

# **Pain Research and Children with Severe Intellectual Disability: Ethical Challenges and Imperatives**

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## **Abstract**

Children with severe intellectual disabilities face inequities in pain-related care, yet there is a relative lack of pain research in the population. A significant obstacle to pain research in this population is its ethical complexity. This article addresses ethical challenges to conducting pain research in children with severe intellectual disabilities. There are two central issues. First, some of the standard methods for assessing pain and pain sensitivity are not suitable for children (and adults) with severe ID, who are often non-verbal and unable to understand or follow directions. Second, children with severe ID cannot provide informed consent (or even assent) to participate in pain research, nor is it obvious that their dissent will be recognized as such. The International Association for the Study of Pain's existing ethical guidelines for pain research provide helpful but only general guidance. Our article goes beyond those guidelines and uses a well-established framework for assessing the ethics of clinical research to highlight points relevant to designing, conducting, reviewing, or evaluating research involving children with severe ID, focusing on issues unaddressed in existing guidance.

## Key Messages Panel

- Children (and adults) with severe intellectual disabilities present with co-occurring physical disabilities and medical conditions that render them especially vulnerable to pain, yet they face inequities in pain research and care.
- Pain research involving this vulnerable population is urgently needed but ethically and methodologically challenging, as individuals with severe ID are often non-verbal and unable to understand and follow directions or assent to participate.
- These obstacles can be overcome by applying an ethical framework for clinical research, giving particular attention to, among other things: the social value of pain research involving individuals with severe ID; involving stakeholders with intimate understanding of this population; ensuring fair selection of subjects; maintaining scientific validity in adapting standard experimental pain research methods; and ensuring a favorable risk-benefit ratio.
- Systematically excluding individuals with severe ID from participating in research that will improve understanding of their somatosensory function and pain experience compounds existing health-related inequities.

## Introduction

This viewpoint addresses ethical challenges to conducting pain research in children with severe intellectual disabilities. Following the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the International Classification of Diseases, we understand “intellectual disability” (ID) as a set of disorders involving deficits in intellectual functions and adaptive functioning, with an onset during the developmental period, such that diagnosis and management during childhood is expected (1,2). ID is “severe” when conceptual development is limited and spoken language is either significantly limited or absent.<sup>i</sup> We focus on pain research involving children—since ID is identified and cared for in childhood—but our analysis is relevant for research involving individuals with ID across the lifespan.

Children with severe ID are disadvantaged: they are more likely to have limited movement or play abilities and have greater health needs and higher need for health-related services (3,4), making them particularly vulnerable to health disparities. While children with ID have more comorbidities and undergo medical interventions that can be painful as typically developing children do, they are seldom enrolled in clinical research. The resulting lack of population-specific knowledge could further contribute to health inequity in this vulnerable population (5). The experience of pain in children with severe ID is poorly understood. On the one hand, some conditions associated with severe ID are also associated with altered pain sensitivity, suggesting that children with these conditions may have increased pain tolerance (3,4). On the other, such children may be unable to communicate or self-report their pain, raising the possibility that their pain sensitivity is normal, but their expression of pain is atypical or unrecognized (6). Consider, for example, parents of children with Wilms tumor, aniridia, genitourinary (WAGR) Syndrome, who describe a child who does not

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<sup>i</sup> Severe ID here includes individuals diagnosed with both severe and profound intellectual disability.

react when he “got his toe caught in our gate and it ripped a big ½-inch gouge in it. It was bleeding heavily and the skin was just hanging off,” or a child who tried “to sit on a lunch table bench at school, missed, and hit her collar bone” ultimately breaking her clavicle “but since she hardly complained they let her finish out the day” (7,8). Further research is needed to understand whether such cases involve altered pain sensitivity or atypical pain expressions, or both.

