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Articles

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Preface

The Fall edition features an article by Deirdre T. Little, MBBS, Elvis I. Šeman, MBBS, Ph.D., and Anna L. Walsh, LL.M., which addresses the essential elements of informed consent to the novel, provisionally registered, COVID-19 vaccines. First, it addresses the ethics of obtaining informed consent based upon the medical facts, by structuring the nature of informed consent into twelve component parts. Second, as guidance for family physicians, it explores reasonable medical concerns arising from COVID-19 disease and the various available vaccines. The provision of ethically obtained, fully informed, consent is very pertinent to an experimental vaccine notwithstanding the pandemic context. To ascertain informed consent to the best of our ability, the gap between officially delivered information and reasonable concerns must be addressed in a structured manner by physicians. Consent should not be coerced, but should be free of inducements and reprisals, and respecting human rights, because of the experimental nature of COVID-19 vaccines. Each potential vaccine recipient needs sufficient information to make his or her own judgment. The process of informed consent must include discussion of personal concerns as well as the most up to date information about vaccine risks and benefits.

The second article, by Maria Howard, Ph.D., and Pamela S. Kohlmeier, M.D., J.D., explores how current healthcare law fails to offer adequate protections during a pandemic: (1) to healthcare workers practicing under significantly altered standards of care, and (2) to individuals involved in the allocation of scarce medical resources. Using research on Second Victim Syndrome and Medical Malpractice Stress Syndrome, legal protections are proposed in order to provide healthcare workers a form of "moral buffering" and to help prevent further traumatizing them at a time when they are shouldering extraordinary burdens during the COVID-19 pandemic. The authors advocate the passage of appropriate legal protections as not only a relevant legal issue, but also an ethical one.

In the third article, Akhil Patel, M.D., et al., examine the morbidity of neonates and families with Neonatal Opioid Withdrawal Syndrome (NOWS), and develop a voluntary program to prevent NOWS. The opioid epidemic resulted in a vast increase in NOWS. To mitigate NOWS, and opioid dependency among women, the authors established a gender specific, patient driven, autonomy based, outpatient therapeutic substitution program. Patients underwent universal urine drug screens to identify illicit drug use with dependency and offered addiction counseling with voluntary outpatient therapeutic substitution in an obstetrical-addictions combined clinic to achieve abstinence with oral Buprenorphine tapering protocol. Urine substance screening and cord blood testing were obtained at delivery. Birth outcomes compared among groups who achieved abstinence at birth, were successful at ta-

pering, or continued opioid use. The authors conclude that outpatient therapeutic substitution with oral Buprenorphine with abstinence is possible in pregnant patients and results in zero NOWS. More data are needed to confirm findings and explore methods for enhanced success in obtaining abstinence.

The fourth article, by Blanka Bartos, Dr. Jur., LLM, examines newborn screening policy for Spinal Muscular Atrophy (SMA). One in every 10,000 children is born with SMA and half of them will not survive two years. It is a hereditary genetic disorder. If it is discovered immediately after birth, newborns may benefit from the newest medicines to sustain their lives. Unlike some other common genetic diseases (e.g. Down-Syndrome), SMA may be screened prior to pregnancy to determine whether the parents are carriers. In Hungary, due to the baby Zente case, people have urged reform. Australia and Germany have also discovered the need for screenings. The U.S. has already introduced newborn screening for SMA. National policies should adhere to the same path to contribute to appropriate family planning and to make the treatment available as soon as possible in order to provide a longer and better life for affected infants.

In the final article, Steven Andrew Jacobs, J.D., Ph.D., surveys biologists around the globe to determine whether there is a consensus on when human life begins. Since a recent study suggested that 80% of Americans view biologists as the group most qualified to determine when life begins, experts in biology were surveyed in order to provide a consensus perspective. Biologists from 1,058 academic institutions around the world assessed survey items on when human life begins and, overall, 96% (5337 out of 5577) affirmed the fertilization view. The founding principles of the field Science Communication suggest that scientists have an ethical and professional obligation to inform people about scientific developments so members of the public can be empowered to make life decisions that are consistent with the best information available. Given that perspective, science communicators should work to increase the level of public awareness of the fertilization view, as it stands alone as the leading biological perspective on when life begins.

Barry A. Bostrom, J.D.
Editor-In-Chief

Articles

COVID-19 Vaccination: Guidance for Ethical, Informed Consent in a National Context

Deirdre T. Little,* Elvis I. Šeman,** and Anna L. Walsh***

ABSTRACT: This Guidance addresses the essential elements of informed consent to novel, provisionally registered COVID-19 vaccines which conform to the current definition of an investigational vaccine namely, lacking requirements for approval for full registration. [1] First, it addresses the ethical obtaining of informed consent in a setting of short and long term knowns and unknowns, by structuring the personal nature of informed consent into its twelve component parts. Second, as a guidance for family physicians, it explores reasonable medical concerns arising for individuals from both knowns and unknowns about COVID-19 disease and vaccines.

