No. 21-2875

IN THE UNITED STATES COURT OF APPEALS
FOR THE EIGHTH CIRCUIT

DYLAN BRANDT, et al.,

Plaintiffs-Appellees,

v.

LESLIE RUTLEDGE,
in her official capacity as the Arkansas Attorney General, et al.,

Defendants-Appellants.

On Appeal from the United States District Court
for the Eastern District of Arkansas
Case No. 4:21-cv-00450 JM (Hon. James M. Moody, Jr.)

BRIEF OF *AMICI CURIAE* BIOMEDICAL ETHICS AND PUBLIC HEALTH SCHOLARS IN SUPPORT OF PLAINTIFFS-APPELLEES AND AFFIRMANCE

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STATEMENT OF INTEREST[1]

Amici curiae listed in the Appendix are professors of law, medicine, and public health who teach and write about biomedical ethics. Biomedical ethics, sometimes referred to as bioethics, is "the discipline of ethics dealing with moral problems arising in the practice of medicine and the pursuit of biomedical research." J. R. Vevaina et al., 39 *Issues in biomedical ethics* 869–925 (1993), https://pubmed.ncbi.nlm.nih.gov/8243220. *Amici* have a strong interest in ensuring that principles of biomedical ethics are accurately described and properly applied. They submit this brief to explain how Arkansas' House Bill 1570 is inconsistent with foundational principles of biomedical ethics.

INTRODUCTION

Arkansas' House Bill 1570 (the "Health Care Ban") is an extreme and unjustified intrusion by the State into the medical profession. The law categorically prohibits health care professionals from providing gender-affirming care to their transgender minor patients with gender dysphoria, even when the patient, the patient's parents, and the patient's medical providers all agree that the care is medically appropriate and in the patient's best interest. Although the State claims

[1] Pursuant to Federal Rule of Appellate Procedure 29(c), *amici* certify that no person or entity, other than *amici curiae*, their members, or their counsel, made a monetary contribution to the preparation or submission of this brief or authored this brief in whole or in part. The parties have consented to the filing of this brief.

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that the law is necessary to promote medical ethics, the Health Care Ban in fact contravenes fundamental and well-established principles of biomedical ethics and misunderstands how medical knowledge is generated, creating serious, harmful consequences for individual patients and public health more generally.

Core principles of biomedical ethics include respect for autonomy, beneficence, and justice. The Health Care Ban eviscerates each of these principles. It deprives minor patients of their ability to decide whether to receive medically necessary and appropriate treatment to which they and their parents have given informed consent (autonomy). It forces providers to deny their patients care that is known to alleviate suffering, and thus to abandon their patients to serious physical and mental harm (beneficence). And it compels providers to deny care that only patients who are transgender need, thereby exacerbating stigma and inequity and damaging trust in the medical profession (justice).

The State endeavors to rationalize these harms by suggesting that gender-affirming care is unsound or experimental, but its arguments about randomized control trials and off-label use of prescription drugs badly misunderstand how medical knowledge is credibly generated, particularly in the context of pediatric care. Randomized control trials are not, and have never been, requisite for medical care to be considered appropriate, and in fact are ill-suited for many types of treatment. And off-label use is legal, commonplace, and often necessary to serve a

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patient's best interest. Far from being "experimental," the gender-affirming care prohibited by the Health Care Ban was developed through rigorous and appropriate methods and is recommended by every major medical association in the United States.

In sum, the Health Care Ban singles out and bans gender-affirming care for transgender minors based on false notions of biomedical ethics, science, and public health, without considering the grave harm that will come from denying vulnerable patients critical health care. The District Court properly enjoined the law, and this Court should affirm.

ARGUMENT

I. THE HEALTH CARE BAN CONTRAVENES KEY TENETS OF BIOMEDICAL ETHICS.

Although the State attempts to justify the Health Care Ban by reference to concerns about ethics, the Ban is directly at odds with key tenets of biomedical ethics: respect for autonomy, beneficence, and justice. Tom L. Beauchamp & James F. Childress, *Principles of Biomedical Ethics*, 13 (8th ed. 2019). These universal principles, which are the cornerstones of modern-day healthcare standards, guide providers' treatment decisions regardless of the type of medical care they are providing, including care for gender dysphoria.

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A. The Health Care Ban Forces Providers to Disregard Patients' Autonomy.

