

**IN THE UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF ARKANSAS
CENTRAL DIVISION**

DYLAN BRANDT, et al.,

PLAINTIFFS,

v.

No. 4:21-CV-00450-JM

LESLIE RUTLEDGE, et al.,

DEFENDANTS.

SUPPLEMENTAL DECLARATION OF PAUL W HRUZ, M.D., PH.D.

Pursuant to 28 U.S.C. 1746, I declare:

1. I have been retained by counsel for Defendants as an expert witness in connection with the above-captioned litigation. I have actual knowledge of the matters stated in this declaration. A detailed summary of my background and credentials was provided in my initial declaration on this case, dated July 7, 2021. A true and accurate copy of my CV is attached as Exhibit A to that initial declaration.

2. I have reviewed the supplemental declarations provided by Drs. Adkins and Antommaria and the new declaration provided by Dr. Turban in reference to this case. I provide here additional scientific evidence and discussion of key assertions made by the Plaintiffs' witnesses that are false or highly misleading. This response is not exhaustive of all of my opinions. Many of the claims made by the Plaintiffs' witnesses were addressed in part or fully in my first declaration.

3. My opinions as detailed in this declaration are based upon my knowledge and direct professional experience in the subject matters discussed. The materials that I have relied upon are the same types of materials that other experts in my field of clinical practice rely upon when forming opinions on the subject including hundreds of published, peer reviewed scientific research (and clinical) articles.



4. Below is a summary of my supplemental opinions regarding the Plaintiffs' Supplemental Expert Witness Declarations and Dr. Turban's new declaration:

a. The studies cited by the Plaintiffs' experts suffer from methodological flaws. This includes the studies that Dr. Turban cites to argue that gender-transition procedures lead to long-term benefits. Accurate assessment of the relative strengths and weaknesses of current approaches to the care of children must include knowledge of the limitations of scientific study that is based upon convenience sampling, failure to include properly selected control groups, lack of randomization of study subjects, and *a priori* rejection of alternate hypotheses.

b. Neither the size nor number of professional organizations issuing endorsements for gender affirming medical interventions including use of puberty blockers and cross-sex hormones guarantees the veracity of the claims made. The relevant scientific community includes investigators who are able to objectively consider the merits of claims made.

c. The most recent studies addressing questions of psychological health in youth with gender dysphoria continue to have major weaknesses and limitations which prevent definitive conclusions to be made on long-term benefit.

d. In the absence of higher quality data in children, recently published evidence for lack of long-term benefit in treated adults must be considered.

e. Assertions regarding the experimental nature of the gender affirmation including use of puberty blockers and cross sex hormones are based upon lack of understanding of long term effects including treatment related side effects and efficacy in preventing suicide.

I. SUPPLEMENTAL DECLARATION OF DR. ADKINS:

5. Although Dr. Adkins continues to assert that youth who experience gender dysphoria after the onset of puberty do not desist, she provides zero experimental evidence to support this claim. Her single reference to a book chapter co-authored by Dr. Turban does not represent scientific evidence for this claim.

6. Dr. Adkins' reiteration of her claim that the number and size of professional organizations endorsing the affirmative model for addressing gender dysphoria guarantees the veracity of the recommendations made is not supported by high quality research. As discussed in more detail below, significant limitations and weaknesses are pervasive in the existing peer reviewed gender dysphoria literature. Dr. Adkins' claim that papers referenced by the Endocrine Society and WPATH represent rigorous research appear to reflect a lack of understanding of what constitutes scientific rigor. It is important to recognize that nearly all of the recommendations made in the Endocrine Society Guidelines were rated by the GRADE system as "low" or "very low" evidence. By definition, this rating means that that there is a high likelihood that the recommendations are likely to change once higher level evidence is gathered (Atkins D., et al. (2004). Grading quality of evidence and strength of recommendations. *BMJ*, 328(7454):1490). The mere number of published studies does not obviate these concerns. While this is not unique to the field of transgender medicine, the strength of recommendations made and the failure to consider alternate hypotheses regarding treatment are unique to this emerging discipline.

