No. 23-5110

UNITED STATES COURT OF APPEALS
FOR THE TENTH CIRCUIT

PETER POE, by and through his parents and next friends, PAULA POE and PATRICK POE, et al.,

Plaintiffs-Appellants,

and

DR. SHAUNA LAWLIS, on behalf of her patients,

Plaintiff,

v.

GENTNER DRUMMOND, in his official capacity as Attorney General of the State of Oklahoma, et al.,

Defendants-Appellees.

On Appeal from the United States District Court
for the Northern District of Oklahoma
Case No. 4:23-cv-00177-JFH-SH

BRIEF OF ALLIANCE DEFENDING FREEDOM AS AMICUS CURIAE IN SUPPORT OF APPELLEES AND TO AFFIRM

JACOB P. WARNER
ALLIANCE DEFENDING FREEDOM
15100 N. 90th Street
Scottsdale, AZ 85260
(480) 444-0020
jwarner@ADFlegal.org

JOHN J. BURSCH
JAMES A. CAMPBELL
ALLIANCE DEFENDING FREEDOM
440 First Street NW
Suite 600
Washington, DC 20001
(202) 393-8690
jbursch@ADFlegal.org
jcampbell@ADFlegal.org

Attorneys for Amicus Curiae

CORPORATE DISCLOSURE STATEMENT

Under Fed. R. App. P. 26.1 and 10th Cir. R. 26.1, Amicus Curiae Alliance Defending Freedom, states that it has no parent corporation and that it does not issue stock.

Dated: December 18, 2023

Respectfully submitted,

/s/ Jacob P. Warner
Jacob P. Warner

Attorney for Amicus Curiae

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Other Authorities

Regulations

IDENTITY AND INTEREST OF AMICUS CURIAE[1]

Alliance Defending Freedom is the world's largest law firm dedicated to religious freedom, free speech, the sanctity of life, parental rights, and marriage and family. Because the law should protect life—including from irreversible and unproven medical interventions—ADF advocates for laws that protect children from drug treatments that could potentially harm them with permanent consequences.

ADF is deeply concerned about the use of puberty blockers and cross-sex hormones for children with gender dysphoria. Systematic reviews have shown insufficient evidence to support such use. Many studies even suggest these interventions are dangerous. This has led many European nations and American states to forbid puberty blockers and cross-sex hormones for children with gender dysphoria. ADF believes such caution is best, given the uncertain science and serious harm.

ADF has served as co-counsel defending states that protect children from potentially dangerous interventions, *e.g.*, *Boe v. Marshall*, No. 2:22-cv-184-LCB (M.D. Ala.), and it submits this brief supporting Oklahoma's Senate Bill 613 ("the Minors Protection Act" or simply the "Act").

[1]No counsel for a party authored this brief in whole or in part, and no person other than amicus and its counsel made any monetary contribution intended to fund the preparation or submission of this brief. All counsel were timely notified of this brief and consented to its filing.

INTRODUCTION

Oklahoma seeks to protect children from unproven drug treatments that risk permanent harm. It enacted the Minors Protection Act to regulate puberty blockers and cross-sex hormones for children with gender dysphoria. Consistent with medical literature and best practices around the world, Oklahoma found such drug use is harmful or at least reckless because it is experimental, unsupported by high-quality evidence, and has unknown risks. Plaintiffs challenge this protection, seeking a constitutional right to inject children with experimental drugs.

The district court preliminarily upheld the Act, holding that Oklahoma can rationally protect children from harmful interventions. That was the correct decision. No high-quality evidence supports using puberty blockers and cross-sex hormones to treat children with gender dysphoria, and multiple studies suggest that such interventions may be dangerous. Regulating these interventions is both reasonable and critical to protecting children.

As science continues to develop, States may decide for themselves how to best protect their citizens. Courts give legislatures wide discretion to pass legislation when there is medical and scientific uncertainty. This Court should not abandon judicial restraint on a critical issue and constitutionalize a new right to unproven drugs.

Accordingly, ADF asks this Court to affirm the ruling below and allow Oklahoma to continue protecting its children.

ARGUMENT

An injunction "is an extraordinary remedy never awarded as of right." *Winter v. Nat. Res. Def. Council, Inc.*, 555 U.S. 7, 24 (2008). It "may only be awarded upon a *clear showing* that the plaintiff" deserves it. *Id.* at 22 (emphasis added). This is especially true when plaintiffs seek to enjoin the "enforcement of a presumptively valid state statute," *Brown v. Gilmore*, 122 S. Ct. 1, 1 (2001) (Rehnquist, C.J., in chambers), which "demands" unusually strong "justification." *Lux v. Rodrigues*, 561 U.S. 1306, 1307 (2010) (Roberts, C.J., in chambers). To obtain a preliminary injunction, Plaintiffs must at least prove they are "likely to succeed on the merits." *Winter*, 555 U.S. at 20. Plaintiffs have not done so here because while rational-basis review applies, the Act satisfies even intermediate scrutiny by reasonably protecting children from unproven drugs.