Where there are waves of pandemic pressure impelling political, economic, social and public health forces to promote vaccination to health care providers and their patients, the necessary constituents of valid informed consent can be sublimated and possibly forfeited. This context of informed consent for COVID-19 vaccines is not unique to Australia. The analysis and presentation of international data by Aus-

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The views of the authors are their own. The authors wish to acknowledge the invaluable assistance of Dr John Fleming, Dr Renjy Nelson, Dr Mark Hobart, Mr Michael McHugh and Mr Paul Hanrahan.

[1] Council for International Organizations of Medical Sciences. Cumulative Pharmacovigilance Glossary Version 1.0 <https://cioms.ch/wp-content/uploads/2021/03/CIOMS-Cumulative-PV-Glossary-v1.0.pdf>.

tralian Government agencies is a process occurring in all countries. Therefore, the Australian experience of consenting for vaccination is relevant to informed consent across the globe.

The purpose of this Guidance is to assist personalised risk-benefit assessment for the informed consent of the vaccinee. Its aim is not to give a therapeutic guide nor to draw conclusions which can only rightly be drawn pertaining to each individual recipient in discussion with a health care provider. This is especially true in the setting of incomplete research where the many unknowns may be more significant for some than others. Since data is changing over time, national tables have not been used for specifics which the vaccine provider should access at the time of consultation.

While we recommend the Guidance be read in conjunction with Government issued information, this Guidance will address specific fields relevant to informed consent which may not be addressed in those communications, but which a consenting individual as a person with their own values and experiences may wish to know.

Aim: To address the requirements of ethical informed consent of the individual adult in the context of reasonable concerns pertaining to the unknowns and incomplete research attending novel, provisionally registered COVID-19 vaccines.

Methodology: To elucidate what might be reasonable concerns for individuals considering vaccination, Public Assessment Reports of regulatory authorities (Food and Drug Administration and Therapeutic Goods Administration) and published trials of currently available vaccines were reviewed. International Covid-19 vaccine safety discussions were observed for peer-reviewed and, if necessary, pre-print references base. These references were studied for potential relevance to vaccine recipients. Vaccine Development Guidelines were also reviewed for pre-clinical requirements and compared with pre-clinical data presented at licensing. Missing information was requested from the Therapeutic Goods Administration (TGA).

Pertinent unknowns were thereby identified as issues potentially relevant to fully informed consent, and compared with the content of standard Government-issued vaccine consent advice forms. Disparities were selected as relevant unknowns or reflecting incomplete research.

Pertinent issues were incorporated into a twelve point structure for reasonable consideration to guide ethical inform consent. Paediatric COVID disease and vaccination are mentioned briefly due to paediatric vaccination being unapproved in Australia at the time of writing in under 12-year-olds, and exclusion of minors from phase III safety and efficacy trials.

Conclusion: **The provision of ethically obtained, fully informed consent is very pertinent to an investigational vaccine notwithstanding the pandemic context. To ascertain informed consent to the best of our ability, the gap between officially delivered information and reasonable concerns generated by knowns and relevant unknowns, can be addressed in a structured manner by physicians. Consent should not be coerced but be free of inducements and reprisals, respecting declarations of human rights, particularly given the investigational nature of COVID-19 vaccines. Each recipient requires adequate information to make their own judgment. The process of validly informed consent will therefore include discussion of concerns and of relevant information we do and do not yet have. Ethical informed consent should address those concerns as best is possible.**

Background

A programme for vaccination against COVID-19 disease commenced in Australia in 2021. The Therapeutic Goods Administration (TGA) provisionally approved the Pfizer/BioNTech mRNA vaccine BNT162b2 ('Comirnaty') and the University of Oxford/AstraZeneca viral vector vaccine ChAdOx1 nCoV-19 (AZD1222) in February. Provisional, not full, registration was granted as both vaccines are investigational. Additionally, another mRNA vaccine, Moderna, is provisionally registered to become available later in 2021. Australia has determined a fourth vaccine 'Novavax', a protein vaccine with completed phase 3 trials, is eligible to apply for provisional registration in the Australian Register of Therapeutic Goods.