An important obstacle to pain research in children with severe ID is its ethical complexity (5). Exploitation of individuals with ID is well-known in the history of clinical research misconduct. Examples like the Willowbrook State School for Children with Mental Retardation and the Jewish Chronic Disease Hospital make vivid the importance of taking extra ethical precaution when contemplating research with this vulnerable community (9,10). However, there is also a powerful ethical case for including those with severe ID in research, since systematic exclusion contributes to health inequities and effectively compounds their disadvantage by denying them access to potential benefits research might produce (5,11). Indeed, in the authors’ experience, parents and caretakers of children with severe ID are painfully aware of this inequity, understand this potential and advocate on behalf of their loved ones for this research.

Although the ethical imperative to involve individuals with severe ID in research to address the existing inequity in pain research is now better recognized (5,11–14), there are ethical challenges in its conduct. Standard experimental pain methods rely on subjects’ active participation and self-reports and so are not suitable for children with severe ID who are nonverbal or unable to understand or follow directions. Given the theoretical potential for pain research to cause unpleasant experiences, careful consideration must be given to the risks and potential benefits of developing and using alternative research methods. Further, children with severe ID cannot assent,

and even their dissent may be difficult to decipher. Existing ethical guidelines for pain research from the International Association for the Study of Pain's (IASP) are helpful but lack specific guidance for individuals with severe ID (15).

This article applies a well-established ethical framework for clinical research developed by Emanuel *et al*, which is a distillation of key research ethics guidelines worldwide (16,17). We present the resulting analysis in a way that is useful for those designing, conducting, reviewing, or evaluating much-needed pain research involving children with severe ID.

## **The Framework**

Emanuel *et al* describes universally applicable principles grounded in widely-accepted bioethical values that synthesize guidance found in existing codes, regulations, and relevant research ethics literature. Ethical clinical research must reflect the following principles: collaborative partnership, social or scientific value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for subjects (see Table) (16,17). Our discussion focuses primarily on the ethical challenge generated by the possibility of altered pain sensitivity combined with the inability to communicate and self-report pain and the distinctive difficulties this raises for the development of alternative experimental methods appropriate for children with severe ID.

### *Collaborative Partnership*

The principle of collaborative partnership is intended to address issues special to research in developing countries but is relevant whenever research involves especially vulnerable populations (Table). The principle requires that members of these populations have a say in identifying their

health needs most in need of study. Collaborative partnerships also promote trust and guard against exploitation of vulnerable populations who may be distrustful of the research community (17).

In pain research involving children with severe ID, collaborative partnership obliges researchers to seek partnerships with those with intimate understanding of the population's health needs and problems, including parents and caretakers, healthcare providers, and condition-specific support groups or online social communities (5,14,18). As we suggest, these partnerships also help ensure that other principles are satisfied.

#### *Social or Scientific Value*

Ethical research must have potential social or scientific value: to justify exposing participants to the risks of research, research should be expected to lead to improvements in health or well-being or increase knowledge or understanding of a condition (Table) (16). This guards against subjecting participants to risks without sufficient justification, and helps ensure the responsible use of scarce resources like research funding. Given the relative paucity of pain research in children with severe ID, there are various ways such research could produce great social and scientific value, in addition to addressing one of the many inequities that exist in pain research, as recognized by the IASP (5,12).

Children and adults with ID present co-occurring physical disabilities and medical conditions that render them vulnerable to pain (19,20). These include neuromotor disorders including decreased mobility, immobility, spasticity, sustained muscle contractions, and dyskinesia as well as skeletal abnormalities including scoliosis, osteopenia, pathological fractures, and hip subluxation (21–23). Additionally, many interventions needed to treat these disabilities are associated with acute pain. For

example, surgery to repair severe scoliosis is associated with severe pain; however, after scoliosis surgery, children with ID receive significantly less analgesics than those without ID, indicating that pain may be undertreated in this population (24,25). While other sensory modalities, like taste, hearing, smell, and vision, are predominantly informative, pain is informative and protective: it often signals illness or tissue damage and is the most common reason why individuals seek medical care. But individuals with ID seen in emergency departments receive significantly fewer diagnoses associated with physical pain than typically developing individuals (19). Additionally, caregivers making decisions about when to seek medical care based on their child's expression of pain, often do so later than optimal, which can lead to increased risk of complications related to delayed diagnosis (26,27). But poor understanding of their experience of pain makes it difficult to interpret and respond to these findings. To say with confidence that pain in children with severe ID is problematically underdiagnosed and undertreated requires a better grasp on whether and to what extent pain sensitivity of children with severe ID is altered. Thus, identification of altered somatosensory function can improve understanding of pain sensitivity and pain response, which might prevent delayed diagnoses and clinical complications, inform pain management in children with ID, and aid the development of improved analgesic approaches (8).

