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Standardizing the Clinical Definition of Opioid Withdrawal in the Neonate

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OBJECTIVE To Address challenges in clinical care, quality improvement, research, and public policy for prenatally opioid-exposed neonates by standardizing the clinical definition of opioid withdrawal.

STUDY design Between October and December 2020, we conducted two modified-Delphi panels using ExpertLens™, a virtual platform for performing iterative expert engagement panels. Twenty clinical experts specializing in care for the substance-exposed mother-neonate dyad explored the necessity of key evidence-based clinical elements in defining opioid withdrawal in the neonate leading to a diagnosis of Neonatal Abstinence Syndrome (NAS)/Neonatal Opioid Withdrawal Syndrome (NOWS). Expert consensus was assessed using descriptive statistics, the RAND/UCLA Appropriateness Method, and thematic analysis of participants' comments.

RESULTS Expert panels concluded the following were required for diagnosis - *in utero* exposure (known by history, not necessarily by toxicology) to opioids with or without the presence of other psychotropic substances, and the presence of at least two of the most common clinical signs characteristic of withdrawal (excessive/continuous crying, fragmented sleep, tremors, increased muscle tone, gastrointestinal dysfunction).

CONCLUSIONS Results indicate that both a known history of *in utero* opioid exposure and a distinct set of withdrawal signs are necessary to standardize/harmonize a definition of neonatal withdrawal. Implementation of a standardized definition requires both patient engagement and a mother-neonate dyadic approach mindful of program and policy implications.

The rising incidence of opioid use disorder (OUD) across the US has significantly affected pregnant people with a corresponding increase in neonatal abstinence syndrome (NAS) in their infants.^{1,2} Although research indicates NAS is primarily attributed to in utero opioid exposure, the use of other psychotropic substances can also affect the incidence and severity of withdrawal.³⁻⁹ NAS has been described from a neurodevelopmental perspective as dysregulation in four dimensional and interactional neurobehavioral domains: autonomic control, attention/state control, motor/tone control and sensory processing/modulation.¹⁰⁻¹²

Between 2013 and 2016, the US Food and Drug Administration (FDA) introduced new terminology designating neonatal opioid withdrawal syndrome (NOWS) as the specific neonatal withdrawal from opioids.¹³⁻¹⁴ The use of this new terminology has become more widespread and is considered a subset of NAS.¹⁵⁻¹⁶ In 2018, the Department of Health and Human Services (HHS) collaborated with leading experts in maternal-child health and identified a fundamental key knowledge gap in the care of the mother-neonate dyad exposed to psychotropic substances - the lack of a standard clinical definition for withdrawal following in utero opioid exposure.¹⁷

The lack of a standardized definition for opioid withdrawal in the neonate impedes individualized clinical care (e.g., misdiagnosis, over or under or mistimed treatment, punitive response by legal and/or child welfare systems) and the larger health care system approach to care for this population (e.g., lack of evidence-based protocols for identification and/or treatment). Further, the absence of a standardized definition hinders scientific advances in the field of understanding, preventing, and treating neonatal opioid withdrawal because of variability in clinical trial entry criteria, outcome measures, NAS incidence, prevalence, and severity estimates and measurement of short and long-term effects.

To develop this clinical definition of neonatal opioid withdrawal, HHS partnered with national experts using modified-Delphi methodologies, such as the RAND/UCLA Appropriateness Method (RAM).¹⁸ In the absence of consensus guidelines or evidence-based criteria, this method permits expert input in assessing clinical appropriateness and validity. This two-step process initially included a focused literature review examining how NAS has been defined in clinical studies followed by exploring how to standardize the clinical components for the definition which is the focus of the present study.¹⁹

METHODS

Prior to conducting the focused literature review and modified-Delphi approach, HHS assembled an advisory board to inform design, development, and step-by-step evaluation of the study. The board included six experts in maternal-child health specializing in clinical care, research, and NAS policy. Board members determined the study's scope, focus, aims, intent, and content. At study completion, members systematically assessed quantitative and qualitative findings and developed recommendations for a standard clinical definition of neonatal opioid withdrawal.