I. Rational-basis review applies, and the Act easily satisfies both rational-basis and intermediate scrutiny.

Statutory classifications are typically valid if they rationally advance a legitimate interest. *San Antonio Indep. Sch. Dist. v. Rodriguez*, 411 U.S. 1, 55 (1973). Closer scrutiny applies when laws implicate suspect or quasi-suspect classes. *Reed v. Reed*, 404 U.S. 71, 76 (1971). Laws that implicate a quasi-suspect class like sex must advance an "important" goal through "substantially related" means. *Tuan Anh Nguyen v. INS*, 533 U.S. 53, 60 (2001). A perfect fit is not required. *Id.* at 70; *see Michael M. v. Sonoma Cnty. Super. Ct.*, 450 U.S. 464, 473 (1981) (relevant inquiry

"not whether the statute is drawn as precisely as it might have been, but whether the line … is within constitutional limit[s]."). Rational-basis review applies here because the Act does not target a suspect or quasi-suspect class; it regulates drugs used on minors of both sexes. *See L.W. by & through Williams v. Skrmetti*, 83 F.4th 460, 479-89 (6th Cir. 2023); *Eknes-Tucker v. Governor of Ala.*, 80 F.4th 1205, 1228 (11th Cir. 2023). Regardless, the Act satisfies even intermediate scrutiny.

A. The Act protects children from unproven drug treatments no matter how they identify.

Oklahoma enacted the Minors Protection Act to protect the health and welfare of minors. *Poe v. Drummond*, No. 4:23-cv-00177-JFH-SH, 2023 WL 6516449, at *13 (N.D. Okla. Oct. 5, 2023). The State asserts that using puberty blockers and cross-sex hormones to treat children with gender dysphoria is unsafe. *Id.* at *13-16. As shown below, such interventions may increase the risk of depression, sexual dysfunction, cardiovascular disease, stroke, breast cancer, and more.

The Act reasonably protects *all* children. While Plaintiffs say the Act targets transgender people, Opening Br. for Pls.-Appellants (Opening Br.) 25-28, the Act evenly protects all children. Gender dysphoria is a recognized mental health condition. Am. Psychiatric Ass'n, *Diagnostic & Statistical Manual of Mental Disorders* 512 (5th ed. 2013). It requires six-month "marked incongruence between one's experienced/expressed gender and assigned gender" that is "associated with clinically significant

distress." *Id.* In contrast, transgender *identification* is not a mental disorder. People can identify as transgender without experiencing gender dysphoria. *Expert Q&A: Gender Dysphoria*, Am. Psychiatric Ass'n, https://perma.cc/3YJ4-F2A2 (last accessed July 13, 2023).

What's more, adolescent gender dysphoria often does not lead to adult transgender identification. Until recently, most minors presenting with gender dysphoria were pre-pubescent males. The Cass Review, *Independent review of gender identity services for children and young people: Interim report* 32 (2022), https://perma.cc/9CT5-J6NU. The Dutch protocol analyzed this population exclusively. E. Abbruzzese et al., *The Myth of 'Reliable Research' in Pediatric Gender Medicine: A critical evaluation of the Dutch Studies—and research that has followed* 12, J. Sex & Marital Therapy (2023), App.94.[2] With psychotherapy alone, the study showed the vast majority of these children ceased to experience gender dysphoria during adolescence and identified with their natal sex as an adult. Wylie C. Hembree et al., *Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinial Practice Guideline*, 102:11 J. Clinical Endocrinal Metab. 3869, 3879 (2017),

[2] "App." refers to the Appendix in Support of the Brief of *Amicus Curiae* Alliance Defending Freedom, which catalogues sources cited in this brief only for the Court's convenience. *See* Order, *K.C. v. Individual Members of the Med. Licensing Bd. of Ind.*, No. 23-2366 (7th Cir. 2023), ECF No. 47 (denying motion to strike identical appendix filed for this purpose).

App.726; James M. Cantor, *American Academy of Pediatrics policy and trans- kids: Fact-checking* 1, Sexology Today! (2018), App. 464.

