

Informing the Development of Standardized Clinical Definitions of Neonatal Abstinence Syndrome and Neonatal Opioid Withdrawal Syndrome

Results of Two Modified-Delphi Expert Panels

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Preface

This publication reports on the results of two modified-Delphi expert panels consisting of national experts on substance-exposed mother-infant dyads. The results of these panels will be used to inform the work of a federal steering committee on neonatal abstinence syndrome (NAS) to develop standardized clinical definitions of NAS and a related diagnosis of neonatal opioid withdrawal syndrome (NOWS).

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Table of Contents

Preface.....	iii
Figures.....	v
Tables.....	vi
Acknowledgments.....	vii
Abbreviations.....	viii
1. Introduction.....	1
Methods.....	2
Organization of This Report.....	3
2. Clinical Signs of Withdrawal.....	5
Presence of Clinical Signs of Withdrawal.....	5
An Alternative Approach to Assessing Withdrawal: Domains of Dysfunction.....	8
3. In Utero Substance Exposures.....	11
Types of Substance Exposures.....	11
Ascertainment of In Utero Exposures.....	12
4. Experts' Proposed Clinical Definitions of NAS and NOWS.....	14
Proposed Definitions in the Experts' Own Words.....	14
Distinguishing Between NAS and NOWS.....	17
Suggested Alternative Names for These Syndromes.....	18
5. Discussion.....	20
Limitations.....	21
Considerations for Developing Definitions of NAS and NOWS Based on ExpertLens Findings.....	21
Next Steps.....	24
Appendix A. Methodology.....	25
Appendix B. Final Rating Results.....	32
Appendix C. Proposed Definitions of NAS and NOWS.....	34
References.....	36

Figures

Figure 1.1. ExpertLens Process	2
Figure A.1. Round Two Screenshot.....	29

Tables

Table 2.1. Necessity of Including Information About Clinical Signs of Withdrawal in the Definitions of NAS and NOWS.....	6
Table 2.2. Clinical Signs Characteristic of NAS and NOWS.....	7
Table 2.3. Dysregulation in Domains of Infant Functioning.....	9
Table 3.1. Information About In Utero Exposures.....	11
Table 3.2. Information About Toxicology Test Results.....	12
Table 4.1. Components of Proposed Definitions of NAS and NOWS Explicitly Mentioned, by Expert, by Panel, and Overall.....	15
Table A.1. Participant Characteristics.....	26
Table A.2. Pieces of Information About Mother-Infant Dyads for Panelists to Consider in the ExpertLens Process.....	27
Table A.3. Four Domains of Dysfunction.....	28
Table B.1. Final Rating Results for Round Three.....	32
Table C.1. ExpertLens Participants' Proposed Definitions of NAS and NOWS.....	34

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Abbreviations

HHS	U.S. Department of Health and Human Services
NAS	neonatal abstinence syndrome
NOWS	neonatal opioid withdrawal syndrome
RAM	RAND/UCLA Appropriateness Method
SES	socioeconomic status
SSRI	selective serotonin reuptake inhibitor
UCLA	University of California-Los Angeles

1. Introduction

From 2010 to 2017, the United States experienced a significant increase in maternal opioid-related diagnoses and neonatal abstinence syndrome (NAS),¹ which is a postnatal withdrawal syndrome typically caused by in utero exposure to both prescribed and illicit substances.² NAS is increasingly being referred to as neonatal opioid withdrawal syndrome (NOWS), because opioids are becoming the most common cause of neonatal withdrawal, whether alone or in the presence of other substances.³ According to some estimates, an infant is diagnosed with NAS every 15 minutes in the United States.⁴ NAS incidence varies widely across the country, from 0.7 cases per 1,000 live births in Hawaii to 33.4 per 1,000 births in West Virginia.^{5,6} Moreover, infants with NAS have longer and more costly birth hospitalizations than infants without NAS.¹

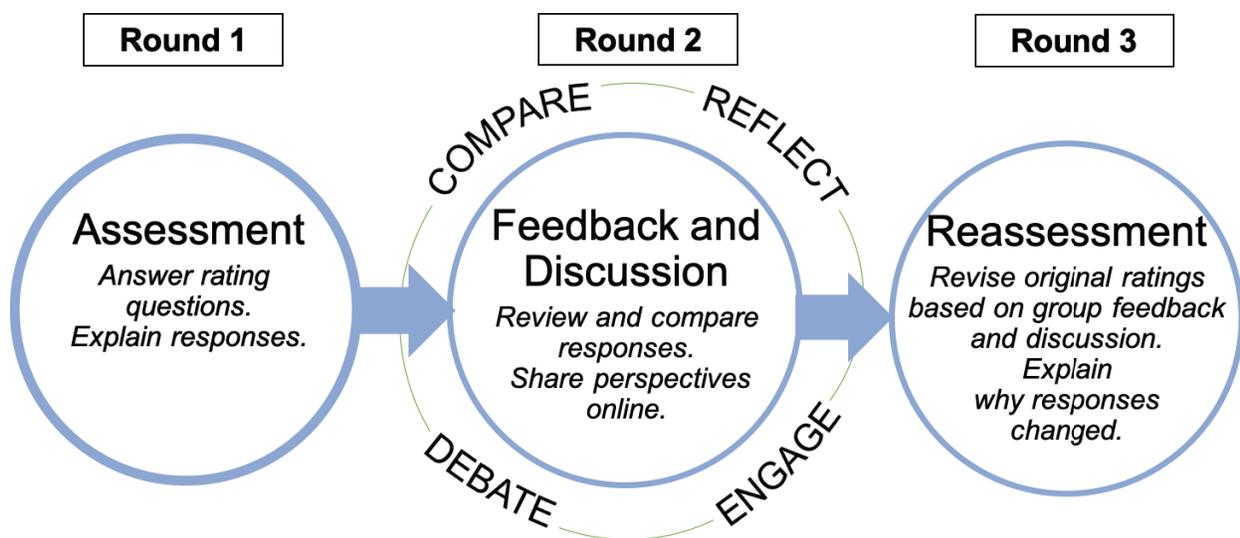
A major challenge in the field is the lack of a standardized clinical definition of NAS, which is associated with variation across the country in diagnosis and management, coding and billing practices, reporting to public health agencies for surveillance purposes, and ultimately, allocation of resources for supporting mother-infant dyads affected by substances. NAS and NOWS are heterogeneous conditions that can be caused by maternal nonprescribed opioid use and prescribed opioids such as medication for opioid use disorder (e.g., methadone and buprenorphine).² Other in utero exposures such as selective serotonin reuptake inhibitors (SSRIs) and nicotine may also lead to withdrawal.⁷ The clinical presentation of NAS and NOWS is quite variable.⁸ Some infants experience only mild withdrawal signs that can be managed with targeted non-pharmacologic interventions; others require multiple medications and weeks-long hospitalizations to manage their withdrawal.⁹ The heterogeneity of both precipitating exposures and clinical manifestations has led to a lack of consensus about how to define these complex conditions, as well as how to distinguish between NAS and NOWS.

To address these challenges and to contribute to an ongoing U.S. Department of Health and Human Services (HHS) initiative on NAS that is working on developing a clinical definition of neonatal withdrawal,¹⁰ the Office of the Assistant Secretary of Health contracted with the RAND Corporation to engage leading national experts with diverse backgrounds in a systematic, data-driven process to help **identify key components of standardized clinical definitions of NAS and NOWS that could be used at the bedside.** The purpose of developing these standardized clinical definitions is to reduce variation in the application of the clinical diagnoses of NAS and NOWS, conduct more accurate public health surveillance,¹¹ and, ultimately, develop more effective clinical, public health, and policy interventions for the near- and long-term support of opioid-affected mother-infant dyads.

Methods

To systematically engage experts on NAS and NOWS, we designed and convened two modified-Delphi panels using key principles of the RAND/UCLA (University of California-Los Angeles) Appropriateness Method (RAM) for conducting expert panels.¹² To facilitate data collection, we engaged experts using ExpertLens™—a previously evaluated platform for conducting online expert panels that allows participants to answer study questions by providing quantitative ratings and open-ended responses; review how their responses compare to those of other participants and asynchronously and anonymously discuss them using online discussion boards; and revise their answers, if needed, based on the discussion (Figure 1.1).¹³⁻¹⁵ By design, the ExpertLens platform facilitates the conduct of mixed-methods studies by helping to collect logically linked and seamlessly integrated quantitative and qualitative data. One panel (Panel A) focused on NAS and another (Panel B) on NOWS; otherwise, the data collection protocols for both panels were identical.

Figure 1.1. ExpertLens Process



NOTES: This figure describes a three-round ExpertLens process. In Round One, participants answer questions and explain their responses. In Round Two, they review how their own responses compare to those of other participants and discuss their perspectives using online discussion boards. In Round Three, participants revise their original responses based on Round Two feedback and discussion and explain why their responses changed or remained the same from Round One.

A detailed description of our methods is presented in Appendix A and can also be found in our study protocol published in *JMIR: Research Protocols*.¹⁶ Briefly, we invited 20 neonatologists, internists, nurse practitioners, and general pediatricians to provide input (by using 9-point Likert scales to answer close-ended questions, explaining their answers in open-text boxes, and

participating in an online discussion) in three areas to help us develop a set of criteria for defining NAS and Nows as follows:

- the necessity of including each of 14 pieces of information about mother-infant dyads in a clinical definition of NAS or Nows to be used at the bedside (see Table A.2)
- the degree to which ten common clinical manifestations of withdrawal are characteristic of NAS or Nows¹⁷
- the utility of using an alternative approach to diagnosing NAS and Nows that assesses for dysregulation in four areas or domains of infant functioning that has been proposed in the literature¹⁸⁻²⁰ (see Table A.3).

To validate the rating results, we asked experts to suggest their own definitions of NAS and Nows. Finally, we asked participants to identify the term(s) they prefer to use in their practice.