As a general matter, Arkansas law repeatedly recognizes the importance of obtaining informed consent and respecting patient decision making, reflecting the core biomedical ethical principle of respect for autonomy. That principle requires that patients have the ability to decide whether to receive appropriate medical care within the framework of informed consent. Beauchamp & Childress at 105. For example, the State has codified a definition of "informed consent"; has rendered the failure to adequately obtain informed consent tortious; and has created a statutory scheme governing how to evaluate such claims. *See, e.g.*, *Brumley v. Naples*, 320 Ark. 310, 317–18 (1995) (discussing medical malpractice claim involving lack of informed consent); Ark. Code Ann. § 16-114-206(b)(1) (2003) (defining "informed consent"). Arkansas also has enacted a "Right to Try" law, which allows a terminally ill patient, in "consultation with [their] physician," to "give[] informed consent" to use non-FDA approved drugs and medical products in order to treat their illness. Ark. Code § 20-15-2104 (2015). And Arkansas has provided that minors generally can consent to medical care, including surgery. *See, e.g.*, Ark. Code Ann. § 20-9-602(7) (2019) (allowing unemancipated minors to consent to "any surgical or medical treatment or procedure not prohibited by law that is suggested, recommended, prescribed, or directed by a licensed physician" if they are "of

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sufficient intelligence to understand and appreciate the consequences of the proposed surgical or medical treatment or procedures").

In stark contrast to these manifold laws reflecting the core principle of autonomy, the outlier Health Care Ban attacks autonomy by preventing individuals from pursuing, and health care professionals from providing, beneficial medical treatment with due regard for a patient's interests.

Empowering a patient's autonomy is essential to the integrity of the provider-patient relationship, as well as the patient's individual liberty and ability to determine the course of their life. In keeping with that bioethical principle, "the physician's professional role [is] to make recommendations on the basis of the best available medical evidence and to pursue options that comport with the patient's unique health needs, values, and preferences." Lois Snyder Sulmasy & Thomas A. Bledsoe, *American College of Physicians* ("ACP") *Ethics Manual* 170, Annals of Internal Medicine 86 (7th ed. 2019), https://www.acpjournals.org/doi/10.7326/m18-2160; *see also* Beauchamp & Childress at 105 (respect for autonomy requires health care professionals "to disclose information, to probe for and ensure understanding and voluntariness, and to foster adequate decision making"). Informed consent is a crucial mechanism for ensuring respect for autonomy. In all non-emergency encounters, the provider is obligated to offer the patient material information and guidance, but the patient must be trusted and empowered to make the informed and

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voluntary decision that best advances their interests. *See* Parth Shah et al., *Informed Consent* (2021), https://www.ncbi.nlm.nih.gov/books/NBK430827/. After the patient makes their decision, the provider's duty is to "protect and foster [the] patient's free, uncoerced choices." ACP *Ethics Manual* at 74.

Where, as here, the patients at issue are minors, the informed consent process usually involves the provider, the minor patient, and the minor's parents. When that is so, each actor has an important role to play: the provider offers medical instruction, the parents provide stewardship and consent, and the minor—assisted by that medical instruction and parental stewardship—provides assent. *See* Am. Med. Ass'n ("AMA"), *Code of Medical Ethics Opinion 2.2.1*, *Pediatric Decision Making*, https://www.ama-assn.org/delivering-care/ethics/pediatric-decision-making (discussing the importance of "[r]espect and shared decision making" between parents and minors "in the context of decisions for minors"); Beth A. Clark, *Ethics in Child & Youth Care Practice with Transgender Youth*, 8 Int'l J. of Child, Youth & Fam. Studies 74 (2017), http://dx.doi.org/10.18357/ijcyfs82201716754 (discussing relational ethics).

The process of informed consent (which, for minors, also frequently includes their parents) involves five core elements: 1) patient competence, 2) disclosure, 3) comprehension, 4) voluntariness, and 5) consent. Beauchamp & Childress at 122. As to the first element, parents generally have competence to participate in the

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informed consent process on behalf of their minor children, and many adolescent patients also have the competence to participate in the informed consent process, including in the context of gender-affirming care. *See* Jessica Kremen et al., *Addressing Legislation That Restrict Access to Care for Transgender Youth*, 147 Pediatric Perspectives (2021), https://pubmed.ncbi.nlm.nih.gov/33883246/ (minor patients who are transgender "possess decisional capacity, and with guardian consent and the support of a multidisciplinary team, [] are able to contribute to decisions in their own best interests about [Gonadotropin Releasing Hormones] and gender-affirming hormones"); Beth A. Clark & Alice Virani, *This Wasn't a Split-Second Decision: An Empirical Ethical Analysis of Transgender Youth Capacity, Rights, and Authority to Consent to Hormone Therapy*, 18 J. Bioethical Inquiry 151–164 (2021), https://pubmed.ncbi.nlm.nih.gov/33502682/ (concluding, based on qualitative empirical analysis, that "trans[gender] youth demonstrated the understandings and abilities characteristic of the capacity to consent to hormone therapy and that they did consent to hormone therapy with positive outcomes"); Richard E. Redding, *Children's Competence to Provide Informed Consent for Mental Health Treatment*, 50 Wash. & Lee L. Rev. 695, 707 (1993), https://scholarlycommons.law.wlu.edu/cgi/viewcontent.cgi?article=1759&context=wlulr ("Research . . . indicates that children often are capable of making important

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life decisions in a rational manner, including decisions about medical and psychological treatment.").