7. It is erroneous to draw conclusions on the purported safety of puberty blockers in adolescents with normally timed puberty based upon data collected in children treated for precocious puberty. These are different conditions and the effects of the timing of the intervention is highly relevant to assessment of safety. The statement that "there is no evidence

of short or long term negative effects on patients who receive puberty blockers” either reflects an ignorance of the published literature addressing this question or a failure to appreciate the significance of the data that was cited in my declaration. This includes information contained within the product labels for this class of medication. It is particularly relevant that “Psychiatric events have been reported in patients taking GnRH agonists, including LUPRON DEPOT-PED. Postmarketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger and aggression.” (AbbVie, Lupron Depot (Leuprolide acetate) Product Monograph. 2018, AbbVie Corporation).

8. Dr. Adkins’ statements regarding the effects of puberty blockade on bone density are inaccurate. She references two studies to assert that while bone density is lower during treatment, bone density normalizes after initiation of cross-sex hormones. The paper by Klink et al. (Klink, D., et al. (2015). Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria. *The Journal of Clinical Endocrinology & Metabolism*, 100(2): E270-E275) is a retrospective study that looked at bone mineral density (BMD) in 34 young gender dysphoric adults at the average age of 22, who had been given puberty blockers to suppress or delay puberty for 1.3–1.5 years, followed by cross-sex hormones for about 3 years. The main finding of this study is that young adults treated with GnRH agonists (i.e. puberty blockers) during adolescence have decreased bone mineral density (BMD) and loss of bone mass despite the subsequent administration of cross-sex hormones. Importantly, most of the study subjects were relatively late in their puberty when puberty blockers were initiated (average age 15 years), so much of their bone mass development had already occurred. From this study, it cannot be known how much BMD in children and younger adolescents treated with puberty blockers at a

younger age will be affected, nor can it be known whether these losses will lead to increased risk of fractures in later life. The second study she cites specifically addressed bone geometry not bone density. The authors note many limitations to the interpretation and application of the data generated. While assessment of bone geometry adds to the overall assessment of bone health, it does not negate the concern for adverse effects of pubertal suppression on bone density in adolescent youth.

9. Dr. Adkins' dismissal of published literature on known and potential adverse effects of cross-sex hormones by an ipse dixit statement that these side effects are rarely seen in patients with well managed treatment should not be accepted by this Court as a reliable source of evidence. Rather, rigorous examination of scientific studies examining verifiable outcomes with known error rates should be considered. The review article by Weinand and Safer that Dr. Adkins cites (Weinand, J. D. & Safer, J. D. (2015). Hormone therapy in transgender adults is safe with provider supervision; A review of hormone therapy sequelae for transgender individuals. *Journal of clinical & translational endocrinology*, 2(2): 55–60) contains references to multiple studies reporting the same known and potential adverse effects included in my original declaration. In many cases, Weinand states that the evidence is inconclusive. Thus, despite the claim that cross-sex hormones are safe, the existing literature provides evidence for significant adverse effects including changes in body weight, insulin sensitivity and thromboembolism (i.e. stroke).

10. Contrary to the comments of Dr. Adkins in criticizing Dr. Levine regarding infertility following gender affirming medical interventions, concern for impaired fertility is a known and significant risk of cross-sex hormone administration, particularly when given to adolescent children who have not undergone full gonadal maturation, often because of pubertal

blockade. Recognition of this risk is the basis for offering counseling on fertility preservation prior to starting such interventions. Despite the routine offering fertility preservation, <5% of adolescents accept this intervention (Nahata, L., et al. (2017). Low Fertility Preservation Utilization Among Transgender Youth. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine*, 61(1): 40–44). However, studies have provided evidence that nearly half of transgender adults regret not being able to have biological children (see De Sutter, et al. (2002). The desire to have children and the preservation of fertility in transsexual women: A survey. *International Journal of Transgenderism*, 6(3): 215–221; and Wierckx, K., et al. (2012). Reproductive wish in transsexual men. *Human reproduction*, 27(2): 483–487). The attempt to minimize the significance of infertility in this patient population provides additional evidence of a biased assessment of the risk of gender affirming medical interventions.