Such desistence is good. The affected individual no longer has a mental health condition and needs no more treatment. While Plaintiffs say these lifetime drugs are safe and effective, Opening Br. 46, the Act seeks to protect children from "iatrogenic" intervention—treatments that *create* disease rather than cure it. Kenneth J. Zucker, *Debate: Different strokes for different folks* 1-2, Child & Adolescent Mental Health (2019), App.517-18. This intervention substantially risks disrupting the ordinary resolution of gender dysphoria. Children subject to it are far more likely to *persist* in experiencing gender dysphoria than those who aren't. Kristina R. Olson et al., *Gender Identity 5 Years After Social Transition*, 150:2 Pediatrics 3 (2022), App.521. So early transition "is not a neutral" decision. Cass Review 38, 62-63. The Act allows space for children's gender dysphoria to resolve.

This space is critical because a new group dominates gender clinics: mid-adolescent females *without* childhood history of gender discordance. Riittakerttu Kaltiala-Heino et al., *Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development*, 9 Child & Adolescent Psychiatry & Mental Health 6 (2015), App.615; Lisa Littman, *Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria* 3, PLOS ONE (2018), https://perma.cc/E8ZH-FWP6; Cass Review 38. Early

research did not study this group. Abbruzzese, *supra*, at 12, App.94. And modern research lags because this group is newly developing. Littman, *supra*, at 3. But as with males, nothing suggests this group will necessarily identify as transgender in adulthood. Caution is critical.

Because the Act aims to protect Oklahoma children no matter how they identify, it does not distinguish based on a suspect or quasi-suspect classification. *Eknes-Tucker*, 80 F.4th at 1227 (A law regulating "specific medical interventions for [all] minors [is] not one that classifies on the basis of any suspect characteristic under the Equal Protection Clause."). The Act's goal of protecting children is both legitimate and "compelling." *New York v. Ferber*, 458 U.S. 747, 756-57 (1982).

B. The Act reasonably advances its important goal of protecting children from risky drug treatments.

1. The Endocrine Society guidelines and WPATH standards of care lack evidence-based support.

Rejecting Oklahoma's concerns about unproven drug interventions, Plaintiffs invoke the WPATH and Endocrine Society policies to challenge the Act. Opening Br. at 5-8, 39-50. But "optimal clinical decision making requires" support "from systematic summaries" based on high-quality evidence. Gordon Guyatt et al., *Users' Guides to the Medical Literature* 10 (McGraw Hill Education, 3rd ed. 2015). The Endocrine Society guidelines and WPATH standards of care lack such evidentiary support.

The GRADE method is widely accepted for rating available medical evidence. *Id.* at 16. It ranks the evidence into four tiers. High-quality evidence means the "true effect [of intervention] lies close to that of the estimate." Howard Balshem et al., *GRADE guidelines: 3. Rating the quality of evidence*, 64 J. Clinical Epidemiology 401, 404 (2011), App.461. Moderate-quality evidence means the "true effect is likely to be close to the estimate…, but [it may be] substantially different." *Id.* Low-quality evidence means the "true effect may be substantially different from the estimate." *Id.* And very-low-quality evidence means the "true effect is likely to be substantially different from the estimate." *Id.*

When applied properly, the GRADE method "achieves explicit and transparent judgment" by requiring evaluators to disclose all evidence and reasons supporting their rating. Gordon Guyatt et al., *GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes*, 66 J. Clinical Epidemiology 151, 155 (2013), App.455. In general, strong recommendations should *not* be made based on low-quality evidence—only when "a panel would have a low level of regret if [later] evidence showed that their recommendation was misguided." Jeffrey C. Andrews et al., *GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength*, 66 J. Clinical Epidemiology 726, 731 (2013), App.490.

The Endocrine Society guidelines are not evidence-based. They lack support from systematic evidentiary reviews on key questions, including

whether the recommended treatments ease gender dysphoria, improve mental health, affect brain development, or impact fertility. Hembree, *supra*, at 3873, App.720; Jennifer Block, *Gender dysphoria in young people is rising—and so is professional disagreement* 2-3, BMJ (2023), App.496-97. The authors did not systematically list the evidence supporting their recommendations or justify their evidence ratings. Hembree, *supra*, at 3881-83, App.728-30. They alarmingly made strong recommendations based on low-quality evidence without saying whether or why they believe those recommendations satisfy GRADE criteria. *Id.*; Block, *supra*, at 2-3, App.496-97. This is advocacy—not good science.

Exemplifying this problem, one co-author acknowledged that the Endocrine Society had no data—"none"—to support Guideline 2.5, which suggests "there may be compelling reasons to start cross-sex hormones prior to age 16" when treating gender dysphoria. Icahn Sch. of Med., *State of the Art: Transgender Hormone Care* at 5:38-6:18, YouTube (Feb. 15, 2019), https://www.youtube.com/watch?v=m7Xg9gZS_hg; Hembree, *supra*, at 3871, App.718. This change, he said, gave doctors "cover" to provide cross-sex hormones to children. *State of the Art* at 5:38-6:18. Such disregard supports his earlier boast that most in "the medical world [are] more conservative than [endocrinologists]." *Id.* at 4:33-4:38. So as one developer of evidence-based medicine has said, the Endocrine Society guidelines have "serious problems." Block, *supra*, at 2, App.496.

