Analysis of Committee Procedures: Decision Modeling, PHSI, and Cost Assessments

Presented to the Advisory Committee on Heritable Disorders in Newborns and Children

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Project Objective

- Analyze the Committee's evidence-based review process for nominating, reviewing, and recommending conditions for addition to the RUSP
- Identify and describe recommendations for improving the Committee's procedures

Presentation Plan

- Overview of the update process
- Recap of the decisions regarding the approach to evidence review
- Deeper dive into
  - Modeling
  - Public Health System Impact Assessment
    - Cost

Background

- In February 2019, we held an expert advisory panel (EAP) meeting to address the process through which a condition is considered for or included on the RUSP, including
  - nomination
  - evidence review process
  - decision making

- This meeting also included a consideration of how to review conditions already on the RUSP

Timeline

- Summary report due March 2020
- Facilitated discussions, led in partnership with Dr. Powell, at each of the ACHDNC meetings from March 2019 – February 2020
  - ✓March 2019 – Overview of expert advisory panel meeting
  - ✓April 2019 – Systematic evidence review
  - August 2019 – Decision modeling, public health system impact (PHSI) assessment, cost assessment, values
  - November 2019 – Decision matrix
  - February 2020 – Review of RUSP conditions, nomination process

Evidence-based Reviews of Expanding Newborn Screening

Newborn Screening Saves Lives Reauthorization of 2014 *(enacted March 2015):*

- The ACHDNC shall
  - "…evaluate public health impact, ***including the cost,*** of expanding newborn screening."
  - "Deadline for review. —For each condition nominated…, the Advisory Committee shall review and vote on the nominated condition ***within 9 months*** of …referr[ing] the nominated condition to the condition review workgroup."

Evidence Review Goals to Facilitate ACHDNC Decision-Making Process

- ❑ Evidence for Clinical Effectiveness/Net benefit to the Individual/Family
  - ✓ Magnitude/Strength of Evidence
  - ✓ Certainty of Evidence
- ❑ Public Health Impact - Population
  - ✓ Net benefit to the Population
- ❑ Public Health Impact - System
  - ✓ Feasibility and Readiness to Expand Screening
  - ✓ Cost of Expanding Screening

Condition Review - Target Timing by Component

CR Components	Description	Main Information Sources	Timing Q1 (M1)	Timing Q1 (M2)	Timing Q1 (M3)	Timing Q2 (M4)	Timing Q2 (M5)	Timing Q2 (M6)	Timing Q3 (M7)	Timing Q3 (M8)	Timing Q3 (M9)
Systematic Evidence Reviews (SER)	Net benefits of early detection, diagnosis, and treatment on individual	Published literature Pilot programs/States	X	X	X	X	X	X			
SER		Grey literature, Unpublished evidence			X	X	X	X			
SER		Analysis				X	X	X	X	-	-
Public Health Impact – Population	Net benefits of newborn screening on population-level health	Published literature – major health outcomes Decision analysis modeling	X	X	X	X	X	X	X	X	X
Public Health impact – NBS system	Feasibility of population-based screening, Readiness of states to expand screening	Screening procedures Survey of all NBS programs Interviews with states screening/mandated			X	X	X	X	X		
NBS system		Costs to expand screening			X	X	X	X	X	X	

Condition Review REPORTING OBJECTIVES

TQ0 Month 0 **AC Meeting - Nomination/Request for Review**

TQ1 (Month 3)	AC Meeting - Condition Review Presentation 1	SER	DA	PHSI
Scope of Review, Key Questions	Case definitions, parameters	Yes		
Preliminary Search Results/PRISMA		☑		
Pilot Screening Overview	Algorithm, resources, results	☑	☑	☑
Draft Decision Analysis Structural Model	Population-level impact		☑	
Draft Screening Fact Sheet				☑
Draft list – Screening States				
Technical Expert Panel (TEP) Members		☑	☑	☑
TEP 1 Input		☑	☑	☑

TQ2 (Month 6)	AC Meeting - Condition Review Presentation 2	SER	DA	PHSI
Review of Evidence Assessment of quality		☑		
Major outcomes of interest		☑	☑	
Rev Decision Analysis Structural Model			☑	
Key Studies for Decision Model			☑	
Screening Fact Sheet & Webinar				☑
PHSI Surveys, Interviews Update				☑
TEP 2 Input		☑	☑	☑

Condition Review

TQ3 (Month 9)	AC Meeting - Condition Review - Final Report	SER	DA	PHSI
Summary of Evidence and Quality		☑		
TEP 3 Input		☑	☑	☑
Decision Analytic Model	Population-level impact		☑	
PHSI Survey results	Feasibility and Readiness			☑
PHSI Follow up Interview summaries	Screening States			☑
Cost Assessment Results	Cost estimates, screening states			☑