Once competence has been established, the elements of disclosure and comprehension require the provider to accurately and sensitively present relevant information about any diagnosis; the nature and purpose of recommended interventions; the burdens, risks, and expected benefits of all options, including forgoing treatment; and any limitations to the medical community's knowledge regarding burdens, risks, and expected benefits. AMA, *Code of Medical Ethics Opinion 2.1.1*, *Informed Consent*, https://www.ama-assn.org/delivering-care/ethics/informed-consent; Aníbal Torres Bernal & Deborah Coolhart, *Treatment and Ethical Considerations with Transgender Children and Youth in Family Therapy*, 23 J. of Fam. Psychotherapy 296, 287–303 (2012), http://dx.doi.org/10.1080/08975353.2012.735594.

For the fourth element, voluntariness, the provider must then assess the patient's (and, if not a mature minor, the parents') ability to understand relevant medical information and the implications of treatment alternatives and to make an independent, voluntary decision. AMA *Informed Consent*. Fifth, and finally, the patient—and, where the patient is a minor, usually the parents as well—decides how to proceed.

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From the perspective of biomedical ethics, a decision that is made jointly by a parent and child, aligns with a provider's recommendation, and is discerned through a process of informed consent should be fully respected. Indeed, medical professionals, parents, and adolescents are regularly entrusted to together decide the best course of treatment, including when the treatment has significant risks or permanent consequences. Pediatric chemotherapy or radiation, for example, are subject to principles of informed consent, despite the potential lasting effects on growth development and reproductive capabilities. *See, e.g.*, Am. Cancer Soc'y, *Late Effects of Childhood Cancer Treatment* (Sept. 18, 2017), https://www.cancer.org/treatment/children-and-cancer/when-your-child-has-cancer/late-effects-of-cancer-treatment.html. Pediatric breast reduction performed to address excess breast tissue, back pain, or social anxiety; pediatric rhinoplasty; and orthopedic surgery on minors following sports injuries likewise can have enduring impacts. There is nothing unique about gender-affirming care that demands a different scheme than allowing care when the provider, patient, and parents all agree about the best course of action.[2]

[2] Although the State claims an interest in safeguarding minors from procedures with long-term consequences, the Health Care Ban expressly allows surgical inventions to be performed on minors with intersex conditions, including infants too young to participate in the decision-making process, even though such procedures have irreversible, long-term consequences and raise serious ethical concerns. *See* H.B. 1570 § 3, Ark. Code Ann. § 20-9-1501(6)(B)(i); Human Rights Watch, *"I Want to Be Like Nature Made Me": Medically Unnecessary Surgeries on Intersex Children*

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By prohibiting health care providers from offering medically necessary and appropriate treatment to adolescents with gender dysphoria and denying patients the ability to access such care when they and their parents have given informed consent, the Health Care Ban disrespects autonomy and undermines the provider-patient relationship.

B. The Health Care Ban Forces Providers to Violate Their Duty of Beneficence.

The duty to act in the best interest of the patient is called beneficence, and is best understood as "a group of norms pertaining to relieving, lessening, or preventing harm and providing benefits and balancing benefits against risks and costs." Beauchamp & Childress at 13; *see also id.* at 217 ("[M]orality requires that we treat persons autonomously and refrain from harming them, but morality also requires that we contribute to their welfare.").[3] Medical professionals all over the world take oaths and are held to duties that encompass beneficence. For example, the World Medical Association's "Modern Hippocratic Oath" requires physicians to attest upon admission to the medical profession that the "health of [their] patient[s] will be [their] first consideration." World Medical Association, *Declaration of Geneva*

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in the US (2017), https://www.hrw.org/sites/default/files/report_pdf/lgbtintersex0717_web_0.pdf.

[3] A related principle, nonmaleficence, concerns avoiding the causation of harm. Nonmaleficence thus prohibits action while beneficence requires it. The Health Care Ban contravenes both principles.

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(1948). Likewise, the United Kingdom's General Medical Council requires physicians to "make the care of your patient your first concern." *Good medical practice: Duties of a doctor registered with the General Medical Council*, Gen. Med. Council 70–78 (2001), https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-medical-practice/duties-of-a-doctor. And the American Medical Association recognizes that "[t]he practice of medicine, and its embodiment in the clinical encounter between a patient and a physician, is fundamentally a moral activity that arises from the imperative to care for patients and to alleviate suffering." AMA, *Code of Medical Ethics Opinion 1.1.1*, *Patient-Physician Relationships*, https://www.ama-assn.org/system/files/code-of-medical-ethics-chapter-1.pdf.