In 2020, HHS contracted with the RAND Corporation to apply the modified-Delphi methodology using a virtual platform called ExpertLensTM to explore expert agreement/disagreement on key clinical elements used in the literature to define NAS and NOWS.²⁰⁻²³ Among other use cases, the modified-Delphi method previously has been used to develop recommendations on treatment approaches for pregnant women with OUD and their neonates.²⁴⁻²⁵ In the current study, expert panels focused on prenatal exposure to opioids $\pm$ other psychotropic substances, clinical signs of withdrawal, and toxicology testing. The framework centered on term neonates (>37 weeks gestation) with no known medical conditions being

evaluated for withdrawal in the first week of life. Our goal was to develop a bedside definition of opioid withdrawal distinct from other diagnoses (e.g., hypoglycemia) that may have similar clinical signs. For this study, neonatal withdrawal focused on opioids with/without other substances. The RAND Human Subjects Protection Committee approved the study (Study ID: 2020-0293) and the research team developed the modified-Delphi protocol before study launch; the protocol is summarized below.²⁶

Twenty experts were recruited with an emphasis on clinical care of neonates with opioid withdrawal, diverse professional disciplines, and geographic diversity. Two expert panels of 10 participants (9 non-federal) each were then constructed, with a goal of ensuring that at least 9 experts complete the modified-Delphi process as is standard for RAM panels¹⁸. This panel size helped ensure participant diversity in terms of their areas of expertise as suggested by RAM guidance, while enabling them to interact meaningfully during the online discussion. Moreover, this number of participants met specific requirements on the total number of participants for each panel (maximum 9 non-federal participants permitted for compliance with the Paperwork Reduction Act - PRA). Panelists' backgrounds included neonatology, general pediatrics, internal medicine, nursing, and clinical pharmacology. Panel A focused on elements key to a clinical definition of NAS and panel B on a clinical definition of NOWS. The principal distinction between panels A and B was the substitution of the term NOWS for NAS. Both terms were integrated into the study to explore any differences in definitions related to terminology. Stratified randomization was used to assign participants to one of the two expert panels. Balance was achieved between panels by assigning participants based on professional background and discipline, institutional location, and preferences for using NAS vs. NOWS (if disclosed).

Data were collected virtually between October and December 2020 during two rating rounds and one round of moderated, anonymous, asynchronous discussion. Rating was performed by experts using a 9-point Likert-type scale to answer structured questions focusing on clinical elements used in the literature to define NAS and NOWS. In round 1, panelists provided input on the assessment of neonatal substance withdrawal including the need for *in utero* opioid exposure ($\pm$ other psychotropic substances) by clinical history and/or maternal/neonatal toxicology, the most common clinical signs of withdrawal (less common clinical signs were not included), and neurodevelopmental theory on dysregulation in neonatal functioning (Table I).^{10-12, 27} In round 2, a moderated discussion centered on areas of disagreement and clarity.²⁸ Panelists received feedback on how their responses compared with those of other participant responses in Round 1 and if the group reached agreement for each question.¹⁸ Round 3 offered the opportunity for the research team to modify how the questions were asked to address any inconsistencies identified during Round 2 and allowed panelists to review and revise their responses.

For enhanced clarity, two round 1 questions asking how “necessary” and “sufficient” experts considered the referenced clinical information were reorganized into one round 3 question exploring necessity of information for a clinical definition of NAS and NOWS, with 1 = not at all necessary and 9 = very necessary. Scores of 1-3 indicated the information should not be included; 4-6 indicated the information was helpful but not required; and 7-9 indicated information that should be included in the definitions.

Medians and inter-quartile ranges were calculated from the quantitative rating data and the qualitative data were analyzed thematically. Consensus was determined automatically after each rating round.¹⁸ Qualitative data were analyzed thematically to provide additional

explanation of why participants considered only some information necessary for inclusion into the clinical definition of withdrawal²⁶.

To elicit feedback from the broader clinical and research communities, these data and results together with a proposed clinical definition for neonatal opioid withdrawal were shared and discussed at a national HHS convening in March 2021. Discussants included 75 experts in obstetrics/gynecology, primary care, developmental pediatrics, hospital medicine, neonatology, family medicine, psychiatry, mental/behavioral health, internal medicine, public health, social work, and bioethics.