11. Dr. Adkins incorrectly summarizes my conclusions regarding the most prudent approach to addressing morbidity associated with sex-gender identity discordance. My opinion, succinctly stated, is that with the current evidentiary base, provision of gender affirming medical interventions for gender dysphoric youth does not meet the minimum standards of risk–benefit analysis. Until higher quality evidence is available, such interventions should be reserved for properly controlled and supervised clinical trials. This can and should include studies to test alternate hypotheses regarding etiology and approaches to treatment.

II. DECLARATION OF DR. TURBAN:

12. Dr. Turban’s portrayal of the concerns I and other Defense expert witnesses have raised about properly interpreting the statements made by professional organizations regarding the care of children with gender dysphoria, particularly the claim that this represents scientific consensus is inaccurate on multiple levels. There is no basis for dismissal of the emerging concerns in other countries regarding the “Dutch model” (i.e., pubertal suppression and cross-sex

hormones) for gender dysphoric youth. Dr. Turban assumes that the conclusion made in the evidence based reviews from Sweden, Finland and the United Kingdom are due to a lack of consideration of recently published literature. However, as discussed in detail below, each of the studies published in the past year that he cites contain several serious methodological weaknesses. This is in agreement with the conclusions reached in the NICE reports and the data that formed the basis of the decisions reached in Sweden and the UK.

13. Dr. Turban lists 8 studies on puberty blockers and 6 studies on cross-sex hormones to assert that these interventions have been demonstrated to be safe and effective in the medical treatment of gender dysphoria. It is therefore important to objectively review study design, data, and conclusions that can be made from these reports.

14. With respect to studies on the effect of pubertal blockade on gender dysphoric youth:

a. De Vries 2011 – While this study (De Vries, A. L., Steensma, T. D., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2011). Puberty suppression in adolescents with gender identity disorder A prospective follow-up study. *The Journal of Sexual Medicine*, 8(8), 2276-2283) did show improvement in psychological function over baseline with use of puberty blockers, the authors acknowledged that they do not know why these improvements occurred and that psychological support or other reasons may have been responsible for the observed effect. This study highlights the need for proper control groups.

b. De Vries 2014 – The strength of this study (De Vries, A. L., McGuire, J. K., Steensma, T. D., Wagenaar, E. C., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2014).

Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*, 134(4), 696-704) is that it evaluated psychological outcomes from the start of pubertal blockade to at least one year following gender affirming surgery. It is limited by potential for selection bias, a relatively small cohort size (55 patients out of the 196 consecutively referred patients qualified for the study), and similar to the 2011 De Vries study did not contain a control group. It is also noteworthy there was a patient in this cohort who died from surgical complications.

c. Van der Miesen 2020 – This paper (van der Miesen, et al. (2020). Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. *The Journal of adolescent health: official publication of the Society for Adolescent Medicine*, 66(6): 699–704) reports on a cross-sectional study comparing 272 youth who had just been referred to the gender center and 178 youth who had received gender affirming medical interventions. These do not represent randomly selected patients such as what could be obtained from a non-clinical probability sample. The authors of this study themselves acknowledge: “The present study can, therefore, not provide evidence about the direct benefits of puberty suppression over time and long-term mental health outcomes. Conclusions about long-term benefits of puberty suppression should thus be made with extreme caution needing prospective long-term follow-up studies with a repeated measure design with individuals being.”

d. Turban 2020 – This paper (Turban, J.L., et al. (2020). Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*, 145(2): e20191725) was cited and discussed in my initial declaration. I note that Dr. Turban uses

this study as support for benefit of pubertal blockade. However, the only statistically significant difference related to “lifetime suicidality.” This does not demonstrate that it improved suicidality. Since this measure includes the study subjects’ entire lifetime, it is entirely possible that there were baseline differences in suicidality that influence whether or not study subjects were offered pubertal blockade. It is also important to note that the study did not show statistical difference in past year suicidality. Conjecture regarding the influence of social stress on outcomes, while perhaps a testable hypothesis, was not examined in this study. There are also concerns with the data used (i.e. the 2015 US Transgender Survey) as I will discuss in more detail below.

e. Achille 2020 – Similar to the studies described above, limitations of this study (Achille, C., et al. (2020). Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. *International Journal of Pediatric Endocrinology*, 2020(1): 8) include small number of subjects, short-term follow up (1 year), potential for recruitment bias, and lack of any control group.