1. The Health Care Ban's Treatment Prohibition Forces Providers to Violate Their Duty of Beneficence.

Applying the principle of beneficence to the treatment of a patient with gender dysphoria is straightforward. When untreated, gender dysphoria has serious mental and physical consequences, including anxiety, depression, self-harm, and suicidality. *See, e.g.*, Norman P. Spack et al., *Children and adolescents with gender identity disorder referred to a pediatric medical center*, 129 Pediatrics (2012), https://pubmed.ncbi.nlm.nih.gov/22351896; Kristina R. Olson et al., *Mental health of transgender children who are supported in their identities*, Pediatric Collections: LGBTQ+: Support and Care (Part 3: Caring for Transgender Children) (2016) https://publications.aap.org/pediatrics/article-

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abstract/137/3/e20153223/81409/Mental-Health-of-Transgender-Children-Who-Are. By contrast, evidence from both research and clinical experience makes clear that gender-affirming care improves patients' health and alleviates their suffering. *See* Br. of Am. Pediatric Ass'n et al. as *Amici Curiae* Supporting Plaintiffs at 12–13, *Brandt v. Rutledge*, No. 4:21-CV-00450-JM (E.D. Ark.), ECF No. 30 (June 24, 2021) (collecting evidence showing that gender-affirming care improves overall well-being; significantly lowers risk of depression, anxiety, and other negative mental health outcomes; and reduces rates of substance abuse and suicide attempts). Withholding care for gender dysphoria as the Health Care Ban requires thus can result in serious harm to patients, contrary to the core principle of beneficence.

2. The Health Care Ban's Referrals Prohibition Forces Providers to Violate Their Duty of Beneficence and Undermines Public Health.

In addition to prohibiting health care professionals from providing gender-affirming care to adolescents with gender dysphoria, the Health Care Ban also prohibits them from making referrals for such care. H.B. 1570 § 3, Ark. Code Ann. § 20-9-1502(b). The Health Care Ban thus prevents patients and their parents from learning from trusted sources about where to access treatment for gender dysphoria, undermining their ability to receive that care. Depriving patients of information from their health care providers about treatment options is dangerous for individual patient health and for public health more broadly.

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The duty of beneficence encompasses a provider's obligation—if they cannot personally provide care—to refer the patient to someone who can. *See* ACP *Ethics Manual* at 14 (explaining that a provider is not "obligated to recommend, perform or prescribe" a reproductive service, but, as in any other medical situation, "has a duty to inform the patient about care options and alternatives or refer the patient for such information, so that the patient's rights are not constrained"). The Health Care Ban forces providers to violate this duty by leaving their patients both without care and without referrals to get that care elsewhere. By design, the Health Care Ban requires providers to stay silent in the face of their patients' actual medical needs. *Cf. Sorrell v. IMS Health Inc.*, 564 U.S. 552, 566 (2011) ("[T]he free flow of . . . speech" has "great relevance in the fields of medicine and public health, where information can save lives." (quotation marks omitted)).

Stifling the flow of information between patients and their providers about accessing treatment undermines the integrity of the provider-patient relationship and individual patient health. "An integral component of the practice of medicine is the communication between a doctor and a patient." *Conant v. Walters*, 309 F.3d 629, 636 (9th Cir. 2002); *see also Wollschlaeger v. Governor, Fla.*, 848 F.3d 1293, 1313 (11th Cir. 2017) (en banc) (similar). Being able to engage in open dialogue with and access accurate and reliable information from one's provider about treatment options is critical to a patient's health in multiple respects, including promoting patient

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adherence to treatment plans. *See, e.g.*, Rainer S. Beck et al., *Physician-Patient Communication in the Primary Care Office: A Systematic Review*, 15 J. Am. Bd. Fam. Pract. (2002), https://pubmed.ncbi.nlm.nih.gov/11841136 ("When patients are informed and involved in decision making, they are more adherent to medical recommendations and carry out more health-related behavior change"). This is so even when—and perhaps especially when—there is societal debate about a proper course of treatment. If patients are denied competent information from a reliable source—their health care provider—about where they can obtain medically competent care, they will be forced to obtain that information elsewhere. "But word-of-mouth and the Internet are poor substitutes for a medical doctor; information obtained from chat rooms and tabloids cannot make up for the loss of individualized advice from a physician with many years of training and experience." *Conant*, 309 F.3d at 644 (Kozinski, J., concurring).