RESULTS

Of the 20 ExpertLens panelists, 18 completed all three rounds and 19 completed at least one round. Quantitative analysis indicated expert agreement on the need for specific substances to which the neonate was exposed be included in the definition (Table II). Overall, it was apparent that exposure to opioids with or without other psychotropic substances is necessary to establish opioid withdrawal in the neonate. In contrast to exposure history, toxicology testing for the mother and neonate was not deemed to be essential for the diagnosis of NAS or NOWS but was considered helpful for a better understanding of the clinical presentation (Table II). Collectively, experts indicated that known history was more important than toxicology. If a comprehensive history is not available, then an alternative approach could include toxicology testing (mother following informed consent and/or neonate) that is positive for opioids (with/without other psychotropic drugs). Experts also agreed that NAS and NOWS are used inconsistently and interchangeably when in utero opioid exposure is present. Moreover, they indicated that NAS is often used when a neonate has polysubstance exposure and NOWS when the predominant prenatal exposure is opioids. Several experts suggested renaming the syndrome to be more precise about the type of in utero exposure in conjunction with the development of

clinical signs of withdrawal. Their answers to rating questions, open-ended comments, and proposed definitions of NAS and NOWS demonstrated varied opinions about several aspects of these clinical definitions. , The terminology currently being used was considered unclear even after discussing their perspectives with other expert panelists.

In addition to in utero exposures, experts agreed that the presence of clinical signs of withdrawal are necessary for a definition of NAS/NOWS (Table II). Although the NAS panel considered pharmacologic treatment an important component of the definition, the NOWS panel did not. Though reasons for this disagreement were not readily apparent, experts clearly agreed on five of the most common signs that are characteristic of both NAS and NOWS (excessive crying, fragmented sleep, tremors, increased muscle tone, alterations in feeding) (Table II). Three other signs were deemed characteristic of NAS only (excessive sucking, feeding intolerance, loose/watery stools); this was an unexpected distinction between the NAS and NOWS panels. Although feeding intolerance and loose/watery stools demonstrated lower median scores across both NAS and NOWS panels, they were considered to be clinically pertinent signs of withdrawal and were included in an overarching category created to denote gastrointestinal dysfunction (e.g., altered feeding – hyperphagia or poor feeding, loose/watery stools, feeding intolerance – vomiting or spitting up). In contrast, some experts indicated that individual clinical signs of withdrawal and the time they take to develop after birth should not be included because NAS/NOWS has variable expression and these signs can be non-specific and occur secondary to other causes. Multiple signs seen concurrently increased confidence that NAS/NOWS had developed.

When assessing an alternative approach to evaluating neonatal withdrawal using neurobehavioral domains of dysregulation (autonomic control, attention/state control, motor/tone

control, sensory processing/modulation) experts in both panels agreed that the approach is feasible and either useful or potentially useful [data not shown]. Additionally, both panels indicated the need for further research to evaluate this alternative approach for neonate assessment.

At the national convening, several important themes arose from discussions of key considerations for standardizing the clinical definition of neonatal opioid withdrawal: a clear delineation of definition use case including how it should and should not be used, requirement of two clinical signs vs. one to balance specificity of withdrawal with other neonatal conditions while remaining sensitive to milder presentations of withdrawal, and thoughtful consideration on avoiding unintended consequences, stigmatization, and broader implications of the clinical definition on the dyad and family. Accordingly, foundational principles were created to specify uses for the definition (Table III). These principles are grounded in both evidence-based medicine and bioethics, prioritize the dyad, and avoid mis-utilization of the clinical definition. Specifically, the definition of opioid withdrawal in the neonate is for clinical, research, and public health purposes only and should not be misconstrued as evidence of harm or used to prosecute, punish, or to remove neonates from parental custody.