Systematic Evidence Review Recommendations (Recap)

- Case Definition – will be streamlined with a more focused approach
- Key Health Outcomes – will include standard, pre-specified outcomes as well as as condition-specific outcomes
- Time Horizon for Outcomes – will be more clearly described and the risk of lead-time bias will be evaluated
- Key Treatments – Drug and Non-Drug, specific and non-specific

Systematic Evidence Review (Recap)

- Evidence Summary – Quality appraised by article and across each key question
- Gray Literature – criteria for inclusion better specified and a plan to have investigators supplement what is available within an abstract

Population-level decision modeling

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Decision analytic modeling overview

- A systematic approach to decision making under conditions of uncertainty
- Can be used to simulate randomized controlled trials for new interventions, to project beyond trial time frame, or to compare treatment protocols not directly compared in head-to-head trials
- Used to identify which alternative is expected to yield the most public health benefit
- Also characterizes uncertainties of long-term clinical and economic outcomes as well as data gaps

Decision analytic modeling in condition reviews

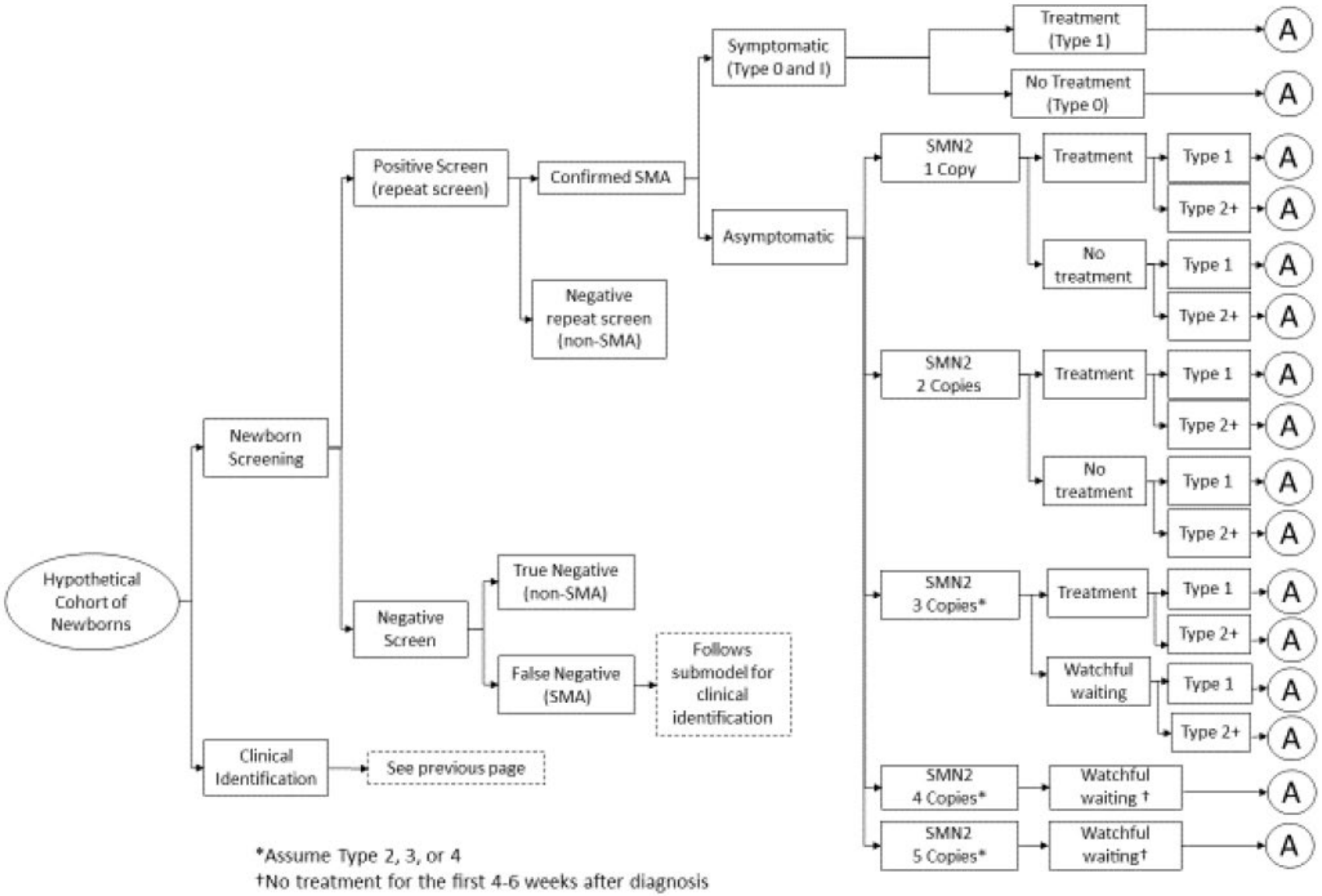
- Aids in estimating the range of health outcomes expected for universal newborn screening for a condition compared to clinical detection
- Results in estimates, based on US birth cohort of 4 million babies, for…
  - Projected number of cases of condition detected at birth
  - Projected health outcomes (e.g., deaths averted, cases of ventilator dependence avoided)