WPATH standards also lack evidence-based support. The group admits its standards lack support from systematic reviews of available evidence and so do not rate the quality of its evidence. E. Coleman et al., *Standards of Care for the Health of Transgender and Gender Diverse People, Version 8*, 23 Int'l J. Transgender Health S1, S42 (2022), https://www.wpath.org/publications/soc. In their view, "a systematic review … is not possible," but a co-developer of evidence-based medicine says such reviews "are always possible," and the group would "violat[e] standards of trustworthy guidelines" by making "a recommendation without one." Block, *supra*, at 3, App.497. What's more, others *have* systematically reviewed the evidence, and the results are disturbing.

2. Systematic reviews have shown insufficient evidence to use puberty blockers and cross-sex hormones to treat minors with gender dysphoria.

Many groups, including the U.K. National Institute for Health & Care Excellence, have systematically reviewed available evidence supporting the use drug intervention to treat gender-dysphoric minors and concluded it has "very low" quality under the GRADE method. *Evidence review: Gonadotrophin releasing hormone analogues for children & adolescents with gender dysphoria*, NICE (2020) (NICE I), App.307-437; *Evidence review: Gender-affirming hormones for children & adolescents with gender dysphoria*, NICE (2020) (NICE II), App.151-306. So England's National Health Service has *stopped* using puberty blockers to

treat gender-dysphoric youth in clinical settings. *Implementing advice from the Cass Review*, NHS (2023), https://perma.cc/L2CV-M7ND.

Swedish and Finnish authorities have also systematically reviewed the evidence and concluded its quality is insufficient to justify using puberty blockers and cross-sex hormones for children with gender dysphoria in clinical settings. *Medical treatment methods for dysphoria associated with variations in gender identity in minors – recommendation* 1, Council for Choices in Health Care in Finland (2020), App.537; *Care of children & adolescents with gender dysphoria* 4, Socialstyrelsen (2022), App.57. Denmark has also begun promoting a "developmentally-informed approach that prioritizes psychosocial support and noninvasive resolution of gender distress" because of the "growing rates of detransition" and "profound uncertainty about long-term outcomes" in performing such "life-altering interventions." *Denmark Joins the List of Countries That Have Sharply Restricted Youth Gender Transitions*, SEGM (Aug. 17, 2023), https://perma.cc/D9XL-73YK. To be sure, European nations that forbid clinical use still allow research to continue, but that does *not* mean drug intervention is safe—clinical research aims to benefit future patients, not those being studied. *Clinical Research Versus Medical Treatment*, FDA (2018), https://perma.cc/8TTD-2HTP.

Likewise, McMaster University, where evidence-based medicine originated, systematically reviewed the "[e]ffects of gender affirming therapies in people with gender dysphoria" and concluded that (1) "there

is great uncertainty about the effects of puberty blockers, cross-sex hormones, and surgeries in young people with gender dysphoria" and (2) available evidence "is not sufficient to support … using these treatments." Romina Brignardello-Petersen & Wojtek Wiercioch, *Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence* 5 (2022), App.623. The Cochrane Library agrees, finding *not a single study* sufficiently rigorous to warrant inclusion in its systematic review. C. Haupt et al., Cochrane Library, *Anti-androgen or estradiol treatment or both during hormone therapy in transitioning transgender women (Review)* (2020), App.26-47.

And last summer, 21 clinicians and researchers from nine countries warned that treating gender-dysphoric minors with puberty blockers and cross-sex hormones "is not supported by the best available evidence," expressly criticizing "the Endocrine Society's claims" to the contrary. Riittakerttu Kaltiala et al., *Youth Gender Transition is Pushed Without Evidence*, Wall St. J., July 13, 2023, https://perma.cc/5P6X-KNHL. Per this report, "[e]very systematic review of evidence to date, *including one published in the Journal of the Endocrine Society*, has found the evidence for mental-health benefits of hormonal interventions for minors to be of low or very low certainty." *Id.* (emphasis added). "By contrast, the risks are significant and include sterility, lifelong dependence on medication and the anguish of regret." *Id.* Oklahoma's caution is warranted here.

3. Using puberty blockers and cross-sex hormones to treat minors with gender dysphoria has no proven benefits and poses substantial risk.

Despite these significant concerns, Plaintiffs say providing gender-dysphoric children puberty blockers and cross-sex hormones "greatly improve[s] the health and well[-]being" of affected children. Opening Br. 8. Yet those drugs have no proven benefits and pose substantial risk.