Taken together with the ExpertLens findings, recommended clinical criteria for the diagnosis of neonatal opioid withdrawal consists of in utero exposure (known by history, not necessarily by toxicology) to opioids $\pm$ other psychotropic substances, and presence of at least two of the most common clinical signs characteristic of withdrawal (excessive/continuous crying, fragmented sleep, tremors, increased muscle tone, gastrointestinal dysfunction). (Table IV) Opioid withdrawal, recognized as a continuum of variable expression in neonates and not limited only to neonates who require pharmacotherapy, assumes that alternative etiologies (e.g.,

hypoglycemia) have been eliminated. Although not intended to determine severity, the definition emphasizes inclusivity of even subtle clinical presentations of withdrawal including those requiring only non-pharmacologic supportive therapies.

DISCUSSION

Using modified-Delphi methodology implemented via the ExpertLens process, we developed a standardized definition of opioid withdrawal in neonates. The overarching goal of this study focused on identifying key clinical elements considered essential to bedside diagnostic criteria, which are practical and broadly applicable to clinical practice. Findings from a focused literature review) suggested that most studies utilized subjective NAS scoring/assessment tools and administrative coding as key elements to define opioid withdrawal in the neonate, with not all studies citing in utero opioid-exposure as an inclusion criterion.¹⁹ Inconsistencies in diagnostic criteria and the way NAS has been historically defined in clinical studies of mother-neonate dyads supports the need for a standardized definition. By examining expert agreement and disagreement on clinical elements that have typically defined NAS and NOWS, this study addresses a historical gap in the definition of opioid withdrawal in neonates.

Principal informants in this discussion included experts caring for the substance-exposed mother-neonate dyad with findings relevant to both clinical care and clinical research. Emphasis was placed on clinical elements completely independent of scoring/assessment tools, non-pharmacologic and pharmacologic care, and administrative coding. Elements demonstrated as necessary in this study included in utero opioid exposure with/without other psychotropic substances and at least 2 of the 5 most common clinical signs characteristic of opioid withdrawal in the neonate. This proposed definition may be applied in the context of NAS and/or NOWS, with NAS considered as exposure to opioids $\pm$ other psychotropic substances and NOWS as

exposure to opioids alone. The emphasis on the clinical definition is important not only for clinical trials of new and existing treatments, but also for advancing needs assessments and care for the mother-neonate dyad which is a priority for public health experts and public advocates.

Although a dedicated evaluation of current coding guidelines was beyond the scope of the current work, standardizing the definition may mitigate inconsistencies in accuracy and reproducibility of claims, surveillance, and scientific data. Although claims data has a high positive predictive value for NAS, it requires an accurate clinical diagnosis and may miss cases of mild withdrawal.²⁹ Likewise, considerable NAS definitional variability exists among states, which may be impacted by longstanding variation in the upstream clinical diagnosis and a corresponding gap in consistent bedside criteria.³⁰⁻³¹ Lack of consistent inclusion criteria/definitions in research limits its utility and promotes variability in clinical trial enrollment.

The diagnosis of opioid withdrawal in the neonate, although necessary for clinical care and follow-up of the neonate, can be of particular consequence to the mother and the mother-neonate dyad. It identifies the mother as having taken opioids during pregnancy and can initiate child welfare investigations, potentially leading to loss of parental custody. Dyadic care is potentially compromised by punitive policies such as defining substance use in pregnancy as child abuse.³³⁻³⁴ Even though maternal well-being is critical to neonatal health and development, pregnant and parenting people with OUD experience discrimination, barriers to care, and criminalization.³⁵⁻³⁸ This recommended clinical definition of opioid withdrawal in the neonate does not imply that the pregnant person has harmed the neonate and mothers should not be blamed for any adverse outcomes. In addition, a diagnosis of NAS or NOWS should not be used to remove a child from parental custody as this diagnosis can be due to a myriad of factors.³⁹

Medications for pregnant people with OUD reduce maternal overdose deaths and preterm birth, but can increase the risk of NAS/NOWS.⁴⁰ We added these foundational principles to ensure clinical definitions were not interpreted as evidence of harm or be used for child welfare determinations (Table III).