Initially, the Pfizer vaccine has been limited to certain population groups and, ultimately, all adults will have access to a COVID-19 vaccine with an AstraZeneca vaccine safety caveat for those under 60 years of age, for whom the 'Pfizer' vaccine is now preferred. Phase III trials on the currently used vaccines, Pfizer and AstraZeneca, are published and accessible.[2,3]

The fast-tracking of anti-COVID-19 disease vaccine development has resulted in products with more known unknowns, and unknown unknowns, than any other vaccine in common usage.[4] While short term safety follow-up involves direct electronic

[2] Fernando P. Polack, et al, 'Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine' (2020) 383 New England Journal of Medicine 2603 <https://www.nejm.org/doi/full/10.1056/NEJMoa2034577>.

[3] M Voysey et al, 'Safety and Efficacy of the ChAdOx1 nCoV-19 Vaccine (AZD1222) Against SARS-CoV-2; An Interim Analysis of Four Randomised Controlled Trials in Brazil, South Africa and the UK' (2021) 397 Lancet (10269) 111 <https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32661-1/fulltext>.

[4] See, eg, Peter Doshi, 'Clarification: Pfizer and Moderna's "95% effective" vaccines—We Need More Details and the Raw Data' BMJ Opinion (Blog Post, 5 February 2021) <https://blogs.bmj.com/bmj/2021/02/05/clarification-pfizer-and-modernas-95-effective-vaccines-we-need-more-details-and-the-raw-data/>.

patient contact on Day 3 post vaccination and mandatory healthcare provider reporting of Adverse Events Following Immunization (AEFI), longer term safety information will rely more heavily on the recognition and voluntary reporting of adverse events by General Practitioners, nurses, hospital officers, and patients.[5] These unknowns, together with a lack of knowledge of long term consequences of COVID-19 infection, make the consent process more complex.

The Australian Government has produced a consent form for COVID-19 vaccination and providers of medical indemnity have produced information on how to obtain informed consent for such vaccines.[6] We are concerned these documents are inadequate for informed consent due to missing or unclear information, specifically:

As of August 6th 2021 there is no reference on government issued vaccine consent forms to:

- the investigational nature of the provisionally registered vaccines and unknowns arising therefrom (see section 3.f);
- Developmental And Reproductive Toxicity (DART) studies which do not give access to ovarian and testicular histology reports (see section 3.j);
- cluster reports eg myocarditis associated with mRNA vaccines; new onset menstrual irregularities with AstraZeneca and Pfizer vaccines etc., as yet unexplained (see section 3.e):

Also, there is unclear vaccine consent form information:

- incomplete short term safety data, and consent form internet links to government downloads to which a person may not have ready access or comprehension and,
- the absence of long term safety data and knowledge of potential outcomes.

This Guidance therefore delves deeper into the process of facilitating fully informed consent utilising a 12 point structure appropriate to an investigational intervention, published and formerly used by the National Health and Medical Research Council.[7] Other authors have produced detailed documents to support the informed consent process for COVID-19 vaccination, including one example from the United Kingdom based on the Montgomery Judgement and General Medical Council (GMC) Guidelines.[8]

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[5] On-line reporting of problems or side effects can be made to the Australian Government Department of Health's Therapeutic Goods Administration at <https://www.tga.gov.au/reporting-problems>.

[6] See, eg, 'Consent Form for Covid Vaccination', Australian Government, Department of Health (Web Page) <https://www.health.gov.au/sites/default/files/documents/2021/02/covid-19-vaccination-consent-form-for-covid-19-vaccination_2.pdf>; 'Novel Covid-19' MIGA (Web Page, updated 1 April 2021) <https://www.miga.com.au/coronavirus>.

[7] National Health and Medical Research Council, 'General Guidelines for Medical Practitioners on Providing Information to Patients' (1993).

[8] Letter from UK Medical Freedom Alliance to the Medicines and Healthcare Products Regulatory Agency and the Joint Committee on Vaccination and Immunisation, 23 November 2020 <https://uploads-ssl.webflow.com/5fa5866942937a4d73918723/5fbd13488af2de09d68bd61c_UKMFA_Letter_to_MHRA_JCVI.pdf COVID-19_Consent_Form_v3.pdf>.

Upholding this informed consent process with provision of relevant information for an investigational vaccine is consistent with our professional values of beneficence, non-maleficence, justice, veracity, fidelity and autonomy.[9] The Australian Government strongly supports vaccination[10] under appropriately trained supervision of COVID-19 vaccine eligibility and contraindications. However, with the exception of certain health care workers, vaccination is not mandatory and individuals may choose not to vaccinate. This is consistent with the Universal Declaration of Human Rights provision for the right to bodily integrity.[11] This Guidance provides detailed information to enhance personal risk-benefit assessment to determine the suitability of vaccination, or alternative measures, case by case.