Of the 20 invited experts, 19 participated in at least one study round, and 18 completed all three rounds. We analyzed all quantitative data using the RAM's approach to determining consensus in expert panels.¹² We considered a piece of information about a mother-infant dyad to be a necessary component of a clinical definition of NAS or Nows only if there was no disagreement among the experts on each panel and if the median value of the panel's Round Three responses to a given question was 6.5 or higher on a 9-point Likert scale (see Appendix A for details). Using Excel, we conducted thematic analysis of all qualitative data collected throughout the ExpertLens process. Specifically, we sorted all Round One and Three comments for a given question by the numeric ratings to which they correspond, grouped all Round Two discussion comments by the definitional component, and collated all responses to the open-ended questions.^{21,22} D.K. and L.J.F. reviewed and coded all comments inductively to identify recurrent themes.

Organization of This Report

This report is organized around key pieces of information about mother-infant dyads that were identified as necessary for inclusion in the clinical definitions of NAS and Nows by the study participants.

Chapter 2 describes experts' perspectives on the necessity of knowing whether or not infants exhibit **clinical signs of withdrawal**. In doing so, we incorporate participants' ratings and comments on questions about signs of withdrawal from different substances, individual clinical manifestations of withdrawal, and an alternative approach to assessing neonatal withdrawal that looks at dysregulation in four domains of infant functioning.¹⁸⁻²⁰

Chapter 3 discusses experts' perspectives on the necessity of including the **type of substances to which an infant has been exposed in utero** (opioid alone versus other substances) and **how exposure was ascertained** (e.g., maternal report, toxicology testing) in the clinical definitions of NAS and Nows.

Chapter 4 reviews the **experts' own proposed definitions** of NAS and NOWS and is designed to triangulate the rating results. At the end of this chapter, we also explain how experts' views on NAS and NOWS differ and propose potential alternative terminology for these syndromes.

Chapter 5 summarizes our findings and **presents five considerations for the Federal NAS Steering Committee** as it develops standardized clinical definitions for NAS and NOWS to be used at the bedside.

2. Clinical Signs of Withdrawal

This chapter describes expert perspectives on the inclusion of clinical signs of withdrawal in the definitions of NAS and Nows.

Key finding 1: Experts generally agreed that the presence of clinical signs of withdrawal was necessary for a definition of NAS and Nows.

Key finding 2: They identified five clinical signs that are most characteristic of NAS and Nows, but emphasized that the combination of signs of withdrawal, which present differently in each infant, is most important for making these diagnoses, not any particular sign in isolation.

Key finding 3: Experts agreed that the domains-based approach to assessing withdrawal, which they felt offered a different way of organizing individual signs of withdrawal, has the potential to be feasible and useful, but they noted concerns about ease of implementation given the perceived complexity of this alternative approach.

Presence of Clinical Signs of Withdrawal

First, we asked experts to rate the necessity of including five different pieces of information about clinical signs of withdrawal in the definitions of NAS or Nows using a 9-point scale, where 1 = not at all necessary and 9 = very necessary. Experts agreed that **the presence of clinical signs of withdrawal was necessary for inclusion in the definitions of NAS and Nows**. Indeed, the infant showing signs of withdrawal was the highest-scoring item in both panels (medians = 9, Table 2.1).

As Expert A07 stated: “NAS is characterized by withdrawal symptoms, so these symptoms need to be present to label as NAS. If the infant did not have signs of withdrawal, they do not have NAS.” Expert B09 made a similar comment about Nows diagnosis: “Nows is a withdrawal syndrome after antenatal exposure to opioids. Cannot have Nows if there are no signs of withdrawal.”

To further explore known variation in diagnosing NAS and Nows, we also asked experts whether information about non-pharmacologic management or medication was necessary to include in the definitions of NAS and Nows. Only experts on the NAS panel agreed that knowing “infant requires medication to treat signs” is necessary (median = 6.5) for inclusion in the definition of NAS (Table 2.1).

The remaining pieces of information in Table 2.1 were rated as either “potentially necessary” or “unnecessary” to include in these definitions.

Table 2.1. Necessity of Including Information About Clinical Signs of Withdrawal in the Definitions of NAS and NOWS

Rating Items	NAS Panel			NOWS Panel		
	<i>n</i>	Median	Decision	<i>n</i>	Median	Decision
The infant . . .						
. . . shows signs of opioid withdrawal	8	9	Necessary	10	9	Necessary
. . . requires medication to treat signs of withdrawal	8	6.5	Necessary	8	3	Unnecessary
. . . shows dysregulation in at least one domain of infant development such as motor control or responses to stimuli	8	6	Potentially necessary	9	5	Potentially necessary
. . . requires non-pharmacologic measures to manage withdrawal	8	5	Potentially necessary	9	4	Potentially necessary
. . . shows signs of withdrawal from substances other than opioids	8	5	Potentially necessary	9	3	Unnecessary

NOTES: This table presents final (Round Three) ratings from both panels. Column *n* lists the number of participants providing a response to each numeric question. The decision column lists the final panel decision for each question as determined using the RAM’s approach to determining consensus in expert panels. Blue shading indicates items that were deemed “necessary” to include in the definitions of NAS and NOWS, based on agreement among the experts and a group median of 6.5 or above.

Individual Signs of Withdrawal

Next, because NAS and NOWS can present very differently in different infants, we asked experts to identify which of ten clinical signs of withdrawal drawn from the literature¹⁶ were most characteristic of NAS or NOWS. Of these, **five signs were deemed characteristic of both NAS and NOWS** (crying, fragmented sleep, tremors, altered muscle tone, and feeding alterations). **Three other signs were deemed characteristic of NAS only** (excessive sucking, feeding intolerance, and loose or watery stools) (Table 2.2).

When asked by the discussion moderators whether the highest-rated signs and symptoms should be included in the definitions of NAS and NOWS as examples, experts expressed a range of opinions. Some experts agreed that providing some clinical signs for illustrative purposes might be a “great place to start” (Expert B07), but cautioned that more research was needed to see if the highest-rated signs were “corroborated” by clinical research (Experts B01, B07). Expert A05 noted that “A number of papers have come out in the past few years which have looked at large data sets of Finnegan scoring to identify which individual elements were most predictive of the larger score. A review of this empiric evidence would be a good place to make quantitative assessment[s].” Other experts disagreed, commenting that the definition should be more general, and that details such as individual clinical signs of withdrawal, time they take to

Table 2.2. Clinical Signs Characteristic of NAS and NOWS

Rating Items	NAS Panel			NOWS Panel		
	<i>n</i>	Median	Decision	<i>n</i>	Median	Decision
Crying (excessive or continuous)	8	8	Characteristic	10	8	Characteristic
Fragmented sleep (<1 hour after feeding or <2 or 3 hours after feeding)	7	8	Characteristic	9	8	Characteristic
Tremors (disturbed or undisturbed)	8	8	Characteristic	9	7	Characteristic
Increased muscle tone	7	7	Characteristic	10	8	Characteristic
Alterations in feeding (e.g., hyperphagia, poor feeding)	8	7	Characteristic	10	7	Characteristic
Excessive sucking	8	7	Characteristic	9	7	Disagreement
Loose or watery stools	8	6.5	Characteristic	9	6	Potentially characteristic
Feeding intolerance	8	6.5	Characteristic	10	5	Potentially characteristic
Respiratory rate >60/min	8	5	Potentially characteristic	8	5	Potentially characteristic
Nasal stuffiness	7	5	Potentially characteristic	9	3	Uncharacteristic

NOTES: This table lists clinical signs that the experts agreed were characteristic of both NAS and NOWS based on Round Three ratings, as well as those that they agreed were characteristic of NAS only. Column *n* lists the number of participants providing a response to each numeric question. The decision column lists the final panel decision for each question as determined using the RAM's approach to determining consensus in expert panels. Blue shading indicates items that were deemed characteristic of NAS or NOWS based on agreement among the experts and a group median of 6.5 or above.

develop after birth, and how they may present differently in preterm infants should not be included in the definition. According to several experts, these signs and symptoms are “non-specific and have other causes” (Expert A02). Expert B06 agreed: “It is hard to pick specific signs or specific Finnegan numbers because they don’t fully represent the entire picture. If a baby is requiring increased care above normal newborn care, we call that signs of withdrawal. We have been able to standardize this in our state with some ongoing discussion and example caveats.”

Signs in Combination

During the discussion of clinical signs, participants felt that many individual signs are not specific to NAS and NOWS and should always be considered in combination and in the appropriate clinical context. As Expert A08 stated, “You really need to understand the individual symptoms but look at how they are impacting the baby as a whole. Are yawning or hiccups really important individually?” Expert B06 also advocated for a more holistic approach: “Symptoms that are beyond those seen in normal transition and can’t be accounted for by other disease processes are those that count for the [diagnosis] of withdrawal . . .”

Although the field generally agrees, broadly speaking, on how neonatal withdrawal typically presents, painting a more specific, consistent picture has been a significant challenge, given the innumerable different combinations of signs that infants may display. That is why, after considering the clinical signs individually, we asked participants to picture infants with NAS or Nows and describe the combination of signs these infants typically exhibit. The lists of combinations that participants generated included more than a dozen different signs of withdrawal. As Expert B06 put it: “Any combination of signs that require intention[al] non-pharm[acologic] care in [order] to overcome meet the definition of Nows.” Not surprisingly, we did not identify any clear patterns in their responses, because each expert provided a slightly different combination of signs. The following examples illustrate the variation:

- “Hypertonicity, excessive crying/irritability, poor sustained sleep, hyperphagia, exaggerated moro, increased motor activity, hypersensitivity to environment, diarrhea” (Expert A01)
- “Fussiness/irritability, hypertonia, tremors, excessive suck, sweating” (Expert A07)
- “Inconsolable crying, feeding difficulties and poor weight gain, loose stools, jitteriness, and sweating” (Expert B02)

An Alternative Approach to Assessing Withdrawal: Domains of Dysfunction

One way to group signs of withdrawal is to look at dysregulation in key domains of infant functioning, including autonomic control, motor/tone control, state control and attention, and sensory reactivity¹⁷⁻¹⁹ (Table A.3 provides more detail on the domains). Both panels agreed that this **alternative approach is potentially different** (NAS panel median = 6; Nows panel median = 4.5, on a scale from 1 = not at all different to 9 = very different) from how withdrawal signs are currently assessed in clinical practice, but felt that **it could be a feasible** (NAS panel median = 5.5; Nows panel median = 4, on a scale from 1 = not at all feasible to 9 = very feasible) **and either a useful** (NAS panel median = 7) **or potentially useful** (Nows panel median = 6) approach to diagnose NAS and Nows (on a scale from 1 = not at all useful to 9 = very useful) (Table 2.3).