Start with supposed benefits. No reliable evidence suggests that drug intervention reduces the risk of suicide. WPATH's own commissioned review shows no link between the use of cross-sex hormones and decreased suicide rates in gender-dysphoric individuals. Kellan E. Baker et al., *Hormone Therapy, Mental Health, & Quality of Life Among Transgender People: A Systematic Review*, 5:4 J. Endocrine Soc'y 1, 12 (2021), App.511. Multiple studies have also found high suicide rates before, during, and after attempted gender transition. C.M. Wiepjas et al., *Trends in suicide death risk in transgender people: results from the Amsterdam Cohort of Gender Dysphoria study (1972-2017)*, 141 Acta Psychiatrica Scandinavica 486, 490 (2020), App.52; Jay McNeil et al., *Suicide in Trans Populations: A Systematic Review of Prevalence and Correlates*, 4:3 Psychology of Sexual Orientation & Gender Diversity 341, 348 (2017), App.479; Cecilia Dhejne et al., *Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden*, 6:2 PLOS ONE 1, 5 (2011), App.64. And more alarmingly, a recent study found that rates of suicidal ideation, suicide attempts, and non-suicidal

self-harm *increased* after minors began using puberty blockers and cross-sex hormones, Laura E. Kuper et al., *Body Dissatisfaction & Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy*, 145:4 Pediatrics 1, 8 (2020), App.533.

Likewise, no reliable evidence shows that drug intervention improves psychosocial outcomes. As the NICE systematic review found, studies showing puberty blockers and cross-sex hormones' effect on mental health outcomes trigger "very low certainty" and suggest little or no change. NICE I, *supra*, at 13, App.319; NICE II, *supra*, at 50, App.200. Indeed, many studies report *no* mental health improvement after such intervention. Riittakerttu Kaltiala et al., *Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria*, 74:3 Nordic J. Psychiatry 213, 217 (2020), App.607; Annette L. Cantu et al., *Changes in Anxiety & Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic*, 5:3 Transgender Health 196, 198 (2020), App.19; Polly Carmichael et al., *Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK*, 16:2 PLOS ONE 1 (2021), App.576-601; Elizabeth Hisle-Gorman et al., *Mental Healthcare Utilization of Transgender Youth Before & After Affirming Treatment*, 18 J. Sexual Med. 1444, 1447 (2021), App.122.

Moving to risks, drug intervention may impair cognitive development. Researchers know that "the pubertal and adolescent period is associated with profound neurodevelopment," which depends heavily on sex-specific hormones; and many academics worry that "pubertal suppression may prevent key aspects of development during a sensitive period of brain organization." Diane Chen et al., *Consensus Parameter: Research Methodologies to Evaluate Neurodevelopmental Effects of Pubertal Suppression in Transgender Youth*, 5:4 Transgender Health 246, 248-249 (2020), App.72-73. In response, a respected research group published a "consensus parameter" requesting more research on this issue, *id.*—a point other reviews and reports support—and noting the critical information deficit. NICE I, *supra*, at 38, App.344; Cass Review 38-39.

Next, these drug uses increase infertility risk. The Endocrine Society itself admits this. Hembree, *supra*, at 3878, App.725. Children who persist through their guidelines and take cross-sex hormones in early to mid-adolescence will lack "fertility preservation" options because they never develop fertility. Dep. of Armand H. Antommaria at 207:16-209:23, *Boe v. Marshall*, No. 2:22-cv-184-LCB (M.D. Ala. Apr. 21, 2023), App.751-52. And though two studies suggest a non-representative survey of females self-reported pregnancy after taking testosterone as adults, Alexis D. Light et al., *Transgender Men Who Experienced Pregnancy After Female-to-Male Gender Transitioning*, 124:6 Obstetrics & Gynecology 1120, 1126 (2014), App.7; Knudson, G., & De Sutter, P., *Fertility options in*

transgender and gender diverse adolescents. 96(10) Acta obstetricia et gynecologica Scandinavica 1269 (2017), these studies include no representative samples or adolescents who persist taking puberty blockers and cross-sex hormones. Indeed, "it is not possible for children who have not undergone natal puberty (and who may have used gender affirming hormones) to preserve gametes." Paula Amato, *Fertility options for transgender persons*, UCFS (June 17, 2016), https://perma.cc/6MJD-JJ9S. Such limited or even supportive studies hardly resolve Oklahoma's concerns.

Drug intervention may also weaken bone density. For adults, osteoporosis is a "well understood" risk of using cross-sex hormones long-term. Cass Review 36. And children face added risks. Because bone mineral density increases during puberty, children undergoing puberty suppression do not experience this full increase. Hembree, *supra*, at 3882, App.729; J.A. 748-51, 1297-98. And evidence suggests these children never catch up. *Id.*; NICE II, *supra*, at 14, App.164.

