Fetal Alcohol Spectrum Disorder (FASD) Research Classification Consensus Meeting

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Rationale and Goals for the Meeting

Currently, there are 11 different classification systems used by researchers around the world to categorize individuals prenatally exposed to alcohol. The populations studied by researchers also vary greatly (e.g., clinical vs. research populations). This combination can lead to uncertainty in the literature.

The goal of research is to produce generalizable information. Therefore, **international adoption of a single research classification system for FASD to harmonize international research efforts (i.e., across different populations) has the potential to advance FASD research.**

Participants in this consensus meeting were charged with identifying elements essential to the research classification of FASD. They were encouraged to identify elements to measure rather than how to measure them. Further, this consensus meeting focused exclusively on research classification. Although a common clinical diagnostic system for FASD is also desirable, clinical diagnosis is beyond the purview of NIH.

A series of preparatory discussions with the participants explored potential areas of consensus and disagreement. The consensus meeting helped to sharpen areas of consensus and narrow areas of disagreement. The meeting was organized around three features of FASD: neurobehavioral impairment, dysmorphology, and alcohol exposure.

Neurobehavioral impairment

Neurobehavioral impairment is considered the most disabling consequence of prenatal alcohol exposure (PAE).

Participants identified three primary domains of neurobehavioral impairment:

- **Neurocognitive**: Areas of impairment include IQ, language skills, executive function, and others
- **Behavioral**: Deficits include inattention and dysregulated behavior such as impulsivity and irritability
- **Adaptive function**: Areas of impairment include communication and daily living skills

The group recommended developing a severity score based on standard deviations from the population mean. The group plans to propose a final delineation of specific deficits within these domains and how to assign relative weight to each deficit.

Although not specific to FASD or uniquely a consequence of PAE, participants also considered **neurological dysfunction** relevant. Neurological deficits occur more frequently in children with PAE and may be helpful in linking neurobehavioral impairment to PAE.

Dysmorphology

The identification of physical abnormalities specific to prenatal alcohol exposure (PAE) aid in differential diagnosis when a child presents with neurobehavioral deficits potentially associated with PAE. In this regard, a research classification system will benefit from including elements of dysmorphology that are associated with PAE.

There was agreement that three essential elements of dysmorphology should be included in a research classification:

- **Facial features** (short palpebral fissures, smooth philtrum, and thin upper lip vermilion)
- **Brain size/structure** (includes head circumference)
- **Impaired growth**

Participants noted that the sentinel facial features of Fetal Alcohol Syndrome (FAS) are relatively specific to PAE during gastrulation and that exposure during other developmental periods might produce different facial dysmorphology. Hence, the characteristic facial dysmorphology upon which the historical diagnostic criteria for FAS depend are reflective of one of many possible patterns of facial dysmorphology caused by PAE.

Both facial and non-facial dysmorphology exist on a continuum. There is not yet consensus on interpretation of the measurements (i.e., to determine what values constitute an abnormality or indicate severity).

Participants agreed that quantifying the elements of facial dysmorphology was important but did not reach consensus on how to accomplish this using current methods. The quantification of facial dysmorphology elements appears within reach using 3D facial imaging, but participants expressed caution over requiring the use of this technology with automated analysis until there is consensus on methods, correction for racial norms, and appropriate algorithms for specific structures.

Alcohol Exposure

Alcohol exposure criteria are important to identify FASD in individuals who lack physical features but have neurobehavioral abnormalities that are known to be associated with FASD (e.g., Alcohol-Related Neurodevelopmental Disorder; ARND). These criteria are particularly important in studies that attempt to

link PAE with specific neurobehavioral abnormalities or that investigate the structural and functional brain abnormalities that underlie the neurobehavioral disorders associated with PAE.

Participants agreed that confirmed PAE should be defined as any exposure (yes/no), and that confirmed PAE should be documented to have occurred in pregnancy. Acceptable sources of information regarding prenatal alcohol use include:

- direct maternal report
- collateral report
- archival data such as medical records, social service records, justice system records, evidence of citation for driving under the influence of alcohol (DUI)
- presence of biomarkers of PAE such as ethyl glucuronide

The group also acknowledged that in research samples drawn from clinical practice, quantity/frequency of PAE is largely unavailable, and often, confirmed PAE at any level cannot be documented. Even among alcohol-exposed samples, concerns about inaccurate reporting remain.

Although the group agreed that full blown FAS can be diagnosed in the absence of a confirmed history of PAE (because the FAS phenotype is sufficiently specific to PAE in the absence of genetic phenocopies), there was not agreement that the facial phenotype alone is a sufficient indicator of PAE.

Absolute cutoffs or thresholds for drinking for FASD classification are difficult to define, because drinking levels are often underreported, susceptibility to PAE is variable, and there is no known "safe threshold" for PAE. However, several diagnostic and research classification systems have adopted thresholds for the purpose of case classification. When quantity, frequency, and timing of drinking are deemed reliable, these data may help estimate the probability that neurobehavioral impairment is related to PAE.

The group reached consensus on various aspects of PAE data that might be useful in a research setting. Further discussion at the conference refined these suggestions.