Experts appreciated that this approach can “mitigate some of the subjectivity of modified Finnegan [scoring] systems” (Expert A03) and can help group signs into domains instead of looking at them in isolation, but stated that the domains essentially include **the same signs they are accustomed to assessing, just grouped into different categories**. Expert B01 agreed that the domains approach represents yet another modification of the Finnegan approach, which may

Table 2.3. Dysregulation in Domains of Infant Functioning

Rating Items	NAS Panel			NOWS Panel		
	<i>n</i>	Median	Decision	<i>n</i>	Median	Decision
How different is this approach from the way withdrawal signs are currently assessed in clinical practice?	7	6	Potentially different	10	4.5	Potentially different
How useful is this approach for assessing opioid withdrawal in an infant?	8	7	Useful	9	6	Potentially useful
How feasible would it be to use this approach to distinguish between infants with and without NAS?	6	5.5	Potentially feasible	8	4	Potentially feasible

NOTES: This table presents final (Round Three) ratings from both panels. Column *n* lists the number of participants providing a response to each numeric question. The decision column lists the final panel decision for each question as determined using the RAM’s approach to determining consensus in expert panels. Blue shading shows that one panel (the NAS panel) reached agreement on the second question, with a group median of 6.5 or above.

“provide more uniformity with scoring and aid in defining withdrawal. I agree that the domain of interest could help tailor the non-pharmacologic approach to the infant. Could be a useful approach to defining NOWS.”

Experts disagreed on how this domains-based approach to assessing withdrawal might be perceived by families. For instance, Expert B04 stated that while “domains may be appealing to clinicians and researchers, [they are] simply not useful for bedside practice and potentially harmful . . . [The domains approach] is quite complex, and I think it could once again put the HCP [health care provider] in the ‘front seat’ as the expert and the mother in the ‘back seat.’” In contrast, Expert B06 felt that the infant’s family could be incorporated in the assessment: “I think this could be taught with simple terms that could help the family understand better what is happening when we are concerned about symptoms. I often am asked by families, why these individual things matter. We could explain in terms they understand how the individual symptoms come together to effect [sic] the baby, and how that is different from a baby who is not showing signs of dysregulation. This could actually help engage the family more.”

Finally, **experts raised the question about implementing the domains-based approach at the bedside.** As Expert A05 put it, “The challenge will be translating this into a reliable and reproducible instrument to use at bedside.” Expert B09 was supportive of the approach but commented, “We have so many potential ways to assess drug withdrawal, some of which have been researched and some of which have not. There needs to be strong evidence to add yet another assessment approach to the clinical arena.” Similarly, Expert B08 noted that this approach and the terms used “seem too theoretical,” whereas Expert A08 stated that “it would be difficult to objectively use in a clinical setting, especially with large nursing pools who would need to be trained.” Indeed, there was a desire to quantify the domains approach to make its implementation more feasible and the approach more useful at the bedside. To use the words of Expert B06, “I

think we could use a 5-point Likert scale between regulated and dysregulated and then define how many points on how many domains was needed to define withdrawal.” Finally, Expert B04 strongly advised that “feasibility [of this approach] would need to be tested in a variety of conditions (language, SES, ethnicity, literacy) etc. I predict it would not be feasible—but perhaps worthy of very well-orchestrated testing.”

3. In Utero Substance Exposures

In this chapter, we present experts’ perspectives on the necessity of including different types of in utero substance exposures and the methods used to ascertain them in clinical definitions of NAS and Nows.

Key finding 1: Experts agreed that Nows is defined by in utero exposure to opioids with or without exposure to other substances, but, if it is known that there is no exposure to opioids, the infant should not be diagnosed with Nows. In this case, NAS would be a more accurate diagnosis.

Key finding 2: Experts agreed that maternal and infant toxicology test results may provide helpful context for understanding an infant’s clinical presentation, but test results are not required for the diagnosis of NAS or Nows.

Types of Substance Exposures

In addition to clinical signs, experts in both the NAS panel and the Nows panel agreed that it was **necessary to include information on the specific substances to which the infant was exposed in the clinical definitions of these conditions**. Specifically, they considered it necessary to know whether the infant was exposed in utero to *opioids alone* (NAS panel median = 7.5, Nows panel median = 6.5) and whether the exposure was to substances *other than opioids* (NAS panel median = 8, Nows panel median = 9) (Table 3.1). As Expert A03 commented, “Many drugs can give withdrawal symptoms, so establishing exposure is key.”

Table 3.1. Information About In Utero Exposures

Rating Items	NAS Panel			Nows Panel		
	<i>n</i>	Median	Decision	<i>n</i>	Median	Decision
The infant had prenatal exposure to . . .						
. . . substances such as benzodiazepines, SSRIs, tobacco, but did not have prenatal exposure to opioids	8	8	Necessary	10	9	Necessary
. . . opioids alone	8	7.5	Necessary	10	6.5	Necessary
. . . opioids plus other substances (e.g., benzodiazepines, SSRIs, tobacco)	8	6	Potentially necessary	10	5	Disagreement

NOTES: This table presents final (Round Three) ratings from both panels. Column *n* lists the number of participants providing a response to each numeric question. The decision column lists the final panel decision for each question as determined using the RAM’s approach to determining consensus in expert panels. Blue shading indicates items that were deemed “necessary” to include in the definitions of NAS and Nows, based on agreement among the experts and a group median of 6.5 or above.

Other experts elaborated on the necessity of establishing the nature of the in utero exposure in their comments. Expert B10 explained: “If we are saying NOWS is OPIOID withdrawal, then by definition there HAS to be at least exposure to an opioid . . . Agree with others that if baby has withdrawal and other drugs and no opioids are found [on toxicology testing], then [it] would be NAS.” Expert B03 said, “NOWS can follow exposure to ‘opioids alone’ or ‘opioids plus other substances.’ If there is no opioid exposure, either with or without other substances, then diagnosis of NOWS is more difficult.” Expert B08 expressed a similar view, commenting, “If no opioids were involved, this rules out NOWS.” Similarly, Expert A05 stated, “If we define NAS/NOWS as driven by opioids, high confidence in no exposure [to] opioids is helpful. Other exposures help provide a source for other signs that fit within a withdrawal pattern.”

Ascertainment of In Utero Exposures

In the clinical setting, in utero substance exposure can be ascertained in several ways, including by maternal report, documentation in the medical record, and toxicology testing. During the panel, we asked experts to rate the necessity of including maternal and infant toxicology test results in the definitions of NAS and NOWS (Table 3.2).

Table 3.2. Information About Toxicology Test Results

Rating Items	NAS Panel			NOWS Panel		
	<i>n</i>	Median	Decision	<i>n</i>	Median	Decision
The mother’s toxicology test is positive for . . .						
. . . opioids alone	6	7	Necessary	9	4	Potentially necessary
. . . opioids plus other substances	8	5	Potentially necessary	9	5	Potentially necessary
. . . substances other than opioids and is negative for opioids	6	5	Potentially necessary	9	5	Potentially necessary
The infant’s toxicology test is positive for . . .						
. . . opioids alone	7	3	Unnecessary	9	3	Unnecessary
. . . opioids plus other substances	8	3	Unnecessary	10	3	Unnecessary
. . . substances other than opioids and is negative for opioids	7	2	Unnecessary	9	4	Potentially necessary

NOTES: This table presents final (Round Three) ratings from both panels. Column *n* lists the number of participants providing a response to each numeric question. The decision column lists the final panel decision for each question as determined using the RAM’s approach to determining consensus in expert panels. Blue shading indicates items that were deemed “necessary” to include in the definitions of NAS and NOWS, based on agreement among the experts and a group median of 6.5 or above.

Maternal Toxicology Testing

As shown in Table 3.2 above, experts agreed that **maternal toxicology test results are potentially necessary (but not required) to make a diagnosis of NAS or NOWS** (median values to questions about maternal toxicology test results generally varied between 4 and 5, depending on the types of substances considered).^{*} As Expert A02 put it, maternal toxicology test results provide important contextual information but are “not completely necessary, because mother can have a negative test at some point. On the other hand, if she reports a history, that is important in the absence of positive lab results.” Other experts expressed similar views that history taking, rather than maternal toxicology test results, is more important for the diagnosis: “I don’t think [maternal] toxicology results are necessary to the diagnosis, as long as there is known exposure based on history taking. If it is unclear whether there is exposure in a symptomatic infant, maternal or infant toxicology would be necessary” (Expert B08).

Infant Toxicology Testing

Similar to the results of the questions on maternal toxicology testing, experts felt that **knowing whether infant toxicology test results are positive for opioids alone** (NAS panel median = 3, NOWS panel median = 3) **or for opioids and other substances** (NAS panel median = 3, NOWS panel median = 3) **is “not necessary to the diagnosis**, as long as there is known exposure based on history taking” (Expert B08) and as long as “the whole clinical picture” (Expert B09) is taken into account. Furthermore, Expert A02 noted that infant toxicology test results may not be accurate: “There is literature that shows that infants exposed by history to opioids not uncommonly have negative laboratory testing even though they have clinical signs. I am sure this is due to variability in protocols for obtaining infant testing which is often influenced to a great extent by hospital protocols shaped by legal precedent.”