Although considerable knowledge gaps remain, the American Academy of Pediatrics (AAP) policy statement on opioid use in pregnancy highlighted that effective care for the dyad centers around a comprehensive focus on the needs of both the mother and neonate.⁴¹ Similarly, the Substance Abuse and Mental Health Services Administration (SAMHSA) 2018 guidance recommends an integrated approach to caring for the mother and neonate including timely and destigmatized access to clinical and supportive care.²⁴⁻²⁵ In 2020, the AAP published its statement on NOWS outlining progress and deficiencies in approaches to maternal OUD, social and mental health needs assessments, connection to appropriate community resources, and post-discharge care for the dyad including Early Intervention.⁴² In many instances these comprehensive resources can only be provided once a formal diagnosis of NAS or NOWS is made. This may explain why post-discharge mortality rates were significantly lower in opioid exposed neonates with a diagnosis of NAS or NOWS compared with those without a diagnosis.⁴³

This study has several limitations. Only 10 participants participated in each panel. Not all participants provided their input; one panelist did not complete the study and one completed only one of three rounds. Although this panel size aligned with both PRA requirements and with a standard RAM panel design, it may have been beneficial to include a broader range of clinicians' perspectives on the topic.¹⁸ By eliciting feedback from a larger national group of key stakeholders with expertise in caring for the substance-exposed mother-neonate dyad, the HHS national convening enabled more extensive expert engagement on study findings and

conclusions. Though diverse professional, geographic and clinical practice backgrounds were represented, family medicine experts were underrepresented, possibly influencing ratings and responses. Assessing severity of opioid withdrawal was considered outside the scope of the present study. Instead, a threshold balancing sensitivity with specificity for criteria that could identify even mild cases of opioid withdrawal (which could otherwise go unrecognized) was emphasized. Whereas the aim was to capture a majority of withdrawal cases, an emphasis on mild signs could conceivably contribute to more diagnoses and/or false positive cases depending on interpretation of the criteria. The qualitative biases that may have influenced the recommended (most common) clinical criteria for a diagnosis typically with variable presentation are recognized. Differences in maternal opioid use were omitted. Coding guidelines were beyond the scope of this clinically focused study and were not addressed. Future studies should explore using the present definition to further refine International Classification of Diseases, Tenth Revision, Clinical Modification (*ICD-10-CM*) coding for increased accuracy. The current recommendations are a set of clinical criteria intended for use at the bedside, distinct from state-level case surveillance definitions and implementation. Prior work by the Council of State and Territorial Epidemiologists (CSTE) to advance standardizing provider-level NAS reporting and coding practices, led to the development of a two-tiered approach to NAS case definitions.⁴⁴ Although Tier 1 relied upon case reporting to public health authorities based on clinical records and provider reporting, Tier 2 reported administrative data from *ICD-10-CM* codes and providers/facilities. This recent step forward can be enhanced with the development of the presently proposed set of clinical “bedside” criteria for opioid withdrawal in neonates. Essential next steps include a focus on measures of severity, and development of a strategic implementation plan using this clinical definition for clinical care at the bedside, engaging

patients with lived experience,) coding and real world data, entry criteria into clinical trials, and 4) policy decisions and public health.

To standardize a clinical definition, findings from this study indicate that clinical criteria required are a known history of in utero opioid exposure and a distinct set of signs of withdrawal. We propose this standardized clinical definition for use by clinicians, researchers, and public health advocates to improve not only scientific discovery, but also, clinical needs assessment and care delivery for mother-neonate dyads and families.

ACKNOWLEDGMENTS available at www.jpeds.com (Appendix)

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ABBREVIATIONS

NAS: neonatal abstinence syndrome

NOWS: neonatal opioid withdrawal syndrome

Table 1. Opioid Withdrawal in the Neonate: Using a Modified-Delphi Method to Assess Clinical Criteria to Define NAS and NOWS