Preventing the flow of information from providers about where to access treatment is harmful not only for individual health, but for society and public health more broadly. Society "regard[s] private, professional communication between doctors and patients as a significant source of expert, dependable information. . .. This knowledge, once received, is pertinent to much more than our personal decisions about receiving medical care. It is relevant to how we think about the provision of medical care generally." Robert Post, *Informed Consent to Abortion:*

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A First Amendment Analysis of Compelled Physician Speech, Univ. of Illinois L. Rev. 939, 977–78 (2007). "[I]f the state could freely . . . manipulate the trustworthy information that we were able to receive from our physicians"—including referrals for treatment—it would raise serious concerns, for society depends on "knowledge that our doctors can uniquely provide, so that we can decide for ourselves what our medical care ought to be." *Id.* at 977–78; *see also Pac. Gas & Elec. Co. v. Pub. Utils. Comm'n of Cal.*, 475 U.S. 1, 8 (1986) (explaining that the First Amendment is concerned with government efforts to "limit[] the range of information and ideas to which the public is exposed").

In short, restricting speech about where to obtain treatment based on a particular viewpoint as the Health Care Ban requires will undermine public trust in health care providers, with the likely consequence of leading people to ignore the recommendations of their providers, or to avoid health care settings altogether. *See infra* I.C (describing distrust resulting from denial of care); *see also 44 Liquormart, Inc. v. R.I.*, 517 U.S. 484, 503 (1996) ("The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good.").

* * *

The principle of beneficence obligates providers to remove conditions that will cause harm to others as well as protect and defend the rights of others.

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Beauchamp & Childress at 219. By mandating that providers deny care to their patients with gender dysphoria when the patient and their parents seek that care and the provider deems it medically indicated, and then abandon them with no referral for alternative sources for treatment, the Health Care Ban forces providers to cause harm to their patients and, thus, to violate their core duty of beneficence.

C. The Health Care Ban Forces Providers to Violate Their Duty of Justice.

A third core principle of bioethics—justice—requires providers to acknowledge inequalities in the delivery of medical care and to work toward fair, equitable, and appropriate treatment for all. Beauchamp & Childress at 267–68; Clark, *Ethics in Child & Youth Care Practice with Transgender Youth* at 79. The Health Care Ban undermines this ethical duty of providers by creating a complete barrier to transgender adolescents receiving gender-affirming care.

The Health Care Ban denies care to a certain class of patients based on their identity as transgender: care is banned only if it is for purposes of "gender transition," which is care that only transgender individuals seek. The Health Care Ban thus imposes medical strain and financial costs on only those patients. For example, as Plaintiffs have explained, the Ban, if allowed to go into effect, will force them to consider moving out of state or to endure the negative health effects from stopping hormone therapy and to fear for their ability to survive without treatment. *See* Plaintiffs-Appellees' Br. at 14–18, 53. These costs are on top of the many

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socioeconomic and geographic barriers to gender-affirming care that transgender youth often already face. *See* Phillip E. Wagner et al., 39.1 *Health (Trans)gressions: Identity and Stigma Management in Trans* Healthcare Support Seeking* 51 (Oct. 2016) (noting "[t]he difficult decisions trans* individuals make in regard to their healthcare have been well documented" and include "[f]inancial barriers, insurance issues, and access to services"). The Health Care Ban exacerbates and reinforces these already significant challenges by preventing transgender youth from accessing the gender-affirming healthcare they require.

By prohibiting medical providers from providing or referring patients for gender-affirming care, the Health Care Ban also would create distrust between transgender people and health care providers, which can lead transgender people to avoid the medical system altogether. Avoiding or delaying care leads "to poorer physical and mental health outcomes," and withholding information from patients "can result in receiving inappropriate care or missed opportunities for preventative care." Luisa Kcomt et al., *Healthcare avoidance due to anticipated discrimination among transgender*, 11 SSM - Population Health 100608 (2020), https://www.sciencedirect.com/science/article/pii/S2352827320302457.

As a matter of biomedical ethics and its core principle of justice, medical practitioners must not cause patients to fear seeking care, nor deny them care that, by definition, only people who are transgender need. The Health Care Ban forces

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health care providers to violate this principle by mandating discrimination against a vulnerable and stigmatized population.

* * *

The State claims the mantle of safeguarding medical ethics, *see* Def.-Appellants Opening Br. ("OB") at 55, but it is not. It is doing the opposite. The Health Care Ban is unsupported by biomedical ethics or any of its core principles; to the contrary, it commands their violation, for no legitimate purpose, resulting in physical and emotional suffering.

II. THE HEALTH CARE BAN RESTS ON A FUNDAMENTAL MISUNDERSTANDING OF HOW SCIENTIFIC KNOWLEDGE AND MEDICAL STANDARDS ARE GENERATED.