f. Kuper 2020 – This study (Kuper, L.E., et al. (2020). Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics*, 145(4)) represents a larger cohort than previous studies (148 subjects) and assesses longitudinal changes in reported outcome measures. It is limited by only assessing short-term (1 year) follow up. It is important to recognize that reports of suicidal ideation, suicide attempt, and non-suicidal self-injury were not statistically improved during the follow-up period. Similar to the 2020 Turban paper, raw numbers were actually increased (see Table 5 of the Kuper paper).

g. Carmichael 2020 – I referenced this paper (Carmichael, P., et al. (2021). 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. *PLoS One* 16(2): e0243894) in my initial declaration. It is notable that Dr. Turban dismisses the lack of evidence for psychological benefit in this study as reflective of insufficient power to detect this outcome. As already noted, small sample size and lack of randomization are general limitations to most of the studies in this field, including this study. The number of subjects in this study is on par with the other published studies discussed above. The power to detect differences is influenced by the magnitude of effect. Based upon the data presented in this report, the intervention clearly did not produce a major effect on psychological outcome.

h. Dr. Turban lists an eighth study comparing 101 subjects who received psychotherapy and 100 subjects who received pubertal suppression plus psychotherapy. He does not provide a reference in his declaration but presumably this is the 2015 paper by Costa et al (Costa, R., et al. (2015). Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. *The journal of sexual medicine*, 12(11): 2206–2214. <https://doi.org/10.1111/jsm.13034>). In this study, both groups demonstrated clinically significant improvement in psychological functioning. While the abstract from this paper reports that the improvement was better at 12 months in patients who received pubertal blockade, at the endpoint of the study (18 months) this difference was no longer present. An unbiased conclusion from this study is that it demonstrates that psychotherapy is beneficial in gender dysphoric youth, not that puberty blockade was responsible for this effect.

15. Of the 6 studies referenced by Dr. Turban to support his conclusion that cross-sex hormones provide psychological benefit, 3 are the same studies used to argue for benefits of puberty blockade. It is important to note that Dr. Turban appears to recognize the limited power of these studies due to small sample sizes, yet he nevertheless ignores this fact in an attempt to build a case that quality scientific evidence of benefit exists in the extant published literature.

a. Lopez de Lara 2020 – Similar to the previously discussed papers, this study is limited by small sample size (23 subjects from a single center), short-term follow up (1 year), significant potential for selection bias based upon convenience sampling, and lack of randomization. The “control group” in this study consisted of untreated children without gender dysphoria matched for age, ethnicity, and socioeconomic status.

b. Kaltiala 2020 – This study is a retrospective chart review. In this case, direct quotation of the study results and conclusions of the authors places this study in proper context. In the summary of results, the authors state: “Those who did well in terms of psychiatric symptoms and functioning before cross-sex hormones mainly did well during real-life. Those who had psychiatric treatment needs or problems in school, peer relationships and managing everyday matters outside of home continued to have problems during real-life.” They conclude: “Medical gender reassignment is not enough to improve functioning and relieve psychiatric comorbidities among adolescents with gender dysphoria. Appropriate interventions are warranted for psychiatric comorbidities and problems in adolescent development.” This is hardly an endorsement for cross-sex hormone use in this patient population.

c. Allen 2020 – The study, while longitudinal in design, is limited by small sample size, lack of randomization, no control group and short-term follow up. The mean duration of treatment was one year with a minimum of only 3 months.

16. In all of these studies, even if one accepts the weakly supported conclusions that there is short-term psychological benefit, this does not establish that this benefit is sustained long-term or that the primary goal of suicide prevention is achieved. In fact, when considering the available data in the papers referenced by Dr. Turban, current suicidality was not significantly impacted. While such long-term studies do not exist for treated adolescents, the analogous data in treated adults indicates that all cause mortality in patients who received gender affirming medical interventions started to diverge from the background population 8–10 years later (see Figure 1 from Dhejne, C., et al. (2011). Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden, *PloS One* 6(2): e16885). The patients who had received such medical interventions were more likely to have died from any cause and from suicide, in particular.