^{*} It is worth noting that the NAS panel considered knowing whether the mother had a positive toxicology test for opioids alone (median = 7) as necessary for inclusion in the definition of this condition. On the one hand, this difference between the two panels may be attributed to a tendency to diagnose “NOWS” when the only in utero exposure is to opioids. Alternatively, it could be explained by a degree of confusion among participants, especially on the NOWS panel, about how in utero exposures were framed in the ExpertLens process, and whether they were being asked to distinguish between infants with NAS versus NOWS, or between infants with and without NOWS (the latter was the intent of the question).

4. Experts' Proposed Clinical Definitions of NAS and NOWS

In this chapter, we present the definitions of NAS and NOWS that the experts suggested for use at the bedside, discuss the difference between NAS and NOWS, and review alternative terminology that experts suggested for these syndromes.

Key finding 1: Experts agreed that NAS is typically caused by polysubstance exposure and that NOWS can result from in utero opioid exposure “with or without exposure to other substances.”

Key finding 2: Nearly all experts viewed NAS and NOWS as interchangeable when in utero opioid exposure is present, with NOWS being a “subcategory” or “single-exposure” version of NAS. However, because NAS and NOWS are not mutually exclusive when there is in utero exposure to both opioids and other substances, the experts noted inconsistent use of these terms in the field and in their own clinical practice.

Key finding 3: Consistent with earlier answers to rating questions, nearly all of the experts' proposed clinical definitions explicitly mentioned in utero substance exposure and clinical signs of withdrawal and noted that toxicology testing was helpful to have for the diagnoses but not required.

Key finding 4: Experts had different perspectives on whether the presence of clinical signs alone was sufficient to define NAS and NOWS, or if the signs had to reach a certain level of severity or require intervention to meet the criteria for these diagnoses.

Key finding 5: Many experts suggested changing the syndrome names, but including “withdrawal” or “dysregulation” in the name. Some felt that the current terminology excludes exposed infants who do not develop withdrawal but do need long-term dyadic supports. They suggested making the name more inclusive of these infants and identifying them through coding practices.

Proposed Definitions in the Experts' Own Words

Seventeen of the 19 experts in both panels provided their own preferred definitions for NAS and NOWS (see Appendix C). As a way to validate our rating results, we inductively coded them to identify the individual components of the experts' proposed definitions of NAS and NOWS.

Table 4.1 below shows the components of the experts' proposed definitions. In their responses to the question that asked the NAS panel to provide a NOWS definition and vice versa, nearly all 17 participants who provided their own definitions considered NAS and NOWS to be essentially interchangeable in the setting of in utero opioid exposure, with NOWS “emphasizing” opioid exposure. In other words, they viewed NOWS as a “subcategory” or a “single-exposure version” of NAS. Conversely, experts considered NAS to be broader than NOWS because NAS may be caused by in utero exposures to not only opioids, but other substances as well. As the majority of

Table 4.1. Components of Proposed Definitions of NAS and NOWS Explicitly Mentioned, by Expert, by Panel, and Overall

Panelist	Signs of Withdrawal	In Utero Substance Exposure	Response to Interventions	Distinguish Between Exposure and Clinical Withdrawal	Toxicology Testing	Long-Term Consequences/Follow-Up	Total No. of Components in Definition
A01	✓	✓		✓		✓	4
A02	✓	✓	✓		✓		4
A03	✓	✓					2
A05	✓	✓					2
A06	✓	✓	✓	✓			4
A07	✓	✓					2
A08	✓	^a					2
A09	✓	✓					2
Panel A Total No. of Experts	8	7	2	2	1	1	
B01	✓	✓	✓			✓	4
B02	✓	✓	✓				3
B03		✓		✓			2
B05	✓	✓					2
B06	✓	✓	✓		✓		4
B07	✓	✓		✓		✓	4
B08	✓	✓					2
B09	✓	✓	✓				4
B10	✓	✓	✓	✓	✓		5
Panel B Total No. of Experts	8	9	5	3	2	2	
Overall Total No. of Experts	16	16	7	5	3	3	

NOTE: This table presents a list of components of clinical definitions of NAS and NOWS that each expert included in his or her definition.

^a In utero substance exposure was not explicitly mentioned but was implied by the term “withdrawal,” which, by definition, requires exposure.

experts on both panels simply said “see above” or “same as above” when asked to provide a definition for the other syndrome (i.e., NOWS for the NAS panel and vice versa), for simplicity, we only show the NAS definitions for Panel A and the NOWS definitions for Panel B.

Table 4.1 also shows that the most common number of distinct components the experts mentioned in their definitions was two. Nearly all definitions mentioned clinical signs of withdrawal and in utero substance exposure. These results are consistent with the experts' ratings that also highlighted the necessity of including these two pieces of information in the definitions of NAS and Nows.

Clinical Signs of Withdrawal

Sixteen of the 17 definitions of NAS or Nows mentioned clinical signs and/or symptoms of withdrawal. One of the 16 experts (A06) clarified that “Clinical withdrawal symptoms may or may not develop.” As discussed below, Expert B03 did not include clinical signs in the definition and called for changing the name to include infants who are exposed but do not become symptomatic. Only Expert A02's definition stated that the clinical signs had to be “not explained by another etiology (e.g., sepsis, intracranial hemorrhage, hypocalcemia).”

However, experts differed on how severe these signs need to be to qualify for a NAS diagnosis, stating that these clinical signs require a “level of severity” that prolongs the birth hospitalization or leads to readmission to treat withdrawal (Expert A02). Experts used a variety of phrases like “observable signs of opioid specific withdrawal” (Expert B02), “any signs or symptoms” (Expert B05), “enough signs that intervention required” (Expert B06), and “positive findings of clinical signs” (Expert B07). In fact, five experts on Panel B and two on Panel A noted that to receive a diagnosis of Nows, **signs and symptoms have to be severe enough to require non-pharmacologic or pharmacologic interventions.** They used phrases like “clinical signs of withdrawal . . . needing assessment and care or intervention greater than regular newborn care” (Expert B01), “signs of opioid specific withdrawal that require medical intervention” (Expert B02), and “withdrawal . . . for which the infant is receiving assessment, non-pharmacologic care, and/or pharmacologic care” (Expert B09).*

Of the two experts who did not consider clinical signs to be a required component of the definitions, Expert A06 stated that “NAS is the physical state of being of an infant after birth. Clinical withdrawal symptoms may or may not develop,” and Expert B03 responded, “I would change Nows to something like ‘Neonatal Opioid Exposure Syndrome’ and have it more broadly reflect newborns with in-utero opioid exposure. Then it can include infants who exhibit physiologic symptoms of withdrawal as well as infants who do not.”

In both panels, experts used a variety of terms for the clinical presentation of NAS and Nows: “signs,” “symptoms,” and both “signs and symptoms.” Seven used “dysregulation” and “functional

* Interestingly, although these definitions all came from experts on Panel B, earlier when panelists rated what information was necessary to include in a clinical definition of NAS, only experts on the NAS panel (Panel A) rated the need to use medication to treat withdrawal as “necessary.”

impairment.” Experts A02 and A06 described clinical signs in terms of a “constellation” and “compilation,” whereas Experts B02 and B08 used “spectrum” or “range.”

In Utero Exposures

Sixteen of the 17 experts explicitly mentioned in utero substance exposure in their definitions (and the 17th expert [A08] implied it by starting the definition with “clinical signs of withdrawal”). Six of seven Panel A experts specified that NAS can result from multiple substances, and one expert’s definition referred only to “prenatal exposure to opioids.” In Panel B, seven of the nine definitions of NOWS mentioned only opioid exposure. The other two described opioid exposure “with or without other exposures” and stated that “polydrug exposure . . . must have opioid exposure to be called NOWS.” Only one definition on either panel specified that NAS and NOWS can result from prescription or illicit opioids, and experts were evenly divided as to whether the exposure had to be “known” or could be “known or reasonably suspected.” The few experts who mentioned **toxicology testing** in their definitions referred to it as **helpful but not necessary information** to establish in utero exposure.

Other Elements of the Definitions

Three experts (A01, B01, and B07) included a reference to **long-term follow-up** in their definitions of NAS and NOWS: “Overall management and follow-up of substance exposed neonates is similar no matter what the substance involved” (Expert A01); “The syndrome is transient or time limited and with time families can learn techniques to help these infants thrive at home” (Expert B01); and “Both exposed and exposed+symptomatic are dyads that require extra attention and follow-up” (Expert B07).

Distinguishing Between NAS and NOWS

Across both panels, experts were divided on which term (NAS, NOWS, both, or other) they prefer to use in clinical practice, and some noted inconsistent use of the terminology—including their own. Four selected NAS only, five selected NOWS only, six selected both, and two selected “other.” Of the two experts who selected “other,” Expert A01 stated: “People don’t really resonate with the word abstinence (which suggests that there is an element of choice on the part of the baby).” The same expert suggested that although NOWS implies that only opioid exposure is important, one advantage of this term is that it “strengthens the idea that only opioid withdrawal should be treated with opioid receptor agents.” The second expert who chose “other” noted that “either is acceptable” (Expert A02). Expert A05 stated they use “NAS in practice, but when I write [manuscripts] I increasing [sic] use NOWS.” Expert A08 noted that “We are using NOWS for the baby who is opioid exposed but NAS with polysubstance.”

Suggested Alternative Names for These Syndromes

Throughout the panel process, **six experts** (one from Panel A and five from Panel B) **suggested changing the names of the syndromes**. Five (Experts A01, B01, B02, B05, B10) found the term “abstinence” to be confusing and imprecise because “[babies] are not abstaining (a voluntary behavior); their umbilical cords are cut and their supply is stopped” (Expert B02).