Round 1: Rating of Two Approaches for Assessing Opioid Withdrawal in the Neonate	
Clinical Signs of Withdrawal (Gomez Pomar et al 2017)	Developmental Domains of Dysregulation (Velez et al 2018)
1) How necessary is this information to determine if the neonate has NAS or NOWS?	1) How different is this approach from the way signs of withdrawal are currently assessed in clinical practice?
2) How sufficient is this information alone to determine if the neonate has NAS or NOWS?	2) How useful is this approach for assessing opioid withdrawal in a neonate?
3) How characteristic is this specified clinical sign of withdrawal?	3) Independent of how you currently assess neonates with opioid exposure, how feasible would it be to use this approach to determine if a neonate has NAS or NOWS?
Round 2: Feedback and Discussion	
Clinical Signs of Withdrawal	Developmental Domains of Dysregulation
1) Panelists received reports of round 1 including: - distribution of group responses to each question, summary of panelist comments - group median score, inter-quartile range - explanation of whether group reached agreement for each question 2) Asynchronous, threaded discussion led by clinical and modified-Delphi experts	
Round 3: Panelist Reassessment of Individual Responses from Rounds 1 and 2	
Clinical Signs of Withdrawal	Developmental Domains of Dysregulation
Panelists were asked: - Modified version of questions from round 1 1) How necessary is this information to determine if the neonate has NAS or NOWS? 2) How characteristic is this information (specified clinical sign) of clinical manifestations of withdrawal?	Panelists were asked: - Same questions as round 1 without modification

Table 1: Illustrated here is the three-round ExpertLens™ process based on the modified-Delphi method used to assess clinical criteria for the definition of neonatal abstinence syndrome (NAS) and neonatal opioid withdrawal syndrome (NOWS).

Table 2. Summary of ExpertLens™ Ratings of Clinical Elements Assessed for Determining Opioid Withdrawal in the Neonate

	NAS Panel			NOWS Panel		
Rating Statements	Number of Responses	Median Rating	Decision	Number of Responses	Median Rating	Decision
A. In Utero exposure to:						
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
B. Maternal toxicology test results positive for:						
Opioids alone	6	7	Necessary	9	4	Potentially necessary
Opioids plus other substances	8	5	Potentially necessary	9	5	Potentially necessary
Neonatal toxicology test results positive for:						
Opioids alone	7	3	Unnecessary	9	3	Unnecessary
Opioids plus other substances	8	3	Unnecessary	10	3	Unnecessary
C. Neonate:						
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	8	6	Potentially necessary	9	5	Potentially necessary
Requires non-pharmacologic measures to manage withdrawal	8	5	Potentially necessary	9	4	Potentially necessary
D. Types of Clinical Signs						
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

Table 2: Final ratings from Neonatal Abstinence Syndrome (NAS) and Neonatal Opioid Withdrawal Syndrome (NOWS) panels. Gray shading indicates agreement among experts and a group median of 6.5 or above (see text for more details).

Table 3. Foundational Principles for the Clinical Definition of Opioid Withdrawal in the Neonate

1. Substance use disorder is a disease requiring compassionate, ethical, evidence-based care
2. The maternal-neonate dyad is the appropriate subject of care; this definition is intended to identify clinical and supportive care needs of the dyad; shared interests should be prioritized
3. A diagnosis of NAS or NOWS does not imply harm, nor should it be used to assess child social welfare risk and/or status. It should not be used to prosecute or punish the mother or as evidence to remove a neonate from parental custody
4. Environmental factors, family influences and social structures strongly influence neonatal outcome and should be recognized

Table 4. Recommended Clinical Definition of Opioid Withdrawal in the Neonate

Substance withdrawal encompasses a continuum of variable clinical expression from neonate to neonate; the diagnosis is not limited only to neonates who require pharmacotherapy.

Purpose: to identify the group of individuals who experience withdrawal after *in utero* exposure to opioids in order to: 1) support the dyad through specific and comprehensive services to both neonates and their parents/caregivers and 2) provide an accurate and universally applied definition for clinical care and research. Alternative etiologies causing similar presentation in neonates should first be eliminated.

Clinical criteria for diagnosis consist of the presence of clinical elements 1 *and* 2:

1. ***In utero* exposure** (recommended to be collected via confidential maternal self-report) to opioids ± other psychotropic substances
2. **Clinical signs** characteristic of substance withdrawal, any **two** signs qualify:

Excessive/continuous crying (easily irritable)

Fragmented sleep (easy arousability to wakefulness)

Tremors (disturbed or undisturbed)

Increased muscle tone (stiff muscles)

Gastrointestinal dysfunction (hyperphagia, poor feeding, feeding intolerance, loose/watery stools)

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