17. Dr. Turban fails to acknowledge the limitations and weaknesses of the 2015 US Transgender Survey which served as the basis for his 2020 Pediatrics paper on lifetime suicidality for patients who were provided puberty blockers and the 2021 JAMA Surgery paper mentioned in Dr. Turban’s declaration (Almazan, A.N. & A.S. Keuroghlian. (2021). Association Between Gender-Affirming Surgeries and Mental Health Outcomes. *JAMA Surgery*, 156(7): 611–618.). This includes convenience sampling, recruitment of patients through transgender advocacy organizations, demand bias (a.k.a. the good subject effect), a high number of respondents who reported having not transitioned medically or surgically (and reported no desire to do so in the future), and several data irregularities. This included a high number of

respondents who reported that their age was exactly 18 years. As noted by D'Angelo and colleagues, these irregularities raise serious questions about the reliability of the USTS data (D'Angelo, R., et al. (2021). One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria. *Archives of sexual behavior*, 50(1): 7–16. <https://doi.org/10.1007/s10508-020-01844-2>)

18. Dr. Turban restates the common but erroneous assertion that it is unethical to conduct randomized controlled trials. This error is reflected in the false conception of how such studies can be performed. Contrary to “randomization to placebo,” the control group need not be left untreated. For a controlled trial to be performed, ideally all interventions would be the same in both the intervention and control groups except for the independent variable. In this context, for example, a randomized controlled trial might involve intervention and control groups both receiving psychological support and treatment of associated co-morbidities while being randomized for one of two possible intervention for a defined period of time with close monitoring for adverse effects under the supervision of a standard institutional review board. There is no claim that such studies can or should be double blinded. Dr. Turban’s assertion is based on the assumption that gender-transition procedures will benefit patients. It is contrary to the scientific method, however, to assume that a hypothesis regarding the effects of a medical intervention is correct without first rigorously testing for evidence to reject the null hypothesis (i.e. that there is no difference between the intervention and control group).

19. In Dr. Turban’s claim that the risks of gender affirming medical interventions are mischaracterized in the defense declarations, he makes several false or misleading statements about the effects of these interventions. A brief summary of these issues is presented in the following paragraphs:

20. Dr. Turban minimizes the risk of impaired fertility and in two important areas conflates data in adolescents to very different patient populations. It is not correct to equate effects of pubertal blockade for precocious puberty to blocking normally timed puberty. During pre-pubertal life, gonadotropin signaling is normally quiescent. Puberty represents a critical period for full gonadal maturation leading to reproductive capacity. Blocking gonadotropin release during puberty restores the body to its pre-pubertal state, with quiescent gonadotropin signaling. A patient placed on GnRH agonists to block normally timed puberty will not have undergone the gonadotropin release necessary to have reached full gonadal maturation and subsequent reproductive capacity. Because of this effect on reproductive development, it is incorrect to infer that the effects of cross-sex hormones on an adult patient who was allowed to complete gonadal maturation during puberty will be the same when applied to adolescents who have not been allowed to complete pubertal development. Additionally, arguing that puberty blockade alone, without proceeding to cross-sex hormones, is reversible ignores the existing data showing that the vast majority of patients who receive puberty blockers will proceed to this later stage of intervention (see De Vries, A. L., et al. (2011). Puberty suppression in adolescents with gender identity disorder A prospective follow-up study. *The Journal of Sexual Medicine*, 8(8), 2276–2283).

21. Dr. Turban's dismissal of the risk of impaired fertility is also belied by the counseling that patients receive prior to starting cross-sex hormones. Recognition of the adverse effect of cross-sex hormones on gonadal maturation is precisely the basis for the requirement to counsel patients on fertility preservation prior to starting this intervention. An entire industry has evolved to provide assisted reproductive technologies to assist transgender patients in conceiving biological children after engaging in gender affirming medical interventions (See Maxwell, S., et

al. (2017). Pregnancy Outcomes After Fertility Preservation in Transgender Men. *Obstetrics and gynecology*, 129(6): 1031–1034 regarding the need for assisted reproductive technology as cited by Dr. Adkins in her declaration footnote 9). Thus, to argue that fertility is not affected is blatantly false.