Overview of current approach

- Develop input parameters, key outcomes, and assumptions from published literature and recommendations from technical experts
  - Input parameters: incidence, probability of clinical form (i.e., SMA Type I – IV), screening outcomes, clinical outcomes
- Iteratively review and revise analytic model with expert guidance
- Key features (SMA as an example)
  - Target population – annual newborn cohort in US (~4 million newborns)
  - Intervention – newborn screening leading to pre-symptomatic/early treatment of disorder
  - Time frame – 1 year
  - Key health endpoints – mortality, ventilator dependence

SMA submodel

5.b. Universal Newborn Screening Submodel



*Assume Type 2, 3, or 4

†No treatment for the first 4-6 weeks after diagnosis

Results: Annual Cases of SMA identified[1,2]

	Clinical Identification	NBS
SMA Type I	196 (82-413)	196 (82 - 413)
Symptomatic	196 (82-413)	45 (1 - 192)[3]
Asymptomatic	--	151 (133 - 363)[3]
SMA Type II+	167 (70 - 351)	167 (70 - 351)[4]
Total SMA	364 (152 - 764)	364 (152 - 764)

[1]Assuming healthy annual newborn cohort of 4 million, not at higher risk of SMA
[2]Ranges represent one-way sensitivity analysis on each parameter
[3]By 11 days of life
[4]All asymptomatic at time of diagnosis (11 days)

Results: Outcomes at 52 Weeks, Type I SMA1[1,2]

Outcomes at 52 Weeks, Type I SMA1[1,2]	Clinical Identification	NBS	Cases or Deaths Averted
Ventilator-dependent cases	52 (17 - 109)	4 (0 - 18)	48 (16 - 100)
Deaths	36 (15 - 75)	3 (0 - 13)	33 (14 - 68)

[1]Assuming healthy annual newborn cohort of 4 million, not at higher risk of SMA
[2]Ranges represent one-way sensitivity analysis on each parameter

Summary

- Projected population-level outcomes
  - 364 (range: 152 - 764) cases of SMA identified annually
  - 196 (range: 82 - 413) Type I SMA cases identified
  - Reduced deaths and cases of ventilator-dependence for newborn screening compared with clinical identification for Type I SMA
- Additional benefits will likely accrue to other subtypes
- Limited data for modeling:
  - 52 weeks treatment effectiveness
  - 52 weeks for “new” natural history
  - Uncertainty for long-term outcomes

Issues raised by the EAP

- Understanding availability and type of evidence on the condition before the evidence review (published, grey lit, none at all)
- Scarcity of published literature necessitates use of grey lit in modeling
- Systematic method for including and assessing unpublished or expert-derived evidence is needed

Limitations and challenges

- Rare disorders – evidence base reflects this (small studies, single arm, etc.)
- Necessary to rely on gray literature and expert input for modeling assumptions (different from USPSTF approach)
- More recently nominated conditions are being nominated for the RUSP soon after intervention becomes available (even lower evidence base)
- Modeling may not be feasible for some nominated conditions

Potential solutions and recommendations

- Transparency
  - Model development
  - Summary tables of studies used in model
    - Ratings of study quality/risk of bias
    - Time horizon/follow up period
- Ongoing and active communication with ACHDNC
- Consider foregoing modeling if the evidence base is insufficient

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Public Health System Impact (PHSI) Assessment

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Committee Charge

The Advisory Committee shall (6) develop a model decision-matrix for newborn screening expansion, ***including an evaluation of the potential public health impact, including the cost of such expansion***, and periodically update the recommended uniform screening panel, as appropriate, based on such decision matrix (Newborn Screening Saves Lives Reauthorization, December 2014).