Many of the suggested alternative names imply that an infant developed clinically apparent signs of withdrawal. Expert B10 elaborated: “If we are talking about only EXPOSURE—but not necessarily neurological signs of withdrawal—that is different. But to have withdrawal in the name—would need to have signs and symptoms/clinical manifestations of withdrawal.”

Some of the suggested alternatives were the following:

- neonatal withdrawal syndrome (Experts B01, B04, and B07)
- neonatal (or newborn) withdrawal (Expert B02)
- syndrome of dysregulation or dysregulation syndrome with subcategories according to type of exposure (syndrome of dysregulation-opioids) (Expert B06).

Expert B06 further elaborated,

Maybe we could rename NOWS to SOD or DOS; syndrome of dysregulation or dysregulation syndrome. Then we are defining it by signs of dysregulation, not by exposure. There could be “[SOD] due to opioids,” “[SOD] due to benzo,” “[SOD] due to mixed exposure which included opioids,” etc. . . . Because dysregulation is not specific to opioid withdrawal, but similar with other exposures as well. I also like that this approach allows for looking at how the symptoms [affect] the overall picture rather than in isolation.

Experts noted that the need to make a distinction between exposed infants who did and did not become symptomatic depends on the context. For instance, clear terminology that indicates if an infant is experiencing clinical signs of withdrawal is important for the purposes of care during the birth hospitalization. On the other hand, experts noted that for long-term follow-up and support of the mother-infant dyad, knowing whether the substance-exposed infant developed withdrawal is irrelevant. Consequently, some experts felt that the current terminology excludes exposed infants who do not become symptomatic. For example, Expert B03 proposed yet another alternative name for the syndrome that does not include “withdrawal”: “I would change NOWS to something like ‘Neonatal Opioid Exposure Syndrome,’ and have it more broadly reflect newborns with in utero opioid exposure. Then it can include infants who exhibit physiologic symptoms of withdrawal as well as infants who do not.” Expert A01 had a similar view: “I still object to the use of ‘NAS,’ which implies. . . that only symptomatic infants should be diagnosed. I believe that drug exposure in utero sets infants up for developmental /cognitive risk—partly because of social milieu—and that such infants deserve a different level of monitoring throughout childhood.” Expert B07 shared some of these concerns but had a different

suggestion: using coding practices to distinguish between exposed infants and infants with exposure who also develop withdrawal rather than changing the syndrome's name. This expert's rationale is that "[an] 'at-risk' neonate who doesn't have symptoms doesn't have the syndrome. To be precise, the exposure coding can remain separate from the coding for withdrawal syndrome. Some babies will have exposure, some will have exposure + withdrawal."

5. Discussion

Through two modified-Delphi online panels, we solicited expert opinion from 19 neonatologists, internists, nurse practitioners, and general pediatricians to inform the development of clinical definitions of NAS and NOWS for use at the bedside as part of the HHS initiative on NAS. Based on the analysis of numeric ratings of different pieces of information potentially needed to diagnose NAS or NOWS and thematic analysis of open-ended comments, we found that experts considered the presence of **clinical signs of withdrawal and in utero substance exposures** (whether to opioids with or without other substances, or only other substances) **to be necessary for inclusion in the definitions of both NAS and NOWS.**

Experts varied in their descriptions of which combinations of signs and symptoms are most typical of NAS and NOWS and tended to agree that infants experiencing withdrawal could present with any number of signs, in any number of combinations. Last, they considered the “domains of dysregulation” approach to be a potential alternative to assessing withdrawal by looking for individual signs, but felt that it could be difficult to implement and should be validated in practice.

The panelists generally agreed that the terms NAS and NOWS are used inconsistently and often interchangeably, but that NAS often is used when an infant has polysubstance exposure, and NOWS is used when the dominant in utero exposure is opioids (“with or without other substances”). The specification “with or without other substances” may be confusing when trying to distinguish between NOWS and NAS. Experts described NOWS as a “subcategory” and as a “single-exposure version” of NAS. **They considered maternal toxicology testing to be helpful but not necessary for the diagnosis of NAS and NOWS and agreed that infant toxicology test results are generally unnecessary for diagnosis.**

Given the diversity of opinions among leading national experts on opioid-exposed infants, it is not surprising that even after a moderated discussion round, in which panelists could engage in conversation with one another, their proposed definitions of NAS and NOWS varied in a few important ways. First, experts disagreed on whether severity of withdrawal mattered; that is, whether infants with any clinical sign of withdrawal should be considered to have NAS or NOWS, or only when these signs reached a threshold of needing intervention. Second, in the discussion round, they debated the utility of using the need for treatment as a criterion for diagnosing the infant with the syndrome, which is not typically done in other conditions. Finally, a sizable minority of experts called for renaming the syndrome but keeping clinically apparent withdrawal as part of the definition for use at the bedside. They suggested terms such as “neonatal withdrawal syndrome,” or “syndrome of dysregulation.”

Other experts expressed a different view that, from a perspective of policy and program planning, the development of clinical withdrawal has little to no bearing on long-term needs or outcomes of substance-affected dyads, and that mother-infant dyads with substance exposure require close follow-up and supports regardless of whether the infants develops signs of withdrawal. These experts suggested yet another name, “neonatal opioid exposure syndrome,” and called for distinguishing more clearly through administrative coding and terminology whether an infant is simply exposed to substances in utero or whether the infant is both exposed and showing signs of withdrawal.

Limitations

Although informative, our study has important limitations. First, these findings are limited to the perspective of experts who participated in our study. As is common in all expert panels conducted using key principles of the RAM, our results may not be representative of the perspectives of other clinicians from similar fields. Furthermore, because the aim of this study was to examine diagnostic criteria for neonatal withdrawal, we did not incorporate the family perspective on having an infant diagnosed with NAS or NOWS. Second, both panels were conducted online using the ExpertLens platform. Although the platform has been used in more than 30 studies that engaged a wide range of participants, including clinicians, some experts might have preferred to discuss their perspectives in person given the complexity of defining NAS and NOWS. Third, not all participants provided a numeric response to every question. Nonetheless, ExpertLens still allowed them to share their views by explaining their perspectives in open-text boxes below each rating question. Because our study used a mixed-methods approach to data collection and analysis, our thematic analysis of qualitative data also allowed us to capture the perspectives of those who preferred not to provide a numeric answer to a particular rating question. Finally, our study was designed to inform the definitions of NAS and NOWS, rather than generate them. As such, the results will be shared with the Federal NAS Steering Committee, including the Advisory Board for the HHS initiative on NAS, which will translate them into clinical definitions of NAS and NOWS.

Considerations for Developing Definitions of NAS and NOWS Based on ExpertLens Findings

Synthesizing findings from both panels, we highlight the following considerations for the Federal NAS Steering Committee as it develops standardized definitions for NAS and NOWS.

Consideration 1: Will the definitions focus on signs of withdrawal, refer to domains of infant neurobehavioral dysregulation, or both?

For example, depending on how these questions are answered, the clinical definitions could be written as follows:

- **NAS** is a syndrome that is characterized by the presence of any clinically apparent signs of withdrawal due to known or suspected in utero exposure to prescription or illicit substances.*
- **NOWS** is a subcategory of NAS characterized by clinically apparent signs of withdrawal due to known or suspected in utero exposure to prescription or illicit opioids, with or without exposure to other substances.

These brief definitions could be extended to also refer to the alternative domains-based approach, if desired, with elaboration and examples.

Consideration 2: Will the definitions list commonly observed signs as examples or simply refer to “signs of withdrawal” in general?

Although quantitative results show that experts generally agreed on the five signs that are most characteristic of NAS and NOWS, the experts stressed that it is important to assess the infant holistically and consider the signs in combination. Some commonly observed signs of withdrawal could be added to the definitions while noting that “signs could include, but are not limited to, the following examples.”

Consideration 3: Will the definitions include language around “any clinically apparent signs of withdrawal,” or will the infant’s signs need to meet a certain threshold of severity for a diagnosis of NAS or NOWS? How might that threshold be articulated, given the disagreement among ExpertLens participants as to whether interventions were required beyond standard non-pharmacologic care?

As mentioned above, the sample definitions refer simply to “any clinically apparent signs of withdrawal,” to align with the majority of ExpertLens participants.

Consideration 4: How will the definitions address the overlap between NAS and NOWS when an infant is exposed to opioids and other substances?

An additional piece of guidance to clinicians that could be incorporated into the definition of NOWS or could be part of implementation guidance if and when the field adopts a version of

* To destigmatize maternal substance use disorder, we avoid use of “maternal substance use” and instead focus on the definitions regarding the infant’s in utero exposures.

these standardized definitions could be as follows: “NOWS is used in place of NAS when the dominant prenatal exposure is opioids.”

Consideration 5: Given some of the experts’ suggestions to identify exposed infants who do not become symptomatic, will the syndromes be renamed?

An option for addressing the experts’ calls to indicate the exposure type *and* whether or not the infant developed withdrawal could be to combine NAS and NOWS into a single newly named entity, such as **“neonate with in utero substance exposure.”**

Then, two types of modifiers could be added to create subtypes of syndrome, as is done in other conditions (e.g., Type 1 or Type 2 diabetes mellitus; subtypes of multiple sclerosis, such as primary progressive or secondary progressive multiple sclerosis). These modifiers could specify (1) the dominant prenatal exposure (“opioid dominant” versus “nonopioid dominant”) and (2) whether or not the infant was experiencing signs of withdrawal (“with signs of withdrawal” versus “without signs of withdrawal”). An alternative phrasing would be “with neurobehavioral dysregulation” or without.