Recent discoveries and in-depth phenotyping of individuals with ID with identified genetic conditions suggest genotypic explanations of potential differences in pain sensitivity. Several genetic conditions associated with atypical pain responses include those with a preponderance of severe ID (28). These include WAGR Syndrome (7), Phelan-McDermid Syndrome (PMS) (29,30), Christianson Syndrome (31), and Rett Syndrome (8,32), among others. Some such conditions, like PMS and WAGR syndrome, can result from chromosomal deletions, which can include varying numbers of genes and are associated with significant interindividual variability and a broad spectrum of ID severity. For some



conditions, studies of implicated genes (i.e. *SHANK3*, *BDNF*) point to alterations in neurobiological pathways resulting from the respective gene mutations, which may relate to differences in pain sensitivity (30,33). Yet despite the genotypic explanation of altered pain sensitivity and wide support from parents and healthcare providers, nearly all existing pain research on children with ID involves only those with mild to moderate ID (34–38). Pain research involving children with severe ID may corroborate these genetic explanations, account for the disparities illustrated above, and clarify whether conditions associated with severe ID are associated with increased pain tolerance or complete lack of pain sensation. Again, this information would have social and scientific value: since lack of pain sensation can be dangerous and contribute to delayed diagnoses and clinical complications, improving awareness of this possibility is worthwhile (39–41).

But pain research might instead reveal little to no differences in pain sensitivity, or even increased pain sensitivity, suggesting children with severe ID do not exhibit the vocalizations, facial expressions, and motor behaviors indicative of pain in typically developing children (7,8,35). This would also have significant social and scientific value. Besides corroborating that pain in children with severe ID is seriously underreported, underdiagnosed, and undertreated, such findings would motivate research to improve pain diagnostics and analgesics in this population and spur the development of better objective tools for pain assessment (19,42). This is significant because lacking these diagnostics, analgesics, and assessment tools leaves parents and caretakers in the psychologically difficult position of constantly worrying that their child (or later, adult) is in pain. This also leaves providers without evidence-based guidance on diagnosing and treating pain in a population with increased risk of polymedication, drug interactions, and adverse side effects (43).

Both the United States Association of the Study of Pain (13) and the IASP (12) recognize the inequities faced by individuals with ID and provide guidance to enhance inclusiveness in pain research. Increasing enrollment of children and adults with severe ID could produce significant social and scientific value, by ensuring that this disadvantaged and underrepresented population equitably benefits from pain research.

### *Scientific Validity*

Research with social or scientific value is ethical only if it uses rigorous methods to produce scientifically reliable and valid results (Table) (16). Rigorous methods must be practically feasible, have a clear scientific objective, be designed using accepted principles and reliable practices, and have sufficient power to test the research question. Poorly designed research yields scientifically unreliable and invalid results and is therefore unjustified because it exposes participants to risks for no purpose (16). Applied to pain research in children with severe ID, the challenge is how to obtain valid scientific data, given participants' inability to communicate about their pain, self-report, and understand or follow directions. Modifying standard pain research methods is necessary to overcome this challenge and enable answering the research questions of given pain studies. But problematically there are no established standards for modifying these methods in a way that balances the safe use of experimental stimuli with the generation of valid data in individuals with severe ID—developing these standards may itself have significant scientific value (44).