Purpose of PHSI

- Inform the committee and stakeholders (including advocacy groups) of difficulties in implementing new condition screening
- Describe the overall feasibility and readiness of newborn screening programs to implement new condition screening
- Describe costs of implementing new condition screening at the program level

Overview of Current Approach

Gather background information and share with NBS Programs

- Develop a screening implementation factsheet
- Conduct a webinar for NBS programs to review the condition, factsheet, forthcoming survey, and timeline

Overview of Current Approach

Implement a PHSI survey for NBS Programs

- Administer an online survey to NBS program directors; programs with a mandate to screen or conducting a pilot will be excluded from the survey
- Phone/email NBS directors to increase response rate
- Analyze survey results for final report

Overview of Current Approach

Conduct follow-up interviews with NBS programs that have a mandate, have begun piloting (or will soon), or have completed budget analysis

- Interview questions are designed to help us understand more about the issues around feasibility of implementing the condition
- Interview participants include program director and follow-up personnel
- Present results anonymously and in aggregate for final report

Issues raised by the EAP

- NBS programs feel that the PHSI does not communicate difficulties of new condition implementation to the committee (e.g., *"1 to 3 years to implement*" is not informative)
- PHSI does not consider the increased burden on primary-care physicians, specialists, and genetic counselors for true- and false-positives
- Public health programs may not be best respondents for questions related to specialist availability
- NBS programs may not understand what long-term follow-up plans will look like for each condition
- Unclear if or how the committee weighs the survey data during the decision-making process

Limitations and challenges of PHSI

- The questions in the survey are hypothetical and responses are subjective
- Funding challenges and a lengthy legislative approval process will be barriers (regardless of disorder being considered) that cannot be controlled by NBS programs
- Survey must be approved by OMB and it is not possible to modify the survey for specific conditions during the 9-month evidence review

Revisions underway or completed

- NewSTEPs Readiness Tool – Initiative to better capture information about state activities to expand newborn screening panels

- Changes to the PHSI Survey and Follow-up Survey/(interview guide) made for OMB renewal

- Encouraging state NBS programs to share the PHSI survey with all pertinent stakeholders of their system

Sample PHSI Survey Revisions

PHSI Survey (v 1.0, *exp* 9/30/2018)

How long would it take to achieve the following ***assuming*** that condition x was added to your state NBS panel and funds were allocated…?

- 1 year or less
- 1 to 3 years
- 3 or more years

- ❑ Obtain and procure equipment for screening for [condition x]
- ❑ Hire necessary laboratory and follow-up staff
- ❑ Select, develop, and validate the screening test within your laboratory *IF you ARE/are NOT multiplexing*
- ❑ Add the screening test to the existing outside laboratory contract
- ❑ Pilot test the screening process within your state, after validation has taken place
- ❑ Implement statewide screening for all newborns, including full reporting and follow-up of abnormal screens after validation and pilot testing

PHSI Survey (v2.0, exp 11/30/2021)

10. Please estimate the time it would take your NBS program to initiate screening *for* [condition x] in your state (i.e. get authority and funds to screen for condition x, go through administrative processes, meet with your state NBS committees and complete all activities needed to implement and commence screening for all newborns in your state).

- 12 months or less
- 13 to 24 months
- 25 to 36 months
- 37 to 48 months
- More than 48 months

11. The question above related to the overall timeline….. Please estimate the total time needed, in general, for each individual activity listed below within your NBS program.

- ❑ Obtain authorization to screen for condition x
- ❑ Availability of funds to implement screening for condition x
- ❑ Meet with Advisory committees and other stakeholders
- ❑ Obtain and procure equipment for screening for [condition x]
- ❑ Hire necessary laboratory and follow-up staff
- ❑ Select, develop, and validate the screening test within your laboratory IF you are NOT multiplexing
- ❑ Select, develop, and validate the screening test within your laboratory IF you ARE multiplexing
- ❑ Develop a screening algorithm, follow-up protocols, and train follow up staff
- ❑ Set up reporting and results systems for added condition (e.g., LIMS)
- ❑ Collaborate with specialists and clinicians in the community to determine which diagnostic tests will be recommended upon identification of an out of range NBS result
- ❑ Add the screening test to the existing outside laboratory contract
- ❑ Conduct an internal validation study for [condition x]
- ❑ Pilot test the screening process within your state, after validation has taken place
- ❑ Implement statewide screening for all newborns, including full reporting and follow-up of abnormal screens after validation and pilot testing

Potential solutions and recommendations

- Describe the process state programs go through to obtain legislative approval (e.g., advisory board, votes, duration of process) and funding
- Have condition nomination team provide a general roadmap for long-term follow-up strategies