If desired, this second modifier could be made even more specific: “with clinically significant signs of withdrawal requiring more than the usual level of non-pharmacologic care provided to infants with in utero substance exposure.” However, there remains disagreement among experts about whether an infant who shows mild signs of dysregulation (e.g., mild hypertonia, irritability) but responds well to targeted non-pharmacologic interventions (e.g., swaddling, skin-to-skin care) should be diagnosed with NAS or NOWS. To provide more clarity on the infant’s clinical picture than simply noting the presence or absence of signs of withdrawal (or dysregulation), another option for the second modifier is: “with [mild/moderate/severe] signs of withdrawal.” Although out of scope for this work, when these definitions are being implemented in the field, it would be helpful to define the criteria for severity of withdrawal (mild, moderate, severe), which could lessen confusion around the subjective issue of whether infants who respond to standard non-pharmacologic measures should receive a diagnosis of NAS, NOWS, or another term.

To illustrate how this potential alternative approach to defining NAS and NOWS could work in practice, take an infant with in utero exposure to methadone and an SSRI, who shows moderate signs of withdrawal (dysregulation) that respond well to targeted non-pharmacologic measures. The infant would receive a diagnosis of **“neonate with in utero substance exposure-opioid dominant, with moderate signs of withdrawal [or neurobehavioral dysregulation].”** Although longer and more technical than simply “NAS” or “NOWS,” this approach is responsive to the experts’ desire for more nuance and precision in the definitions, both to help with short-term management immediately after birth and to signal what long-term supports and services may benefit the substance-exposed mother-infant dyad.

Next Steps

The results from the two ExpertLens panels will inform the work of the Federal NAS Steering Committee, convened by the Office of the Assistant Secretary of Health, which will develop recommendations for a standardized definition of NAS and NOWS, or for potential alternative terminology. Results from our study and the Steering Committee's proposed definition(s) will be presented at a national convening on substance-exposed dyads in March 2021, which will focus on the broader public health, programmatic, and policy implications of these definitions.

This study demonstrates a pressing need for the field to continue efforts to standardize terminology around substance-exposed dyads, develop precise clinical definitions that inform both short- and long-term support of the dyad, and provide clear guidance on their implementation at the bedside. The development of standardized definitions will complement and enhance important federal, state, and local efforts to improve dyadic care and short- and long-term outcomes of dyads affected by substance exposure.

Appendix A. Methodology

To identify a set of criteria for defining NAS and Nows, we conducted two modified-Delphi expert panels using key principles of the RAM, including the reliance on the expertise of clinicians who care for infants with the syndrome in their clinical practices, an iterative approach to data collection, panel size, and a previously validated approach to determining the existence of consensus.¹² We designed the data collection procedures in consultation with an Advisory Board of leading national experts on NAS and Nows who have been engaged with HHS’s initiative on NAS. The study design was informed by a literature review conducted by HHS and national experts prior to the start of this project²³ and by a pilot study we conducted with the members of the initiative’s Advisory Board. The data collection protocol was reviewed and approved by the RAND Human Subjects Protection Committee (study ID: 2020-0293) and later published in *JMIR: Research Protocols*.¹⁶

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Participant Recruitment and Sampling

In October 2020, we invited 22 national experts on NAS and Nows, including neonatologists, nurse practitioners, general pediatricians, as well as experts in internal medicine and psychiatry, to participate in our study. Twenty participants, two of whom were federal employees, responded to our invitation to participate. We used stratified randomization to assign participants to one of the two panels and balance them on such characteristics as professional background, geographic region, stated preference for using NAS or Nows in their clinical practice (if known), and employment by the federal government, which could affect experts’ perspectives on the definition of NAS and Nows. From the list of 20 experts who expressed interest in participating in our study, we assembled two panels of ten experts (one panel focused on NAS and the other on Nows) and invited them to participate in a three-round ExpertLens process (see below).

Of the 20 invited experts, 19 participated in at least one study round and 18 completed all three rounds. Of the 19 participants, 79 percent were female. More than three-fifths (63 percent) were neonatologists; roughly a third (32 percent) were general pediatricians or pediatric nurse practitioners; and one expert (5 percent) specialized in internal medicine. Approximately one-third of participants were from Southeast and Northeast (32 percent from each region); 16 percent were from the West and Northeast; and one participant (5 percent) was from Southwest (see Table A.1).

Table A.1. Participant Characteristics

	Total (N = 19)	Panel A (n = 9)	Panel B (n = 10)
Gender			
Male	4 (21%)	2 (11%)	2 (11%)
Female	15 (79%)	7 (37%)	8 (42%)
Specialty			
Neonatology	12 (63%)	5 (26%)	7 (37%)
Internal medicine	1 (5%)	1 (5%)	0 (0%)
General pediatrics	6 (32%)	3 (16%)	3 (16%)
Region			
West	3 (16%)	2 (11%)	1 (5%)
Southeast	6 (32%)	3 (16%)	3 (16%)
Midwest	3 (16%)	2 (11%)	1 (5%)
Northeast	6 (32%)	2 (11%)	4 (21%)
Southwest	1 (5%)	0 (0%)	1 (5%)

NOTE: This table describes key characteristics of our study participants (overall and by panel), including gender, specialty, and region.

Although experts were randomly assigned to a panel and both panels were balanced on the key participant characteristics, participation in the ExpertLens process differed between Panels A and B. In Panel A, not all experts participated in all three rounds. Panel B's experts were more active during the discussion round by posting 212 comments, as compared with 87 Round 2 comments posted by Panel A experts.

Data Collection

To solicit expert opinion, we conducted two expert panels that used similar data collection protocols. Panel A focused on the components of a clinical definition of NAS, and Panel B focused on Nows. Otherwise, the data collection protocols were the same.

To convene the panels, we used ExpertLens—a previously evaluated platform for conducting multi-round online modified-Delphi panels that allows participants to provide their initial responses to study questions and explain their ratings; review how their responses compare to those of other participants and anonymously discuss them using online discussion boards; and revise their responses based on group feedback and discussion, if needed.^{13–15}

Our panel process consisted of three rounds (see Figure 1.1). In Round One, which was open October 29–November 10, 2020, experts were asked to complete four different tasks. First, we showed them a clinical scenario featuring a full-term infant in the first week of life with no known medical conditions and asked them to rate and comment on pieces of information about the infant and the mother grouped into three broad categories, as shown in Table A.2.

Table A.2. Pieces of Information About Mother-Infant Dyads for Panelists to Consider in the ExpertLens Process

<p>Information about whether or not the infant had prenatal exposure to . . .</p> <ul style="list-style-type: none"> • opioids alone • opioids plus other substances (e.g., benzodiazepines, SSRIs, tobacco) • substances (e.g., benzodiazepines, SSRIs, tobacco) but did not have prenatal exposure to opioids
<p>Information about whether or not the infant . . .</p> <ul style="list-style-type: none"> • shows signs of opioid withdrawal • shows signs of withdrawal from substances other than opioids • shows dysregulation in at least one domain of infant development such as motor control (e.g., hypertonia, tremors) or responses to stimuli (e.g., exaggerated Moro reflex) • requires non-pharmacologic measures to manage withdrawal • requires medication to treat signs of withdrawal
<p>Information about whether or not . . .</p> <ul style="list-style-type: none"> • the infant's toxicology test is positive for opioids alone • the infant's toxicology test is positive for opioids plus other substances • the infant's toxicology test is positive for substances other than opioids and is negative for opioids • the mother's toxicology test is positive for opioids alone • the mother's toxicology test is positive for opioids plus other substances • the mother's toxicology test is positive for substances other than opioids and is negative for opioids

NOTE: This table lists pieces of information about mother-infant dyads that participants in both panels rated in terms of their necessity for clinical definitions of NAS and Nows.

Participants used 9-point Likert-type scales to rate each piece of information in terms of its **necessity** (e.g., How necessary is this information for distinguishing between infants *with and without NAS [Nows]*?) and **helpfulness** (e.g., How helpful is this information for distinguishing between infants *with and without NAS [Nows]*?). They also explained their ratings.

Second, we asked them to review ten common clinical signs and symptoms of NAS or Nows identified by Gomez-Pomar et al.,¹⁷ including crying, excessive sucking, alterations in feeding, feeding intolerance, increased muscle tone, loose or watery stools, nasal stuffiness, respiratory rate >60/min, fragmented sleep, and tremors. We also asked them to identify the most characteristic signs by answering the question “How characteristic is this sign of NAS (or Nows)?” using a 9-point Likert scale. In addition to explaining their ratings, we asked participants to add any signs that might be missing from the list of ten and identify any combinations of signs that infants with NAS or Nows typically present.

Third, we asked participants to provide feedback on an alternative approach to assessing infant withdrawal that focuses on dysregulation in four domains of infant functioning, rather than assessing withdrawal signs and symptoms individually,¹⁸⁻²⁰ to distinguish between infants with and without NAS or Nows (see Table A.3).

Table A.3. Four Domains of Dysfunction

Regulated	Dysregulated
Domain 1: autonomic control	
Occasional yawning, brief color changes (e.g., slight mottling) or intermittent tachypnea, stable body temperature	Frequent yawning, sneezing, sweating, hiccupping, tachypnea, vomiting, excessive gas, diarrhea; color changes that resolve slowly (e.g., duskiness around the mouth or eyes); elevated temperature
Domain 2: motor control/tone	
Appropriate tone, generally smooth movements	Alterations in tone (hyper/hypotonia or fluctuating tone) at rest or with handling, uncontrolled or jerky movements, tremors, excessive movement in all states ^a
Domain 3: state control and attention	
Restful sleep, easy to console, moves easily between sleep and awake states	Cries frequently, irritable, difficult to console; inability to demonstrate a range of states ^a or to transition smoothly between states (e.g., goes from sleeping to crying unexpectedly without passing through in-between states); fragmented sleep (i.e., frequent awakenings during sleep); difficulty remaining alert
Domain 4: sensory reactivity	
Appropriate response to stimuli (visual, auditory, tactile). Appropriate responses to <i>intrusive or poorly timed stimuli</i> (e.g., loud noises, bright lights, being handled too quickly) include aversion or fussiness	Changes in tone, signs of stress, or fussiness with <i>appropriate stimuli</i> , aversion, or minimal/no response to <i>appropriate stimuli</i> (e.g., soft noises, gentle touch)

NOTES: This table shows an alternative approach to assessing infant withdrawal that focused on infant neurobehavior in four domains of functioning. The table provides brief descriptions of how infants present when they are regulated versus dysregulated within each domain.