How can standard methods be ethically modified, or new methods developed, without unduly compromising validity and rigor? Consider quantitative sensory tests (QST) commonly used in pain research involving typically developing children and adults (45,46) and individuals with mild to moderate ID (7,38). QSTs allow researchers to control the intensity of stimuli and require

subjects' active participation. Applying heat, cold, mechanical, or electrical stimuli of varying intensities to various parts of the body, researchers rely on participants to determine the level at which they first perceive the stimuli (the “innocuous” threshold) and the level at which they first perceive the stimuli as painful (the “noxious” threshold), and to use rating-scales to characterize the character and intensity of pain. QST studies can predict pain intensity, subsequent disability, and pain-related negative affect, suggesting that responses measured by QSTs correlate with clinical pain (6,8,28). However, since QST depends on subject participation, its use as a pain assessment or diagnostic tool is strongly discouraged in conditions associated with clinically relevant cognitive deficits (47). Recently, pain researchers have begun to modify standard QSTs and have shown the feasibility of using modified QSTs to study pain response in adults with dementia-associated cognitive impairment and adults with mild to moderate ID (34,37,48–51).

Given the significant unknowns about the experience of pain in children with severe ID, and their inability to communicate how painful the stimulus is or understand and follow directions, when modifying QSTs, researchers should be sensitive to the possibility that the range of stimuli tolerated by typically developing children may not be appropriate for those with severe ID, and modify their methods accordingly. One option is to rely on measures that do not require the ability to self-report pain or to use methods that can increase communication ability otherwise. For example, many behavior observational scales not relying on verbal self-report are used to assess clinical pain and guide its treatment, those could be adapted for investigations of pain response behavior (24,50,52–55). Researchers can also use assistive technology and methods like acoustic analysis of spontaneous vocalization to evaluate pain response (56,57). Other objective surrogate measures to evaluate stimuli response that do not require the ability to self-report pain include electroencephalography, near-infrared spectroscopy, functional magnetic resonance imaging (fMRI), and other physiological

measures (e.g., behavioral reactivity, heart rate variability, blood pressure, galvanic skin response, pupillary response). These measures do not provide the determination of perception or pain thresholds, but do provide a way of comparing the physiological response to a range of stimuli in a standardized way across typically developing children and those with mild, moderate, or severe ID that has relevance to understanding sensory function or dysfunction in this population (7,34,35,48).

Although it is theoretically possible to avoid the intentional application of noxious stimuli by using these objective measures to track response to stimuli known to be noxious in clinical care (e.g., a venipuncture), considerations of scientific validity and methodological rigor still favor their controlled and intentional application. This is for two reasons. First, QSTs allow researchers to control the intensity of stimuli using low levels of noxious stimuli. Experimental pain studies using QST are feasible and tolerated by typically developing children and children with moderate ID (38). Since studies have determined normative values for innocuous and noxious thresholds in both of these groups (7,36,38,58,59), those values can inform the design of QSTs suitable for children with severe ID. There may be reasons to worry about the relevance and validity of this data for this group, but it at least provides a baseline to help minimize risk by eliminating the possibility of inflicting severe pain. Second, QST technically allows for repetitions of the same stimuli, which is important for researchers tracking objective surrogate measures of response to sensory stimulation in lieu of self-reports. Since studies involving individuals with severe ID typically have small sample sizes, this is relevant for the generalizability, reproducibility, and replicability of research findings.

### *Fair Subject Selection*

Ethical research must engage in fair subject selection: the primary basis for determining who is recruited or enrolled in a study must be the scientific goals of the study, and not vulnerability,

privilege, or other factors unrelated to the purposes of the research (16). Fair subject selection guards against the exploitation of vulnerable populations and is therefore particularly salient for research involving children with severe ID, who should be involved only if relevant data cannot be gathered without them.

To satisfy the principle of fair subject selection, researchers should clarify why the social and scientific value of a study requires including children with severe ID who cannot communicate about their pain, understand or follow directions, or provide assent, and why the same data cannot be obtained by generalizing from similar research involving less vulnerable individuals. In other words, researchers should explain why sufficiently relevant data cannot be inferred from children with mild or moderate ID, who are more likely to be capable of communicating about their pain. One reason already noted is that severe ID is common in genetic conditions known to cause altered pain sensitivity (PMS, WAGR, and Rett Syndrome) (8,60–62). There is no way to study the effects of such conditions on pain without enrolling individuals with severe ID, nor, for that matter, can we study the interaction between severe ID itself and pain without their enrollment. Fair subject selection may therefore *require* that we include individuals with severe ID in relevant pain studies; indeed, it may be unfair to exclude them.