Cardiovascular decline is also a risk. As the Endocrine Society admits, evidence shows that cross-sex hormones detrimentally affect adult lipid profiles. Hembree, *supra*, at 3891, App.738. This is a "well understood" risk. Cass Review 36. NICE's systematic review uncovered *only one* cardiovascular study of individuals who began cross-sex hormones in adolescence, and it found statistically significant increases in blood pressure and body mass for both sexes and worsening lipid profiles for natal

females. NICE II, *supra*, at 14, App.164. Both the Endocrine Society and NICE say we need better studies to show how long-term use of cross-sex hormones beginning in adolescence affects cardiovascular health. Hembree, *supra*, at 3891, App.738; NICE II, *supra*, at 14, App.164.

Drug intervention may also limit sexual function. WPATH's president has reported that "about zero" natal males can achieve orgasm after undergoing early puberty suppression followed by cross-sex hormones and vaginoplasty. Michael Biggs, *The Dutch Protocol for Juvenile Transsexuals: Origins & Evidence*, J. Sex & Marital Therapy 12-13 (2022), App.566-67. While this issue needs more study, *id.*, there are substantial concerns with subjecting prepubertal children to interventions that may affect lifelong sexual function in ways they cannot possibly understand. Stephen B. Levine et al., *Reconsidering Informed Consent for Trans-Identified Children, Adolescents, & Young Adults*, J. Sex & Marital Therapy 15 (2022), App.704.

What's more, the long-term safety of "treatments in children and adolescents with gender dysphoria" is "largely unknown" because many identified risks tend to manifest later in life—e.g., the risk of cognitive impairment, cardiovascular decline, and osteoporosis. NICE II, *supra*, at 14, App.164. Indeed, early studies report substantial *increases* in mortality from suicide, cardiovascular events, and other problems more than ten years after drug and surgical intervention. One study found that suicide rates surged *over 19 times* the rate of controls in this population,

and that mortality rates from cardiovascular disease more than doubled. Dhejne, *supra*, at 5, App.64. Another study found that adults treated with cross-sex hormones faced increased long-term risk of death by suicide, stroke, and ischemic heart disease. Henk Asscheman et al., *A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones*, 164:4 Eur. J. Endocrinology 635, 635-42 (2011).

4. Drug companies have not sought regulatory approval for puberty blockers and cross-sex hormones to treat minors with gender dysphoria.

Given these concerns, it's no surprise that drug companies have not sought FDA approval to treat gender-dysphoric minors with hormonal interventions. Under federal law, a pharmaceutical company wanting to introduce any new drug into commerce must first obtain FDA approval. 21 U.S.C. § 355(a). If the FDA finds that the drug is safe and effective for use under conditions prescribed in proposed labeling, the pharmaceutical company can introduce the new drug into commerce using the approved labeling. *Id.* § 355(d). If the company seeks to modify its labeling to add a new use, the company must submit a new drug application seeking FDA approval for the change under the same process as the initial approval. 21 U.S.C. § 355(b); 21 C.F.R. §§ 314.54, 314.70.

Because the FDA typically limits its review to the proposed labeling, the agency does not evaluate the safety of a new drug for off-label

(i.e., unapproved) uses. *Understanding Unapproved Use of Drugs "Off Label,"* U.S. Food & Drug Admin. (2018), https://perma.cc/Y5LE-S9PZ. While clinicians may prescribe approved drugs for off-label uses when they believe it's "medically appropriate for their patient," *id.*, a drug manufacturer may not promote off-label uses of its drug. *See* 21 C.F.R. § 202.1(e)(4). Many manufacturers have faced significant criminal and civil penalties for doing so. *E.g.*, Press Release, U.S. Dep't Justice, *Pfizer to Pay $2.3 Billion for Fraudulent Marketing* (Sept. 2, 2009), https://perma.cc/W3JG-WPBE; Press Release, U.S. Atty's Off., *Abbott Laboratories and AbbVie Inc. to Pay $25 Million to Resolve False Claims Act Allegations of Kickbacks and Off-Label Marketing of the Drug TriCor* (Oct. 26, 2018), https://perma.cc/46HZ-CEPD; Press Release, U.S. Dep't of Justice, *Endo Pharmaceuticals and Endo Health Solutions to Pay $192.7 Million to Resolve Criminal and Civil Liability Relating to Marketing of Prescription Drug Lidoderm for Unapproved Uses* (Feb. 21, 2014), https://perma.cc/56G5-NH7F.