The State claims that the gender-affirming care prohibited by the Health Care Ban is "experimental" and not evidence-based. OB45, 48–49. This is contrary to reality: the gender-affirming care prohibited by the Health Care Ban is not "experimental," but was developed through rigorous and appropriate methods and is recommended by every major medical association in the United States. *See* Jason Rafferty, *Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents*, Am. Acad. of Pediatrics 5–18 (2018), https://publications.aap.org/pediatrics/article/142/4/e20182162/37381/Ensuring-Comprehensive-Care-and-Support-for; Br. of Am. Pediatric Ass'n et al. at 9. In support of its position, the State focuses on the lack of randomized control trials on

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hormone therapy, OB14, and emphasizes that using puberty blockers and hormone therapy for gender-affirming care is not approved by the U.S. Food and Drug Administration, OB8, 31. These arguments reflect a fundamental misunderstanding of medical practice and the ways medical knowledge and treatment guidelines are generated, particularly in the context of pediatric care. Medical providers are not and have never been restricted to providing only those treatments that have been generated via randomized control trial and received FDA approval for the particular indication. Indeed, as explained herein, such restrictions would be impractical and unethical.

A. The Medical Care Targeted By The Health Care Ban Is Not "Experimental."

Although the State and its expert Dr. Stephen B. Levine seek to justify the Health Care Ban as preventing "experimental" treatment—invoking inapposite examples of unethical human subjects research—they wrongly conflate clinical care with clinical research and fail to engage with the ethical standards attendant to each.

Medical care delivered by a clinician to a patient and clinical research have distinct purposes and processes. *See, e.g.*, Nat'l Commission for the Protection of Human Subjects of Biomedical Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (1978) (discussing the importance of distinguishing between research and clinical practice); U.S. Food & Drug Admin., *Clinical Research Versus Medical Treatment* (Mar. 22, 2018),

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https://www.fda.gov/patients/clinical-trials-what-patients-need-know/clinical-research-versus-medical-treatment (describing differences between clinical research and medical treatment in terms of intent, intended benefit, funding, timeframe, and other factors). In the clinical care setting, the provider's aim is to improve a patient's health, and the provider is duty bound to act in that patient's best interest. By contrast, the aim of a research study is to generate knowledge useful for *future* patients. *See* José A. Sacristán, *Clinical Research and Medical Care: Towards Effective and Complete Integration*, 15 BMC Med. Res. Methodol. (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4323129/. A research study's protocols must be ethically designed and administered, but there is no obligation to do what is in each participant's best interest. Contrary to the State's suggestion, receiving gender-affirming care does not automatically render a patient a subject of a research study (and certainly not an "experimental" one unmoored from ethical standards); gender-affirming care is known to advance the individual patient's best interest and is provided as clinical care for that purpose.

The suggestion of the State's expert, Dr. Levine, in the trial court that gender-affirming care provided to an individual patient to advance their best interest is comparable to the Tuskegee and Nazi experiments, *see Brandt v. Rutledge*, No. 4:21-CV-00450-JM (E.D. Ark.), ECF No. 45-1 (Decl. of Stephen B. Levine ¶ 112) (June 24, 2021), is both offensive and wrong, for myriad reasons. For one thing, neither

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the Black men in the Tuskegee study nor the victims of the Nazis' wartime research were willing participants. For another, those efforts were carried out without any person's informed consent and involved extremely disproportionate risk of harm to the people involved.

For example, the government-sponsored Tuskegee study withheld effective treatment from Black men with syphilis, resulting in the deaths of up to 100 study participants and enduring and devastating harms to Black men's health. *See* Allan M. Brandt, *Racism and Research: The Case of the Tuskegee Syphilis Study*, 8 The Hastings Center Report 21 (1978), https://dash.harvard.edu/bitstream/handle/1/3372911/Brandt_Racism.pdf; Vann R. Newkirk II, *A Generation of Bad Blood*, The Atlantic (June 17, 2016), https://www.theatlantic.com/politics/archive/2016/06/tuskegee-study-medical-distrust-research/487439/ (reviewing research finding that the Tuskegee study undermined Black men's trust in the medical system and "was responsible for over a third of the life-expectancy gap between older black and white men in 1980"). The Tuskegee researchers sought to justify depriving the study participants of the contemporary standard of care for syphilis based on their racist beliefs about Black men. Brandt at 23. This case, by contrast, concerns providers who are working to

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ensure that minors with gender dysphoria can access treatment known to be safe and effective and are thus endeavoring to *improve* their patients' health.[4]

B. Medical Knowledge Is Credibly Generated Through Multiple Methods, Not Just Randomized Control Trials.

In addition to conflating research and treatment, the State also misunderstands how medical knowledge is credibly and rigorously generated in suggesting that the lack of randomized control trials is dispositive. OB14. There is no one method used to generate medical knowledge, and no one method is considered requisite to a treatment being deemed medically appropriate. Rather, medical knowledge and practice are informed by a range of research and clinical inputs.