#### *Favorable Risk-Benefit Profile*

Ethical research exposes participants only to risks and burdens necessary to obtain the relevant scientific data (Table). Risks should be minimized consistent with the study's scientific goals and justified by both the expected benefits to participants and the study's social or scientific value (16). The risk-benefit profile of pain research in children with severe ID will vary across studies, but currently, most experimental pain research offers no direct benefit to participants. Thus, given

significant unknowns about the experience of pain in children with severe ID and their vulnerability, researchers must design “minimal risk” studies, meaning the probability and magnitude of expected harm is equivalent to or less than the risks of daily life or routine examinations (63). Given the widespread practice of excluding persons with ID from research (5), it is unsurprising that even studies of minimal risk interventions like distraction techniques for children undergoing procedures seldom enroll children with severe ID (64). Someday there may be clinical trials of promising interventions that specifically target pain management in children with severe ID which could provide participants a prospect of direct benefit (e.g., functional improvement), and therefore would involve assessing whether a minor increase over minimal risk is permissible. The point is simply that ethical research must have a favorable risk-benefit ratio, and the paucity of pain research enrolling children with ID makes the assessment of the risk-benefit ratio rather challenging.

Even if a pain study involves minimal risk, researchers have reasons to be cautious: even among typically developing individuals, pain thresholds vary and researchers cannot rely on those with severe ID to say “stop!” if and when the discomfort is too much. Further, children with severe ID might find some stimuli or methods of studying pain response (i.e., fMRI) more uncomfortable or anxiety-inducing than might typically developing children, especially since the inability to understand what is happening and the purpose of research involving even mild noxious stimuli might induce fear.

To ensure that risks to participants are sufficiently low, researchers might incorporate the following considerations into their study design. If the generalizability, reproducibility, and replicability of a study necessitates repeated application of noxious stimuli, care should be taken to minimize and justify the number of exposures. For example, researchers should explain why their

chosen method requires  $x$  rounds of noxious stimulation at  $y$  seconds each (rather than some lower values), and the procedures in place to minimize the potential risks of repeated application. Similar attention should be given to the selection and justification of the maximum level of noxious stimuli. For example, researchers using QSTs might establish a safe maximum level of stimulation by choosing the 50<sup>th</sup> percentile of innocuous and noxious thresholds in typically developing children and children with mild to moderate ID reported for age category and sex, thereby ensuring that stimuli are known to be well-tolerated by those subjects and mild enough to preclude tissue damage (7,38,62).

Researchers should consider additional safeguards to minimize potential risks, especially if the study involves more than minimal risk (supposing the study's potential benefits justify this minor increase). For example, to observe for stress, anxiety, and perceived but nonverbally communicated dissent (more below), researchers might consider including an independent monitor and the consenting parent or caretaker in the room for the duration of the study. During the informed consent process, researchers should ensure that the consenting individual understands how to withdraw consent, and that they may do so at any point. Researchers should continuously monitor whether the planned number of rounds of noxious stimuli are tolerated by participants and necessary to answer their research questions, and be prepared to modify their experimental design if they are not. Additionally, researchers should consider the other risk-minimizing procedures outlined in the IASP's guidelines, like those regarding the availability of effective, accepted pain relief (15).

Lastly, researchers should consider piloting techniques with closely-related but less severely-affected populations. For instance, when studying PMS, researchers might pilot their modified QST

methods on verbal children with milder ID, as a way to inform the design and methods to be used in children with severe ID (65). However, given that unique technical modifications will likely be required for this population, such pilot studies can only inform rather than replace studies involving children with severe ID. Ultimately this cohort must be included, if researchers are to learn about their specific pain sensitivity and response.