So pharmaceutical companies must decide whether it makes financial sense to seek FDA approval for off-label use. Such applications must prove that the drug is safe and effective under the proposed labeling. 21 U.S.C. § 355(d). This effort may cost companies substantial time and investment and, importantly, may reveal significant safety concerns with the new labeling. Often, companies lack financial incentive to seek such approval. That's true for AbbVie, Inc, manufacturer of the puberty

blocker Lupron, which netted $783 million from sales in 2021, *Financial Release*, AbbVie (2021), App.438-50, and for Endo Pharmaceuticals, manufacturer of the puberty blocker Supprelin, which netted over $114 million from sales the same year. *Endo Reports Fourth-Quarter & Full-Year 2021 Financial Results*, ENDO (2022), App.130-50.

With these massive profits and little scientific support, drug companies have no incentive to seek FDA approval for using puberty blockers and cross-sex hormones to treat gender dysphoria. In fact, Endo has said it "has no plans to seek regulatory approval for the use of its drug for" this purpose. Chad Terhune et al., *As more transgender children seek medical care, families confront many unknowns*, Reuters (Oct. 6, 2022), https://perma.cc/UYT2-GEHC. Without regulatory approval, the Minors Protection Act protects Oklohoma children from becoming human experiments for off-label drug use that the FDA has never approved.

5. That puberty blockers and cross-sex hormones are used to treat different physical illness does not make them safe to treat gender dysphoria.

Plaintiffs criticize the Act for allowing puberty blockers and cross-sex hormones to treat medical issues like "precocious puberty," "delayed puberty," and other physical ills but forbidding them to treat gender dysphoria. Opening Br. 9. This distinction is not arbitrary. The Act validly distinguishes what's safe to treat mental health conditions from what's safe to treat physical conditions that have different etiologies, diagnostic

criteria, and treatment pathways. Ignoring such distinctions would allow litigants to argue it's safe to prescribe chemotherapy drugs to treat anxiety because doctors use them to treat cancer.

Substantial differences separate different uses of puberty blockers and cross-sex hormones. For example, central precocious puberty occurs when a child experiences puberty earlier than normal. It is diagnosed through physical examination and laboratory testing. Melinda Chen & Erica A. Eugster, *Central Precocious Puberty: Update on Diagnosis & Treatment*, 17:4 Paediatr Drugs 273, 275 (2015), App.541. And it is treated through puberty blockers, though the patient stops these drugs in time to undergo endogenous puberty. By contrast, puberty blockers are administered for gender dysphoria *during* the normal ages for puberty, and when stopped, the child is prescribed cross-sex hormones to avoid endogenous puberty altogether. J.A. 575-76, 744, 747-48, 856, 889.

Likewise, polycystic ovary syndrome occurs when females overproduce testosterone. It is diagnosed through observation, imaging, and laboratory testing, and patients are often treated with estrogen to suppress testosterone, which aims to counteract the ill effects of abnormal hormone levels. A recent study shows that treating this condition with testosterone suppression may preserve fertility otherwise impaired by abnormal testosterone levels. E. Elenis et al., *Early initiation of anti-androgen treatment is associated with increased probability of spontaneous conception leading to childbirth in women with polycystic ovary syndrome: a*

population-based multiregistry cohort study in Sweden, 36:5 Human Reproduction 1427, 1433-34 (2021), App.116-17. Yet testosterone blockers for gender dysphoria thwart fertility and normal sexual function, as explained above.

Finally, consider sexual development disorders. All these disorders involve objective chromosomal or physical abnormalities. J.A. 664, 735, 1140, 1259, 1263. When used in these situations, drug intervention helps physically unhealthy individuals develop physically healthy sexual function consistent with their sex. In stark contrast, using puberty blockers and cross-sex hormones for gender dysphoria causes physically healthy individuals to *lose* healthy sexual function consistent with their sex. That critical difference justifies Oklahoma's Minors Protection Act.

6. Consistent with evidence-based medicine, this Court should credit experts based mainly on their analysis of published evidence.

Plaintiffs criticize Oklahoma's experts for never treating "youth with gender dysphoria." Opening Br. 43. But those experts use evidence-based medicine, which relies not on anecdote but on "the best available … evidence from systematic research." David L. Sackett et al., *Evidence based medicine: what it is and what it isn't*, 312 BMJ 71, 71 (1996), App.68; Guyatt, *Users' Guides*, *supra*, at xxiv. Systematic reviews rate evidence quality—placing randomized controlled trials at the top, and

"unsystematic observations of individual clinicians" at the bottom. *Id.* at 15-16. Plaintiffs treat the *least* reliable evidence as the best.