A randomized control trial—where some participants are randomly assigned to a treatment group and others are randomly assigned to a control group—is one of many types of credible research designs used to evaluate a medical intervention. Medical interventions also can be and often are evaluated through observational studies, which include cross-sectional studies (based on data collected from a single point in time), and longitudinal studies (based on data collected from particular individuals over time). *See, e.g.*, Edward L. Hannan, *Randomized Clinical Trials and Observational Studies: Guidelines for Assessing Respective Strengths and*

[4] It should go without saying that gender-affirming care is wholly unlike the ghastly experiments the Nazis performed on unwilling Jewish people and others during the Holocaust.

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Limitations, 1(3) JACC: Cardiovascular Interventions 211–217 (2008), https://www.sciencedirect.com/science/article/pii/S1936879808001702. In addition, randomized *clinical* trials, which compare different established interventions to one another, may be used to inform medical treatment. For example, a randomized clinical trial has been used to evaluate sex hormone treatment for gender dysphoria, comparing different, established pharmacological treatments to one another. *See* Carla Pelusi et al., *Effects of Three Different Testosterone Formulations in Female-to-Male Transsexual Persons*, 11 J. Sex Med. 3002–3011 (2014), https://www.jsm.jsexmed.org/article/S1743-6095(15)30626-3/fulltext.

Study methods other than randomized control trials may be preferable in some circumstances, given that randomized control trials are not always feasible, appropriate, or the most reliable way to evaluate a medical intervention. For instance, randomized control trials are rarely used for interventions focused on children or pregnant people, or for surgical interventions. *See, e.g.*, Denise Thomson et al., *Controlled Trials in Children: Quantity, methodological quality and descriptive characteristics of Pediatric Controlled Trials published 1948–2006*, 5 PLoS One (2010), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2948021/; Katrien Oude Rengerink et al., *Pregnant women's concerns when invited to a randomized trial: A qualitative case control study*, 15 BMC Pregnancy and Childbirth 207 (2015),

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https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-015-0641-x; Natalie S. Blencowe et al., *Interventions in randomized controlled trials in surgery: issues to consider during trial design*, 16 Trials (2015), https://doi.org/10.1186/s13063-015-0918-4. Randomized control trials also are only ethical when there is clinical "equipoise," which means they are only appropriate when there is genuine uncertainty about whether the intervention will be more effective than the control. *See* Benjamin Freedman, *Equipoise and the Ethics of Clinical Research*, 317 N. Engl. J. Med. 141–145 (1987), https://www.nejm.org/doi/full/10.1056/NEJM198707163170304. That is because it is unethical to knowingly expose participants to an inferior intervention or control. This principle plainly applies to hormone therapy for gender dysphoria: performing randomized, placebo-controlled trials on the efficacy of that treatment would be unethical, because the prevailing view among the medical community is that for patients who need it, hormone therapy is superior to a lack of pharmacological treatment. *See* Rafferty at 10.

C. Off-Label Drug Use Is Legal, Common, And, When Medically Indicated, Safe And In Service Of A Patient's Best Interest.

The State also emphasizes that gender-affirming care involves off-label use of FDA-approved drugs. OB8, 31. But off-label use is "a widely employed practice," *Planned Parenthood Cincinnati Region v. Taft*, 444 F.3d 502, 505 (6th

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Cir. 2006), that is legal, accepted, and, when medically indicated, safe and in service of a patient's best interest.[5]

An understanding of the FDA approval process makes clear why there is nothing unsafe or inappropriate about off-label use. Garnering the FDA's approval of a drug requires showing that it is both safe—*i.e.*, the benefits outweigh the potential risks—and effective for its intended use. *See* U.S. Food & Drug Admin., *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective* (Nov. 24, 2017), https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective. It is well-established practice that once a drug has been approved by the FDA, health care providers may then prescribe it for other medically appropriate uses and in other dosages. *See Taft*, 444 F.3d at 505. Such off-label use occurs because medical knowledge about how a drug might be beneficial in a different context or a different dosage continues to develop after FDA approval, but it is often too costly and impractical for drug makers to put each possible use of a drug through the FDA's "formal, lengthy, and

[5] Belying its stated concern with off-label use, Arkansas recently issued guidance providing that clinicians can prescribe certain drugs off label to treat COVID-19, even while acknowledging that the FDA has found that those drugs are not effective or beneficial for that purpose. *See* Arkansas Dep't of Health, *Guidance for the Use of Hydroxychloroquine and Chloroquine for the Treatment of COVID-19*, July 29, 2020, https://www.pharmacyboard.arkansas.gov/wp-content/uploads/2020/08/guidance_using_hydroxychloroquine_and_chloroquine.pdf.

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expensive" approval process. Am. Cancer Soc'y, *Off-Label Drug Use* (Mar. 17, 2015), https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/off-label-drug-use.html (noting that off-label drug use is "well-documented and very common in" oncology, "pediatrics and HIV/AIDS care"). In addition, providers often prefer that drug makers *not* seek approval for every off-label use, given that it could increase the cost of the drug and limit the scope of its clinical application, all of which would make it less available to their patients. *See* Cong. Res. Serv., *Off-Label Use of Prescription Drugs* 4 (Feb. 23, 2021), https://sgp.fas.org/crs/misc/R45792.pdf.