### *Independent Review*

Ethical research always involves independent review (16). Besides ensuring rigorous, scientifically valid methodology and a favorable risk-benefit profile, independent review guards against conflicts of interest that might unwittingly shape the design, conduct, and analysis of research (Table) (16). Are there special considerations for independently reviewing pain research involving children with severe ID? In studies that have unusual risk considerations (e.g., if reasonable people might disagree about whether the study involves minimal risk), then given the importance of accurately assessing risks and benefits, committees might consider including an ad hoc member—perhaps a collaborative partner or consultant with relevant expertise, including lived experience, or experience working with ID. Additionally, if committees are reviewing research involving unfamiliar or especially vulnerable populations, researchers may need to play an educational role, or perhaps recommend an independent expert who can do so.

### *Informed Consent and the Role of Parents/ Guardians and Legally Authorized Representatives*

Once a protocol is determined to be valuable, valid, and acceptable with respect to risks, benefits, and subject selection, individuals are recruited and asked to provide informed consent. The aim of informed consent is to protect autonomy (Table) (16). To provide it, a participant (or surrogate) must be an adult who is accurately informed of the purpose, methods, risks, benefits, and



alternatives to research, understands this information and its bearing on their clinical situation and, on that basis, makes a voluntary decision whether to participate (16).

Although the requirements for informed consent vary across jurisdictions, we illustrate using the United States' standard regulatory framework for pediatric research (66). The informed consent process includes parental (or guardian) permission and child assent, where "assent" means an affirmative agreement to participate and not mere failure to object (66). Minimal risk research typically requires permission from one parent and "adequate provisions" for soliciting child assent such as visual aids or age-appropriate explanations of the purpose and methods of research (63). (Additional provisions are necessary when research involves greater than minimal risk but presents the prospect of direct benefit or a minor increase over minimal risk with no prospect of direct benefit (66).)

Children with severe ID cannot assent, but they may show signs of resistance, distress, or dissent. Most bioethicists and research institutions recognize the importance of these reactions, but there is no settled guidance regarding them. Some bioethicists interpret "dissent" as exhibiting a meaningful request, such that children with severe ID cannot dissent. Nevertheless, these individuals may still show signs of resistance, distress, or discomfort. If these differ from typical behaviors, they should be interpreted as burdens of the research: they should figure into evaluations of overall research risks to ensure that participants' aversive experiences do not exceed the anticipated risks and burdens that were justified by the overall ethical assessment of the protocol (67). Finally, just as with pain, children with severe ID may express or communicate dissent in atypical or unfamiliar ways. To increase the likelihood that their dissent is recognized, children with severe ID should be monitored by parents or other caretakers who know them well and can best represent their interests.

It may be necessary or scientifically desirable to include adults with severe ID along with children, and their inclusion raises different questions about informed consent. Federal regulations in the United States refer to the rightful surrogate as the *legally authorized representative* (LAR), though they generally defer to local and state laws in defining the term. Absent applicable local or state laws regarding LAR consent procedures, at least for federal regulatory purposes, researchers may rely on institutional (e.g., hospital) policies (63). Federal regulations do not stratify the authority of LAR by risk category, but most institutions follow an approach like the regulations for pediatric research. (See for example the National Institutes of Health's Policy 403 "Research With Adults Who Lack Decision-Making Capacity to Consent" (68).)

## **Conclusion**

Although pain research involving children with severe ID has the potential to yield significant social and scientific value, it raises difficult questions. The inability of children with severe ID to communicate about their pain creates challenging and possibly harmful clinical situations, but also raises ethical and methodological challenges. However, it is possible to expand on the IASP's existing ethical guidelines for pain research by applying a well-established ethical framework for assessing clinical research. Such expanded ethical guidance, we hope, will aid in designing, conducting, reviewing, or evaluating pain research involving children with severe ID. For children and adults with severe ID whose disabilities often involve impairment of the peripheral and central nervous systems, and who must rely on others to advocate on their behalf, such research is an ethical imperative.

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