22. The concern for the effects of pubertal blockade on bone density is primarily related to peak bone mass, not current fracture risk. It is well established that the teenage years are critical for bone mineral accrual (see NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy (2001). Osteoporosis prevention, diagnosis, and therapy. *JAMA*, 285(6): 785–795). Studies that have examined the effects of pubertal blockade have consistently demonstrated significant effects on this process (See Vlot, M.C., et al. (2017). Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone*, 2017 Feb. (95): 11–19). There is published literature indicating partial improvement with initiation of cross-sex hormones, but the relevant readout is not just change from baseline, but differences between achieved bone mass and the expected increase in untreated individuals (See Wiepjes, et al. (2017). Bone Mineral Density Increases in Trans Persons After 1 Year of Hormonal Treatment: A Multicenter Prospective Observational Study. *Journal of bone and mineral research*, 32(6): 1252–1260). Fracture risk at 5–10 years is not the relevant concern but rather osteoporosis and increased fracture risk later in life.

23. The apparent dismissal of published studies showing metabolic changes associated with increased cardiovascular risk reflects the general biased assessment of relative risk versus benefit among those advocating for gender-transition procedures. While it is correct to acknowledge that there are many contributing factors to cardiometabolic risk, this does not

diminish the concerns that cross-sex hormones have many known and unknown risks. Even if one accepts the proposition that results are inconclusive, this would imply that they have not been demonstrated to be “safe.” Given the short duration that most adolescents have been exposed to cross-sex hormones (generally less than 10 years) and the time to which metabolic changes could lead to clinically detectable atherosclerosis and myocardial infarction, it is not surprising that the current data remains inconclusive for this outcome measure. The demonstrated increased risk of thromboembolic stroke in biological males exposed to estrogen is not insignificant.

24. Dismissal of known and potential cancer risk, similar to concerns about cardiometabolic risk, is unwarranted. This is another area where a longer timeframe is required to establish meaningful conclusions. At best, the available evidence indicates that the influence of cross-sex hormones on cancer risk is inconclusive. In addition to increased risk from hormone exposure, failure to perform regular cancer screening when presenting to medical providers as a sex that is not in accord with a patient’s internal anatomy and genetics adds another potential risk. While data is limited, it is false to claim that there is no evidence of risk.

25. In addition to the known and potential adverse physical effects of puberty blockers when used to halt normally timed puberty, social harms must also be considered. The Endocrine Society Guidelines include acknowledgement that experiencing puberty on a different timeline than one’s peers has “potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age” and that they may experience “the sense of social isolation from having the timing of puberty be so out of sync with peers.” (See Hembree, W.C., et al. (2017). Endocrine Treatment of Gender-

Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 102(11): 3869–3903.)

26. Claims by Dr. Turban that the reports from the United Kingdom, Sweden, and Finland do not accurately summarize the evidence (§53) appear to reflect an underlying bias. The conclusions in these reports highlight the poor quality of research in this field and the many unanswered concerns about relative risk versus benefit of gender affirming medical interventions. As I have discussed above, the additional studies referenced by Dr. Turban in his declaration do not rectify these concerns but rather continue to reflect the weak evidentiary base. The data cited in formulating the Finland, Sweden, and U.K. reports support the recommendation for, at a minimum, a pause in the unquestioning advocacy for this gender affirming medical interventions as the best, and often only, approach to alleviate suffering in this vulnerable patient population. There remains a clear need for ongoing research that considers alternate hypotheses regarding etiology and approaches to treatment.

27. Similar to Dr. Adkins, Dr. Turban refers to his book chapter to perpetuate the unsubstantiated claim that desistance rarely if ever occurs if a patient continues to self-report a sex discordant gender identity after puberty has started. Yet in his declaration he fails to cite any scientific study to support this claim. As noted in my declaration, the only citation for this claim is another book that does not provide such evidence.