Thus, and contrary to the State's ill-informed argument, off-label use is legal, common, and often essential for delivering medically necessary care.

Off-label use is legal because FDA approval only limits how a drug can be marketed—*i.e.*, a drug cannot be marketed for a use different from its FDA-approved use—but not how a physician can prescribe it. *See Buckman Co. v. Pls.' Legal Comm.*, 531 U.S. 341, 351 & n.5 (2001); John J. Smith, *Physician Modification of Legally Marketed Medical Devices: Regulatory Implications Under the Federal Food, Drug, & Cosmetic Act*, 55 Food & Drug L.J. 251–252 (2000) (discussing off-label use and noting that "regulatory efforts are directed primarily at device marketing by manufacturers, not device use by physicians"). In fact, multiple federal and state laws have been enacted in recent years to promote and protect off-

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label prescriptions. *See, e.g.*, Okla. Rev. Stat. § 63-1-2604 (prohibiting health insurers from excluding coverage of off-label cancer treatments); Am. Soc'y of Clinical Oncology, *Recent Developments in Medicare Coverage of Off-Label Cancer Therapies*, 5 J. Oncology Practice 18–20 (2009), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2790627/ (discussing 1993 legislation requiring Medicare to cover off-label uses of anti-cancer drugs and an expansion of Medicare's off-label coverage in 2008).

Off-label use also is common and "generally accepted." *Buckman*, 531 U.S. at 351; Christopher M. Wittich et al., *Ten common questions (and their answers) about off-label drug use*, 87 Mayo Clinic Proc. 982–990 (2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/ (discussing off-label drug uses that have "become widely entrenched in clinical practice and become predominant treatments for a given clinical condition" and citing studies showing that in a group of commonly used medications, 21% of prescriptions were for off-label use). For example, about half of drugs used to treat cancer are prescribed off label. *See* Am. Soc'y of Clinical Oncology, *Reimbursement for cancer treatment: Coverage of off-label drug indications*, 24 J. Clinical Oncology 3206–3208 (2006), https://ascopubs.org/doi/10.1200/JCO.2006.06.8940. Off-label use is especially common and important in treating minors, as they are often excluded from clinical drug studies, including for ethical reasons. *See* Wittich (citing study finding that

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nearly 80% of children discharged from pediatric hospitals were taking at least one off-label medication and discussing range of widely practiced off-label drug uses in pediatric population); H. Christine Allen et al., *Off-Label Medication Use in Children, More Common Than We Think: A Systematic Review of the Literature*, 111 J. Okla State Med. Assoc. 776–783 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6677268 (surveying ten years of literature and finding that "[t]he use of off-label medications in children remains a common practice for pediatric providers").

Finally, and critically, off-label use is often essential for delivering the best care. James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71–104 (1998), https://pubmed.ncbi.nlm.nih.gov/11795338/ ("Off-label use is widespread in the medical community and often is essential to giving patients optimal medical care, both of which medical ethics, FDA, and most courts recognize."); William Janssen, *A Historical Perspective on Off-Label Medicine: From Regulation, Promotion, and the First Amendment to the Next Frontiers*, SSRN Elec. J. (2014), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2519223 (explaining that in some circumstances, "a physician's failure to prescribe the medical product for such an unapproved use can constitute medical malpractice").

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In sum, and contrary to the State's claims, the Health Care Ban does not prohibit treatment that is "experimental" or non-evidence-based. The State's arguments to support these claims are based on a fundamental misunderstanding of both how scientific knowledge is generated and the FDA approval process. Treatment methods do not require a randomized control trial or on-label use to be safe and effective. The State's contrary position, if accepted, would undermine a significant portion of modern medical practice, including almost all forms of pediatric health care and much of adult health care.

CONCLUSION

The Health Care Ban contravenes multiple, fundamental principles of biomedical ethics and fails to rationally protect minors—to the contrary, it mandates their harm. Unwarranted restrictions on the provision of health care by the State are unethical and detrimental to public health. Were the State permitted such a significant intrusion on health care here, it would open the door to unprecedented State intrusion into medicine and patient rights. This Court should reject such a result and affirm the decision below.

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CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 32(g), I certify as follows:

1. This Brief of Amici Curiae in Support of Plaintiffs-Appellees and Affirmance complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because this brief contains 6,201 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(f); and

2. 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 a proportionally spaced typeface, 14-point Times New Roman, using the word-processing system Microsoft Word 2010.

Dated: January 19, 2022

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CERTIFICATE OF SERVICE

I hereby certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Eighth Circuit by using the appellate CM/ECF system on January 19, 2022.

I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

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