^a Infants normally cycle through six states or levels of alertness: deep sleep, light sleep, drowsiness, quiet alertness, fussiness, and screaming.

Participants used 9-point Likert-type scales to answer the following questions:

- How different is this approach from the way withdrawal signs are currently assessed in clinical practice? (1 = not at all different; 9 = very different)
- How useful is this approach for assessing opioid withdrawal in an infant? (1 = not at all useful; 9 = very useful)
- How feasible would it be to use this approach to distinguish between infants with and without NAS (NOWS)? (1= not at all feasible; 9 = very feasible)

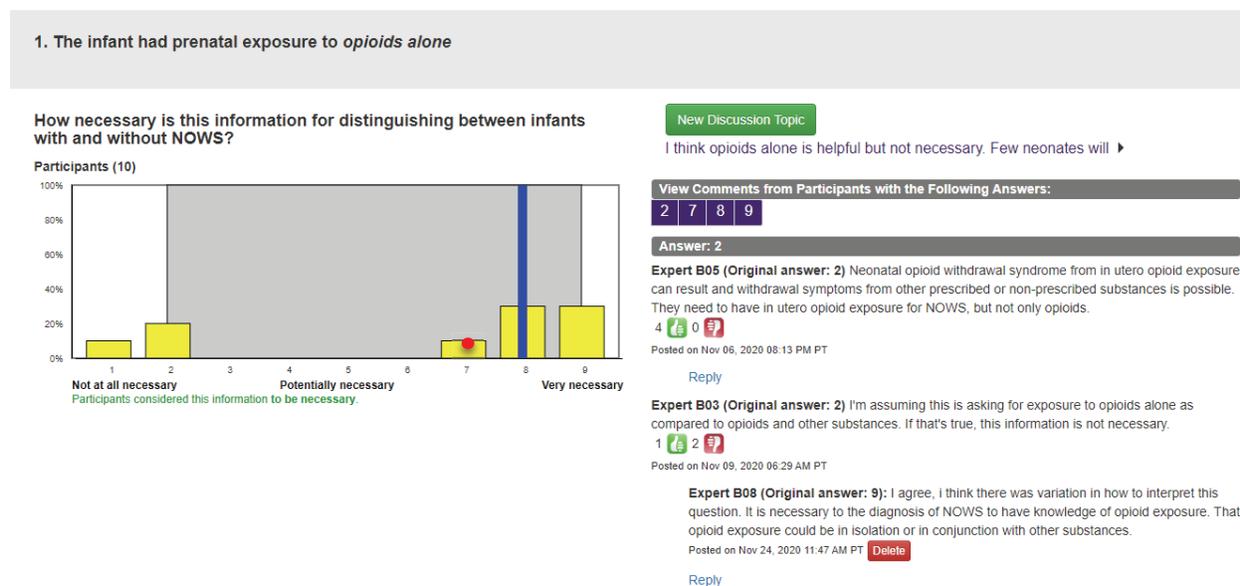
We also asked participants to comment on potential advantages and disadvantages of using this alternative approach to help define NAS or NOWS.

Finally, we asked participants to select the term that they prefer to use in clinical practice (e.g., NAS, NOWS, or no preference) and to use open-text boxes to provide their own preferred clinical definitions of NAS and NOWS for use at the bedside. We added this open-ended question as a way to validate our numeric findings.

In Round Two, which was open November 16–November 30, 2020, participants received an automatically generated personalized report showing how their individual responses to the rating

questions compared with the responses of other participants. The report includes a series of charts showing the distribution of all responses to a given rating question, a group median response, an interquartile range, and a statement stating if the group reached agreement, which was calculated based on the RAM manual guidance¹² (see Figure A.1). In addition to reviewing numeric results, participants saw qualitative comments made in Round One and discussed the results using an asynchronous and anonymous discussion board moderated by L.J.F. and D.K. using previously published guidance for ExpertLens discussion facilitators.²⁴ To encourage discussion participation, participants received discussion digests via email every other day during this round.

Figure A.1. Round Two Screenshot



NOTES: This figure is a screenshot of Round Two—feedback and discussion round. The bar chart represents a distribution of participants' Round One responses. The blue line indicates a group median. The red dot indicates a participant's own response. The statement presented below the chart informs participants about the group decision. In this particular chart, participants considered that the information about the infant's in utero exposure to opioids alone to be necessary for distinguishing between infants with and without NOWS. The median was 8 on a 9-point scale. However, the participant's own response was 7, which is below the median value. Individual participants' comments explain their Round One ratings and Round Two comments.

In Round Three, which was open December 3–December 22, 2020, participants had the opportunity to revise their Round One responses based on Round Two feedback and discussion. In response to comments made during Rounds One and Two, we made one change to our data collection protocol for Round Three. Participants expressed confusion about the intent of the “**necessary**” and “**helpful**” rating criteria we used in the first task in Round One, so in Round Three, we combined these two rating criteria and clarified that its purpose was to identify pieces of information **that are necessary to include in a clinical definition of NAS or NOWS that**

can be used at the bedside. The revised rating question read: “How **necessary** is it to include this information in a clinical definition of NOWS that can be used at the bedside?” In providing additional guidance to participants, we clarified that

- scores of 1 to 3 indicate that this information should not be included in the definition
- scores of 4 to 6 indicate that this information is helpful to know about a dyad but is not required for the definition
- scores of 7 to 9 indicate that this information should be included in the definition.

Analysis

As in other ExpertLens panels, we used simple descriptive statistics, including frequency distributions, medians, and interquartile ranges, and the RAM Manual’s approach to determining consensus in expert panels to analyze Round One and Round Three rating data.¹² The RAM approach looks at the distribution of responses across the response tertiles on the 9-point scale (e.g., scores 1 to 3, 4 to 6, and 7 to 9) to identify the existence of agreement or disagreement in the distribution of responses to a given question. Disagreement exists when more than a third of responses are in the upper and the lower tertiles. If there is no disagreement, a median determines the final group decision. A median below 3.5 indicates a negative decision (meaning that a piece of information is not necessary for a definition of NAS or NOWS or a clinical sign is not characteristic of NAS or NOWS), whereas a median of 6.5 and above indicates a positive group decision (meaning that a piece of information is necessary for a definition of NAS or NOWS or a clinical sign is characteristic of NAS or NOWS). Medians between 3.5 and 6.5 illustrate a range of uncertain responses (meaning that a piece of information is helpful but not required for a definition of NAS or NOWS or a clinical sign is only potentially characteristic of NAS or NOWS).

We analyzed the data from both panels separately. As is common in RAM panels, we used the final rating results to identify pieces of information about the mother-infant dyad that are necessary, potentially necessary (meaning helpful but not required), and not necessary to include in the definitions of NAS or NOWS. We then looked at these results to identify pieces of information that are necessary for both diagnoses. We used a similar approach to compare and contrast the responses to all other rating questions provided by the participants in both panels.

To contextualize our quantitative results and to synthesize all responses to open-ended questions, we thematically analyzed all qualitative data that we collected, including Round One and Three rationale comments, Round Two discussion comments, and suggested definitions of NAS and NOWS in Rounds One and Three. These analyses helped us not only better understand participants’ preferred definitions of NAS and NOWS and validate our rating results, but also explain their ratings, identify why there was disagreement among them, and illustrate why participants rated some items high and others low.

As in previous ExpertLens panels,^{21, 22, 25} we sorted all Round One and Three comments for a given question by the numeric ratings to which they correspond, grouped all discussion comments by the definitional component, and collated all responses to the open-ended questions. D.K. and L.J.F. reviewed and coded all comments inductively to identify recurrent themes. To ensure coding consistency and accuracy of the interpretation of comments, they reviewed each other's coding and discussed any disagreements until consensus was reached. Because of a small number of study participants, all qualitative data were coded in Microsoft Excel.

Appendix B. Final Rating Results

Table B.1. Final Rating Results for Round Three

Rating Items	NAS Panel					NOWS Panel				
	N	Q1	Median	Q3	Decision	N	Q1	Median	Q3	Decision
Information about prenatal exposures										
The infant had prenatal exposure to opioids alone.	8	6.5	7.5	8	Necessary	10	4	6.5	8	Necessary
The infant had prenatal exposure to opioids plus other substances (e.g., benzodiazepines, SSRIs, tobacco).	8	3.5	6	6.5	Potentially necessary	10	2	5	7	Disagreement
The infant had prenatal exposure to substances (e.g., benzodiazepines, SSRIs, tobacco) but did not have prenatal exposure to opioids.	8	6	8	8	Necessary	10	9	9	9	Necessary
Information about infant signs of withdrawal										
The infant shows signs of opioid withdrawal.	8	9	9	9	Necessary	10	8	9	9	Necessary
The infant shows signs of withdrawal from substances other than opioids.	8	3.5	5	6	Potentially necessary	9	3	3	5	Unnecessary
The infant shows dysregulation in at least one domain of infant development such as motor control (e.g., hypertonia, tremors) or responses to stimuli (e.g., exaggerated Moro reflex in response to light touch).	8	5	6	6.5	Potentially necessary	9	5	5	7	Potentially necessary
The infant requires non-pharmacologic measures to manage withdrawal.	8	3	5	7	Potentially necessary	9	3	4	5	Potentially necessary
The infant requires medication to treat signs of withdrawal.	8	3.5	6.5	7.5	Necessary	8	1	3	7	Unnecessary
Information about toxicology test results										
The infant's toxicology test is positive for opioids alone.	7	3	3	6	Unnecessary	9	2	3	4	Unnecessary
The infant's toxicology test is positive for opioids plus other substances.	8	2.5	3	5	Unnecessary	10	3	3	5	Unnecessary
The infant's toxicology test is positive for substances other than opioids and is negative for opioids.	7	2	2	5.5	Unnecessary	9	3	4	6	Potentially necessary