28. Dr. Turban provides an erroneous description of the data available regarding biological influences for sex-discordant gender identity. A key distinction must be made between genetic influences and genetic determinants. There are many conditions (e.g. alcoholism and compulsive gambling) that are known to have a genetic link. However, predisposition does not guarantee outcome. There are numerous ways in which genetic

predisposition can contribute to gender dysphoria but this does not prove that this outcome is predetermined at birth. The best example of this association is the established increased risk of sex-discordant gender identity in autistic children. Reference to neuroimaging studies also fail to establish a biological determinant of sex-discordant gender identity. Dr. Turban ignores the evidence I provided in my declaration regarding wide overlap in structural differences between males and females, neuroplasticity, and unresolved questions regarding cause versus effect.

29. Dr. Turban's dismissive comments regarding the methodological limitations and high potential for bias in the 2105 U.S. Transgender Survey require some comment to allow the Court to properly understand the concerns raised. This survey has been used in a number of recent publications including Dr. Turban's 2020 study published in *Pediatrics* on puberty blockers and lifetime suicidal ideation. One need not invoke a conspiracy theory to understand the high potential for recruitment bias, recall bias, and the inability to substantiate the claims of survey respondents. The most significant limitations of this survey are adequately outlined by the 2021 paper of D'Angelo et al. (see D'Angelo, et al. (2021), cited fully above).

III. SUPPLEMENTAL DECLARATION OF DR. AN TOMM ARIA:

30. A major focus of Dr. Antomm aria's first and supplemental declarations is on the question of what constitutes experimentation versus standard medical practice. Beyond formal definitions and colloquial uses of these terms, the underlying premise is that gender affirming medical interventions (including halting of normally timed puberty, administration of cross-sex hormones and surgical alteration of primary and secondary sexual anatomy) is known to be both safe and effective in alleviating distress in youth who experience sex-discordant gender identity. An associated presumption, used by each of the Plaintiffs' expert witnesses, is that this will prevent affected adolescents from committing suicide. This is reflected in Dr. Antomm aria's comments of his supplemental declaration (¶6). Understanding of the pervasive limitations and

weaknesses in the published literature in this field, most notably the lack of evidence showing that this approach substantially improves long-term suicidality and mental health needs in children is the primary concern that led to the passing of the Arkansas SAFE act. Concerns are augmented by the failure to investigate alternate hypotheses with outright rejection of any intervention that may result, intended or unintended, in realignment of gender identity with biological sex. While medical practitioners in general, and pediatricians in particular, must often engage in attempts to provide care in the absence of definitive outcome data, the degree of caution used in engaging in such treatments is generally aligned with the ambiguities present. Such responsible conduct is largely absent in the rapidly expanding field of transgender medicine. Given the continued poor understanding of gender dysphoria and the relative risks and benefits of various treatment approaches, it is prudent to conduct medical interventions only as part of controlled clinical trials.

31. Dr. Antommara correctly notes that many medications used in pediatric patients have not been FDA approved for children. There are many ways in which “off label” use is permissible. While in some cases “off-label use may be well-supported by evidence,” this is not the case for halting normally timed puberty for gender dysphoric youth. In prescribing medications “off-label,” physicians assume responsibility for the risk of an adverse event and must inform patients of such risk. As demonstrated by the comments of the Plaintiffs’ witnesses in this case, it is doubtful that the use of puberty blockers to halt normally timed puberty is presented in this way. Repeatedly, the assertion is made that the use of puberty blockers is known to be safe and fully reversible. The falsehood of this claim was discussed in my initial declaration including reference to my published article that covers this in greater detail (see Hruz, P.W., L.S. Mayer, & P.R. McHugh. (2017). Growing Pains: Problems with Puberty

Suppression in Treating Gender Dysphoria. *The New Atlantis*, 52(Spring 2017): 3–36). In this context, acknowledgement of the off-label use of this class of medication is appropriate and informative without insinuation that the intent is to portray such use as illegal.

32. In making his assertion that it is justifiable to make strong recommendations based upon low quality of evidence, Dr. Antommara fails to present the entire context for the importance of understanding bias in research and the reasons why the GRADE system was developed in the first place. The creation and intended use of the GRADE system is well described in a series of papers published in the BMJ in 2008. Details and links to these papers are readily available on the GRADE workgroup website (<https://www.gradeworkinggroup.org/>). There are unique aspects to the treatment of gender dysphoria that require specific comment regarding strong recommendations for interventions that are based upon low quality evidence. As clearly stated by the GRADE workgroup, “strong recommendations mean that most informed patients would choose the recommended management and that clinicians can structure their interactions with patients accordingly.” Most patients who present to gender clinics desire (and often demand) gender affirming medical interventions. Under such circumstances, making a strong clinical recommendation does not ensure that this is based upon careful assessment of relative risk versus benefit.