For example, Dr. Cantor is a Ph.D. clinical psychologist and researcher with decades of experience and dozens of peer-reviewed publications. He supported his 304-paragraph expert report with citations to over 250 different sources, most of which were peer-reviewed medical literature, including his own about treating gender dysphoria. The State's other experts are also qualified and similarly support their opinions.

This Court should reject prioritizing Plaintiffs' anecdotal evidence over this evidence-based science. Plaintiffs would have this Court override evidence-based science and declare the Minors Protection Act unconstitutional to allow experimental treatments that European countries—the world leaders in treating gender dysphoria—have concluded are inconclusive at best and harmful at worst. American kids deserve better.

II. This Court should allow state legislatures to decide this difficult medical issue rife with uncertainty and so avoid miring courts further in constitutionalized medicine.

"It is indisputable 'that a State's interest in safeguarding the physical and psychological wellbeing of a minor is compelling.'" *Otto v. City of Boca Raton*, 981 F.3d 854, 868 (11th Cir. 2020) (quoting *Ferber*, 458 U.S. at 756-57); *accord Eknes-Tucker*, 80 F.4th at 1225. And States play a "significant role … in regulating the medical profession." *Gonzales v. Carhart*, 550 U.S. 124, 157 (2007). Here, Oklahoma has enacted the Minors

Protection Act to safeguard children from potentially dangerous and experimental drug treatments. Section I, *supra*. Evidence strongly suggests that Oklahoma's caution is warranted. *Id*. But even if both sides had "medical support for their position," "[m]edical uncertainty does not foreclose the exercise of legislative power," and the State may reasonably act to protect children. *Gonzales*, 550 U.S. at 161, 164.

What's more, both sides have marshaled experts to support their positions. These experts belong to professional groups, but "their institutional positions cannot define the boundaries of" what the Constitution requires. *Otto*, 981 F.3d at 869. "They may hit the right mark," or they may "miss it." *Id*. And sometimes, these professional communities can be wrong "by a wide margin." *Id*. Indeed, it's "not uncommon for professional organizations to do an about-face in response to new evidence or new attitudes." *Id*. That's happened on the very issue presented here, as European nations are now backtracking and forbidding these drug interventions to treat children with gender dysphoria because new evidence suggests that caution is best. Section I.B.2, *supra*.

For this reason, courts give "state and federal legislatures wide discretion to pass legislation in areas where there is medical and scientific uncertainty." *Gonzales*, 550 U.S. at 163. This restraint is both wise and constitutionally required. Take *Roe v. Wade*, 410 U.S. 113 (1973), a case in which the Court constitutionalized abortion without textual support or certainty about unborn human life. Courts then struggled for decades

to apply an "inherently standardless" rule covering an issue "of great social significance." *Dobbs v. Jackson Women's Health Org.*, 142 S. Ct. 2228, 2272, 2284 (2022). Then just last year, the Court reversed *Roe*, admitting that precedent had "departed from [the Court's] normal rule" of legislative deference and regretting the tremendous "turmoil" that deviation inflicted. *Id.* at 2268, 2283. This Court should avoid similar turmoil by deferring to reasonable legislative judgment here.

CONCLUSION

This Court should affirm and uphold Oklahoma's right to protect children consistent with its reasonable legislative judgment.

Dated: December 18, 2023

Respectfully submitted,

/s/ Jacob P. Warner

JACOB P. WARNER
ALLIANCE DEFENDING FREEDOM
15100 N. 90th Street
Scottsdale, AZ 85260
(480) 444-0020
jwarner@ADFlegal.org

JOHN J. BURSCH
JAMES A. CAMPBELL
ALLIANCE DEFENDING FREEDOM
440 First Street NW
Suite 600
Washington, DC 20001
(202) 393-8690
jbursch@ADFlegal.org
jcampbell@ADFlegal.org

Attorneys for Amicus Curiae

CERTIFICATE OF COMPLIANCE

This brief complies with the word limit of Fed. R. App. P. 29(a)(5) because this brief contains 5,431 words, excluding parts of the brief exempted by Fed. R. App. P. 32(f).

This brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in Word 365 using a proportionally spaced typeface, 14-point Century Schoolbook.

All required privacy redactions have been made per 10th Cir. R. 25.5. The digital submission has been scanned for viruses with the most recent version of a commercial virus scanning program, Cortex XDR, Agent version 7.8.1, and according to the program is free of viruses.

Dated: December 18, 2023

/s/ Jacob P. Warner
Jacob P. Warner

Attorney for Amicus Curiae

CERTIFICATE OF SERVICE

I hereby certify that on December 18, 2023, I electronically filed the foregoing brief with the Clerk of the Court for the United States Court of Appeals for the Tenth Circuit by using the appellate CM/ECF system. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

/s/ Jacob P. Warner
Jacob P. Warner

Attorney for Amicus Curiae