Consensus was reached on testing the following criteria in various databases:

- 3 or more drinks on 2 or more occasions
- Established tools (i.e., questionnaires such as AUDIT and T-ACE)
- Quantity, timing, frequency
- Pattern of risky drinking
- Positive biomarkers

Further discussion and exploration in databases are required to decide whether exposure criteria should be tiered for low, medium and high probability that PAE was responsible for neurobehavioral deficits. For brain-behavior research, a cohort might be selected based on a high probability that PAE produced neurobehavioral impairment. Epidemiology research could express a range of prevalence data, including for moderate probability and high probability PAE. Paternal drinking data should be recorded when available.

Principles of Consensus

Through discussion of these three topics over the two-day meeting, the panel agreed upon the following principles for research classification of FASD.

- **A research classification system will require modification for different stages of the lifespan.** For example, structural abnormalities may require greater emphasis for research classification during

infancy, when neurobehavior is more difficult to test or neurobehavioral abnormalities have not yet emerged. Similarly, growth deficits and facial dysmorphia may fade in adulthood.

- **Like clinical differential diagnosis, research classification of FASD should exclude disorders unrelated to prenatal alcohol exposure (PAE) that overlap with FASD.** Hence, medical history, genetic testing, dysmorphology, pregnancy and birth history, prenatal and postnatal environmental (e.g. lead) and drug (e.g. cannabinoids and nicotine) exposures, socioeconomic status, and adverse childhood events should all be considered where possible.
- After delineating a comprehensive classification system that would inform research by well-resourced groups, **a streamlined set of classification criteria for less well-resourced groups should be proposed.**
- **All measures should be assessed in relation to community or population norms to the extent possible.** In certain populations, means of some measures, such as height, weight, and IQ, are lower in the non-alcohol-exposed cohort than in other typically developing populations.
- **Neurobehavioral and dysmorphological elements of FASD exist along a continuum.** Quantifying the dimensionality of neurobehavioral impairment will help identify the structural and functional brain abnormalities that underlie these deficits and the factors of risk and resilience that modify their expression. Similarly, quantifying the dimensionality of the physical and dysmorphological elements of FASD can help estimate the probability that neurobehavioral deficits are related to PAE.
- The accurate and consistent identification of FASD will be important for research on the increasingly recognized medical conditions that arise from PAE through direct toxicity and mechanisms related to the Developmental Origins of Health and Disease (DoHAD).

Potential Framework for Research Classification of FASD

A framework for research classification of FASD is needed for case identification in:

- Epidemiological studies
- Linking neurobehavioral disabilities and dysmorphology to PAE
- Exploring brain-neurobehavior relationships

There was consensus that a research classification system for FASD should fully capture the dimensionality of each of the contributing elements – physical, dysmorphology, neurobehavior, and PAE. This will require testing different formulas for the weighting and grading of individual elements of the FASD classification system to learn which correlate best with PAE and are most predictive of neurobehavioral impairment. Alternatively, grading might also employ the discrete elements of the 4-digit code. The classification system should be adaptable across the lifespan.

FASD: Numerous options were considered for crafting an FASD classification system for research. One approach would identify a single research classification designated FASD, with the spectrum reflected by the severity of component elements. Variants of this approach might include a single discrete category of FAS within the broader FASD spectrum, reference to the presence or absence of sentinel facial features (e.g. Canadian system), or the inclusion of additional discrete categories, such as partial FAS (pFAS), ARND, and Alcohol-Related Birth Defects (ARBD), each with separate inclusion and exclusion criteria. The utility of these categories might be better understood once we learn whether they determine the severity and profile of neurobehavioral impairment.

In each classification system, the severity of the dysmorphology, growth retardation, microcephaly, and neurobehavioral impairment should be quantified. Similarly, profiles of predominantly neurocognitive or

neurobehavioral impairment should be noted if the existence of such neurobehavioral subtypes is validated through empirical analysis.

One possible approach is to begin the process of classification by grading the severity of the neurobehavioral syndrome and then determining whether the constellation of associated physical findings permits linking the neurobehavioral syndrome to PAE. In some circumstances, various combinations of sentinel facial dysmorphology, non-sentinel facial dysmorphology, non-facial dysmorphology, growth retardation, and microcephaly may be deemed sufficiently specific to serve as a proxy for PAE when information about PAE is unavailable.

Listed below are examples of possible frameworks considered for discussion and exploration. All of these presume the presence of neurobehavioral deficits, except for the ARBD category within #5.

- FASD, graded for severity, but without specific designated categories
- FASD, with and without FAS
- FASD, with and without sentinel facial features
- FASD, subcategorized as FAS, pFAS, ARND, and ARBD
- FASD, with or without various identifying elements; e.g. growth deficiency, microcephaly, sentinel facial dysmorphology, non-sentinel facial dysmorphology
- FASD, as described in the 4-digit code

Fetal Alcohol Syndrome: There was consensus that FAS is an historically important, well-recognized syndrome that should be preserved in a research classification system. There remain differences in criteria among different diagnostic systems that should be reconciled through examination of various databases.

Next steps and communications plan

Following the conference, disagreements will be addressed by testing a few discordant classification elements, thresholds, and classification frameworks in various research databases. The empirical results will assist the expert group in reaching consensus on a single research classification system.

The group plans to inform the research community of the efforts of this consensus conference group through presentations at upcoming scientific meetings. Panelists may also spearhead efforts to transition international research from the many different classification systems in current use to a single consensus classification system.