Rating Items	NAS Panel					NOWS Panel				
	N	Q1	Median	Q3	Decision	N	Q1	Median	Q3	Decision
The mother's toxicology test is positive for opioids alone.	6	4	7	7	Necessary	9	2	4	6	Potentially necessary
The mother's toxicology test is positive for opioids plus other substances.	8	4	5	6.5	Potentially necessary	9	2	5	5	Potentially necessary
The mother's toxicology test is positive for substances other than opioids and is negative for opioids.	6	5	5	6	Potentially necessary	9	3	5	6	Potentially necessary
Clinical manifestations of withdrawal										
Crying (excessive or continuous)	8	7	8	8	Characteristic	10	7	8	9	Characteristic
Excessive sucking	8	6	7	7.5	Characteristic	9	3	7	7	Disagreement
Alterations in feeding (e.g., hyperphagia, poor feeding)	8	6.5	7	7	Characteristic	10	7	7	8	Characteristic
Feeding intolerance (e.g., regurgitation, projectile vomiting)	8	6	6.5	7	Characteristic	10	4	5	6	Potentially characteristic
Increased muscle tone	7	7	7	7.5	Characteristic	10	7	8	8	Characteristic
Loose or watery stools	8	5.5	6.5	7	Characteristic	9	5	6	7	Potentially characteristic
Nasal stuffiness	7	3.5	5	5.5	Potentially characteristic	9	2	3	3	Uncharacteristic
Respiratory rate >60/min	8	4	5	6	Potentially characteristic	8	5	5	6	Potentially characteristic
Fragmented sleep (<1 hour after feeding or <2 or 3 hours after feeding)	7	8	8	8	Characteristic	9	6	8	8	Characteristic
Tremors (disturbed or undisturbed)	8	7	8	8.5	Characteristic	9	7	7	8	Characteristic
Dysregulation in domains of infant functioning										
How different is this approach from the way withdrawal signs are currently assessed in clinical practice?	7	5	6	6	Potentially different	10	3	4.5	5	Potentially different
How useful is this approach for assessing opioid withdrawal in an infant?	8	6.5	7	7.5	Useful	9	4	6	8	Potentially useful
How feasible would it be to use this approach to distinguish between infants with and without NAS?	6	5	5.5	7	Potentially feasible	8	2.5	4	6.5	Potentially feasible

NOTES: This table presents final (Round Three) ratings from both panels. The order of items follows the order of questions in the ExpertLens process. Column N lists a number of participants providing a response to each numeric question. Missing responses were not imputed. Q1 presents the value of the first quartile (25th percentile), and Q3 presents the value of the third quartile (75th percentile). Participants rated each item on a scale from 1 to 9, with 1 corresponding to "not at all" necessary, characteristic, different, useful, or feasible and 9 corresponding to "very" necessary, characteristic, different, useful, or feasible (depending on the item). Scores in the middle ranges corresponded to "potentially" necessary, characteristic, etc. The decision columns list the final panel decision for each question as determined using the RAM's approach to determining consensus.

Appendix C. Proposed Definitions of NAS and NOWS

Table C.1. ExpertLens Participants' Proposed Definitions of NAS and NOWS

Panel A Expert	Definition of NAS
A01	Neonatal symptoms related to cessation of prenatal exposure to opioids. (Only opioid withdrawal should be treated with opioid agonists, but non-pharmacologic measures may be helpful to babies exposed to other substances, and overall management and followup of substance exposed neonates is similar no matter what the substance involved.) Opioid use in the neonatal period can also lead to withdrawal. I still object to the use of "NAS," which implies that only opioid use is significant, and that only symptomatic infants should be diagnosed. I believe that drug exposure in utero sets infants up for developmental/cognitive risk—partly because of social milieu—and that such infants deserve a different level of monitoring throughout childhood.
A02	<p>A clinical diagnosis of NAS requires each of the following 3 elements:</p> <ul style="list-style-type: none"> • Presence of a constellation of clinical signs consistent with NAS that is not explained by another etiology (e.g., sepsis, intracranial hemorrhage, hypocalcemia, or a non-opioid drug or substance) • A history of recent maternal use of prescription or illicit opioid-containing drugs (e.g., methadone, buprenorphine, heroin, oxycodone, hydrocodone), benzodiazepines, or barbiturates and/or laboratory confirmation of recent maternal use and/or fetal exposure to such drugs (e.g., a positive maternal or neonatal urine drug screen for opioids) • A level of severity of signs that results in: <ul style="list-style-type: none"> ○ Prolongation of the initial neonatal hospitalization beyond 3 days for the purpose of providing palliative non-pharmacologic care and/or pharmacologic treatment for withdrawal; or <ul style="list-style-type: none"> ▪ Readmission to a hospital at or before 14 days of age for the purpose of treating signs of withdrawal. <p>(there may be very rare instances where there is no history or laboratory confirmation of exposure, but the clinical syndrome, severity, and treatment needs lead to assignment of a diagnosis as one of exclusion—generally there are other maternal historical factors that make exposure suspect.)</p>
A03	NAS: in utero exposure to any substance plus symptoms of withdrawal. In the past, NAS and NOWS have been used interchangeably → my sense is the field is moving to NOWS as withdrawal following in utero exposure to opioids (with or without other substances).
A05	Signs of withdrawal paired with known or highly suspected in utero exposure to opioids, with potential for worsening of symptoms with other substances
A06	NAS is a diagnosis based upon 2 different known factors. First, in infants with known intrauterine substance exposure, NAS is the physical state of being of an infant after birth. Clinical withdrawal symptoms may or may not develop. Second, in infants with or without known intrauterine substance exposure, NAS is a compilation of clinical symptoms and physical exam findings diagnosed within the first 5–7 days after birth. Clinical symptoms most commonly include feeding dysregulation, hyperresponsiveness to stimulation, and difficulty sleeping or settling, but may include many others. Common physical exam findings include elevated tone, excessive suck response, and exaggerated reflexes, but may include others. Additional diagnostic findings that are useful but not necessary to diagnose NAS include known exposures to intrauterine substances and response of withdrawal symptoms to non-pharmacologic care.
A07	Signs and symptoms of neonatal withdrawal from prenatal exposure to opioids with or without the addition of other substances.

Panel A Expert		Definition of NAS
A08		Clinical signs of withdrawal with dysregulation that impacts infant’s wellbeing with excessive weight loss, inability to sleep > 1 hour, or fussiness that is not consolable
A09		Withdrawal syndrome due to in utero exposure to opioids OR opioids + other substances that presents as infant neurobehavioral regulation impacting the neuro, GI, autonomic systems.
Panel B Expert		Definition of NOWS
B01		Neonatal Opioid Withdrawal Syndrome (NOWS) is a sequence of events that starts with maternal/in utero fetal exposure to narcotics of sufficient amount or duration that leads to clinical signs of withdrawal in the newborn ranging from mild to severe functional impairment or dysregulation needing assessment and care or intervention greater than regular newborn care. Assessment tools are used to determine the timing and degree of intervention needed (non-pharmacologic and/or pharmacologic treatment). The syndrome is transient or time limited and with time families can learn techniques to help these infants thrive at home.
B02		Observable signs of opioid specific withdrawal that require medical intervention.
B03		I would change NOWS to something like “Neonatal Opioid Exposure Syndrome,” and have it more broadly reflect newborns with in-utero opioid exposure. Then it can include infants who exhibit physiologic symptoms of withdrawal as well as infants who do not.
B05		An infant with known/suspected opioid exposure in utero who has any signs or symptoms of withdrawal.
B06		Known exposure to opioids (either from maternal report, or + drug screen in mom or baby), with enough signs of withdrawal that an interventions is required (often non-pharmacologic, or prolonged hospital observation beyond the nl observation period for the exposure, could be medical tx) in order for the baby to thrive enough in the hospital to be released with the family.
B07		I would respond that both exposed and exposed + symptomatic are dyads that require extra attention and followup. However, an “at-risk” neonate who doesn’t have symptoms doesn’t have the syndrome. To be precise, the exposure coding can remain separate from the coding for withdrawal syndrome. Some babies will have exposure, some will have exposure + withdrawal. The bedside definition should include: positive findings of clinical signs of dysregulation and/or opioid withdrawal (would include signs such as sneezing and loose stools) AND known or reasonably suspected intrauterine opioid exposure of sufficient duration.
B08		Spectrum of withdrawal symptoms in the setting of known intrauterine opioid exposure (with or without other exposures). Withdrawal symptoms may range from mildly abnormal physical exam findings to severe functional impairment.
B09		Neonatal withdrawal after exposure to antenatal opioids for which the infant is receiving assessment, non-pharmacologic care, and/or pharmacologic care. May include polydrug exposure but must have opioid exposure to be called NOWS.
B10		In a baby with a history of a mother with opioid use, maternal + tox or baby + for opioids—ALTHOUGH NOT necessary Showing signs of withdrawal such as tremors, crying irritability, poor sleep and feeding (as well as the other signs on the Finnegan) Responds to non-pharmacologic or medical therapy Not usually present right at birth. If we are talking about only EXPOSURE-but not necessarily neurological signs of withdrawal—that is different. But to have withdrawal in the name-would needs to have signs and symptoms/clinical manifestations of withdrawal from Opioids with the history and documentation of opioid exposure in utero.

NOTES: This table presents verbatim definitions of NAS and NOWS as written by 17 experts. We list NAS definitions provided by Panel A participants and NOWS definitions provided by Panel B participants, because each participant’s definitions of NAS and NOWS were nearly identical. No experts materially changed their definitions between Rounds One and Three. If a participant provided a definition in both rounds, we include his or her Round Three response. Three participants (Experts A02, A08, and B05) provided a definition in Round One only, which we have included in the above table.

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