33. Dr. Antommara’s dismissal (§14) of the Bränström paper (Bränström, R., & Pachankis, J. E. (2020). Reduction in Mental Health Treatment Utilization Among Transgender Individuals After Gender-Affirming Surgeries: A Total Population Study. *The American journal of psychiatry*, 177(8): 727–734) as being irrelevant to the assessment of risks and benefits of gender affirmation medical interventions for gender dysphoric youth reflects the prevailing but erroneous assumption that this approach is founded on solid scientific grounds. It reflects my

stated concern regarding confirmation bias. When presented with new evidence that challenges the assertion that mental health is improved by cross-sex hormones and gender affirming surgery, Dr. Antommara continues to rely on the low quality evidence contained in the Endocrine Society Guidelines. It is even more revealing that what was actually found in the data from the Bränström study (i.e. that cross-sex hormones and surgery provided no long-term change in mental health needs) is in stark contrast to how this paper was presented. The failure to appreciate or even consider these concerns is highly concerning regarding ability to objectively opine on the scientific evidence related to treatment of gender dysphoria.

34. The Plaintiffs' experts, including Dr. Antommara, associate gender affirming medical interventions with the treatment of patients with disorders of sexual development ("DSDs"). It is important to note the major differences between these two conditions and the basis for medical care.

a. DSDs represent a unique situation where sexual identity can be ambiguous. This is the one situation where sex is tentatively assigned at birth. In the absence of a DSD, sex is correctly identified, not assigned, at birth. As data becomes available on etiology and expected outcomes related to sexual function, sex may be "reassigned." Note the importance of distinguishing the use of term "sex" and "gender" as they are intended to reflect different aspects of sexual form and expression.

b. Gender identity in patients with DSDs will be highly dependent on the underlying defect present.

c. Nearly all patients with gender dysphoria have normally formed and functional genitalia and gonads prior to the start of affirmative interventions. In contrast, many if not most patients with DSD have impaired or absent fertility.

d. Surgeries for minors with DSDs are generally directed to correcting anatomical defects with clinical significance. This would include defects that restrict urinary outflow, increase risk of urinary tract infections, or pose a cancer risk (e.g. intraabdominal testes or other dysgenetic gonads containing a Y-chromosome)

e. DSD advocacy groups strongly argue against medical interventions to change sexual appearance. The focus is on preventing surgeries in infancy. Older patients are quite vocal about the potential harms of genital surgeries.

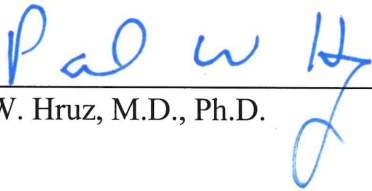
f. The calculation of relative risk versus benefit of surgeries for DSDs most definitively is not the same as performing similar procedures for management of gender dysphoria.

35. Contrary to the biased and inaccurate conclusions of Drs. Turban, Adkins, and Antommaria as conveyed in their declarations, serious questions remain regarding the best approach to care for individuals who express an understanding of their gender identity that is discordant with their biological sex to alleviate dysphoria and associated psychological morbidity. Scientific deficiencies include understanding of etiology, the influence of gender affirming medical care on persistence versus desistence, long-term psychological health following gender affirming medical interventions in affected youth, and adverse physical effects of these interventions. Existing evidence claiming benefit remains of low quality and is hampered by major methodological limitations and weaknesses. When objectively reviewed, these data indicate that suicidality remains high in affected youth even after receiving hormonal interventions. This cannot be explained entirely by the social stress hypothesis. Emerging data challenges prevailing assumptions of the ability of hormonal and surgical interventions to reduce psychological morbidity in affected adults. Under these circumstances, it is appropriate to

restrict such interventions in children to properly designed and supervised clinical trials that explore a full range of alternative hypotheses.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on July 19, 2021.



Paul W. Hruz, M.D., Ph.D.