. **Residual Blood Spots: Policies and Uses**

ACHDNC Update: February 2009 meeting

Translational Research Policies: Introduction to institutional review boards, informed decision-making and consent

Moderator: Jeffrey R. Botkin, M.D., M.P.H.

University of Utah School of Medicine

Edward Bartlett, Ph.D.

Office of Human Research Protection

Alan Fleischman, M.D.

Medical Director, March of Dimes

ACHDNC Update: February 2009 meeting

Moderator: Jeffrey R. Botkin, M.D., M.P.H.

- Provided overview of Regulation and Oversight of Research with Children

Edward Bartlett, Ph.D.

Discussed the following:

- Regulatory options for multi-center research
- Meetings on alternative IRB review models
- Proposal to hold IRBs directly accountable

Alan Fleischman, M.D.

- Translational Research in the Context of Newborn Screening—How Can We Make it Work?
- Provided overview of CA and MA models of obtaining informed consent for newborn screening research

ACHDNC Update: February 2009 meeting

RESIDUAL BLOOD SPOTS: POLICIES AND USES

William Hannon, Ph.D. National Newborn Screening and Genetics Resource Center

- **Storage, Retention, and Use of Residual Dried Blood Spots (DBS)**
  - **Storage of residual DBS by screening labs**
  - **Retention times for residual DBSs**
  - **Use of residual DBSs and the restrictions**
  - **Policies impacting DBS use**

Jeffrey R. Botkin, M.D., M.P.H. University of Utah School of Medicine

- **Ethical and Regulatory Considerations in Research using Residual Specimens**

ACHDNC: Next steps

Directions the Committee is exploring:

- **The Committee is preparing a White paper reflecting possible approaches to long-term follow-up and other translational research activities**
  - **The draft will be discussed at the Committee May meeting.**
- **Recommendations to Secretary on policies for retaining Residual Blood Spots and obtaining informed consent for storage of the samples**