Recently Added RUSP Conditions

RUSP Condition	Date Nominated	Matrix Location	Date Added	No. states screening at time of addition	No. states screening 1 year out	How many states screening 3 years out?	How many states screening today (August 2019)?	Unique considerations for disorder
Pompe	2012 (and 2006 and 2008)	A2	March 2015	1	5	17	20	Late onset
x-ALD	2015 (and 2012)	A2	Feb 2016	1	5	15	15	Neurological/ MRI
MPS I	2012	B3	Feb 2016	2	7	18	18	Pseudodeficiencies/ VOUS
SMA	2017 (and 2008)	B2	July 2018	3	9	n/a	9	Copy number

Cost assessments

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Overview of approach used since 2017

- Budget Impact Analysis – focuses on costs incurred by state NBS programs
- Method – voluntary interviews with states that have mandates for screening, have or are pilot screening, or have conducted budget analysis
- Cost estimation tool – developed and piloted with states, estimates costs per screen, assuming 100,000 births per year
- Broad cost category estimates:
  - Labor - estimated personnel effort (FTEs) for lab screening and short-term follow-up (e.g., tier 1 positives, positive screen referrals)
  - Equipment – either purchase price annualized plus service or rental agreement
  - Supplies - reagents, other disposable supplies
  - Facility overhead/space/maintenance
- Costs of treatment, long-term follow-up may be mentioned if available from literature review
- SMA review – first evidence review using this planned approach

Cost assessment in SMA review

- Assumed multiplexing with SCID test already in operation
  - Overall cost estimate of $0.10-1.00 per infant screened
  - No breakdown of costs provided
    - Labor – no additional FTEs required, no mention of short-term follow-up
    - Equipment – no additional equipment required
- Estimates provided by 2 states
  - NY – pilot screening in 4 hospitals
  - WI – planning screening

Limitations and challenges

- Estimates are projected costs (not actuals) and may be substantially lower than what states calculate when they need to raise fees
- Limited number of programs provide cost estimates, often incomplete and not detailed or using same categories
- Assumptions regarding prorated equipment purchase price and cost of laboratory-developed assays may not be generalizable
- High variability across states (annual births, second screens, screening infrastructure, purchase vs rental, etc.)
- Costs depend on multiplexing vs. stand-alone tests
- Many states are using contract services with labs/vendors and cannot disclose costs
- Short shelf life of estimates due to advances in methods

How are the cost assessments used?

- Cost estimates have been <$10 per infant per condition
- Would a higher cost screening test be considered less favorably?
- Does the Committee need a numerical cost estimate to inform its decisions or would a qualitative estimate be sufficient?
- Have cost estimates been used by states?
  - What is their experience?

How much does it cost to add SMA?

- SMA evidence review, confirmed by data from one additional state, indicates cost of $1 per infant or less to multiplex SMA with SCID assay, including short-term follow-up
  - Cost would be higher if stand-alone test were used
- Other cost estimates may be higher:
  - “There’s no commercial SMA screening test available, so state labs have to build them in-house. It requires a molecular test, which can cost as much as $10 per child, while others like congenital hypothyroidism cost as little as $1, said Linh Hoang, vice president of reproductive health at PerkinElmer, a leader in newborn screening.”

Bloomberg News, July 17, 2019, https://www.bloomberg.com/news/articles/2019-07-17/newborn-screening-for-rare-disease-can-be-a-life-or-death-lottery

Issues raised by the EAP

- Cost estimates need to be both internally valid and generalizable across states
- Which costs are most important, how should they be measured, and how should that information be communicated?
- Follow-up costs (short-term monitoring, treatment) should be included in PHSI
- Cost assessments do not account for director effort, quality control, contractual issues with upgrading equipment, and different levels of support from NIH and other sponsors

Potential solutions and recommendations

- Consistently frame cost assessment questions (what costs should be included, personnel, effort, rentals, etc.)
- Request that all NBS pilot studies funded by HHS agencies report costs using common data elements
- Retrospectively collect cost data from NBS programs that have implemented screening for new disorders
- Analyze actual cost data to predict how costs vary by annual numbers of births in state, number of screens per infant, and annual number of tests performed by screening laboratories

Should cost assessments be broadened?

- Legislative mandate does not detail which costs should be assessed
  - Focus on short-term costs to NBS programs due to time constraints
  - Not feasible to conduct full cost assessment and cost-effectiveness analysis within 6-7-month evidence review process
- Collection and analysis of data on broader costs of NBS expansion could be considered as part of post-RUSP reviews
  - Dependent on availability of resources and priorities

Questions and Discussion