Three Questions to Address During Shared Decision Making:

1. Capacity—Is the patient able to make this decision?

Generally, a patient has capacity to make a decision if they can understand, retain and evaluate the information relevant to the decision, and communicate their decision and understanding. The level of capacity required relates to the seriousness of the proposed intervention. Consent for a patient with diminished capacity for example, an aged care resident with dementia, may be obtained via a substitute decision-maker (medical power of attorney).[12, 13]

2. Voluntariness—Is the patient making this decision freely?

Has the decision been pressured or coerced by other interests? Patients must give their consent freely and have the right to refuse treatment or seek another opinion.[14]

3. Information—Does the patient have enough?

Doctors have a legal obligation to inform patients of the important or 'material' risks involved in a proposed procedure or treatment. The emphasis is on the particular

[9] New South Wales Government, Health, Education and Training (Webpage) <https://www.heti.nsw.gov.au/>.

[10] Australian Covid-19 Vaccination Policy', Australian Government, Department of Health (Policy, August 2020) <https://www.health.gov.au/sites/default/files/documents/2020/12/covid-19-vaccination-australian-covid-19-vaccination-policy.pdf>.

[11] Universal Declaration of Human Rights, GA Res 217A (III), UN GAOR, UN Doc A/810 (10 December 1948). See specifically, International Covenant on Political and Civil Rights, opened for signature 16 December 1966, UNTS 999 (entered into force 23 March 1976) art 7.

[12] Xavier Symons, 'Covid Vaccine Consent for Aged Care Residents' Royal Australian and New Zealand College of General Practitioners GP News (Blog Post, 24 February 2021). <https://www1.racgp.org.au/newsgp/clinical/covid-vaccine-consent-for-aged-care-residents?utm_source=racgpnewsgpnewsletter&utm_campaign=newsgpedm&utm_medium=email>. See also,

[13] Consent: The Essentials' Avant Mutual (Web Page, 15 August 2019) <https://www.avant.org.au/Resources/Public/consent-essentials/>.

[14] Avant Mutual (n 13).

and the individual—what is material to one patient may not be to another. The particular circumstances of the individual patient will ultimately determine which risks are considered to be material by the patient and, ultimately, by the medical practitioner.[15]

Twelve Points to Cover on Information:

a) the possible or likely nature of the condition i.e. COVID-19;
b) the proposed approach to management i.e. vaccination;
c) what the proposed approach entails;
d) the expected benefits i.e. protection against infection;
e) common side effects and material risks;
f) whether the intervention is investigational (experimental) or conventional;
g) other options for management;
h) the degree of uncertainty of the outcome;
i) the likely consequences of not choosing the proposed procedure, or of not having any procedure at all;
j) any significant long term physical, emotional, mental, social, sexual or other outcome that may be associated with the proposed procedure;
k) the time involved; and
l) the cost involved, including out of pocket costs.

Results

3. a) The Possible or Likely Nature of the Condition i.e. COVID-19;

The symptoms of COVID-19 can range from those of a mild flu-like illness to those of pneumonia and acute respiratory distress and thromboembolic disorders. Patients with severe COVID-19 disease have laboured, difficult breathing and progressive hypoxia requiring hospitalization and often need mechanical ventilatory support.

In a New South Wales (Australia) setting, following up all cases of confirmed COVID-19 between April and July 2020 with regular 3 weekly interviews (excluding those who remained hospitalized or in a residential aged care facility), 80% of all confirmed COVID-19 cases reported recovery from symptoms within a month, but about 5% continued to experience symptoms 3 months later.[16]

The common COVID-19 symptoms are fever, cough, sore throat and shortness of breath. Other symptoms can include runny nose, blocked nose (congestion), headache, muscle or joint pains, nausea, diarrhoea, vomiting, loss of sense of smell, altered sense of taste, loss of appetite and fatigue.[17] The long term sequelae of COVID-19 disease and their duration are currently unknown. Recent literature has mentioned newly described

[15] Ibid.

[16] B Liu et al, 'Whole of Population-based Cohort Study of Recovery Time from COVID-19 in NSW Australia' (2021) 12 The Lancet Regional Health-Western Pacific 100193 <https://www.thelancet.com/action/showPdf?pii=S2666-6065%2821%2900102-4>

[17] 'What you Need to Know about Corona Virus (Covid-19)', Australian Government, Department of Health (Web Page, last updated 6 April 2021) <https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/what-you-need-to-know-about-coronavirus-covid-19#symptoms>.

'Long Covid' symptomatology including 'brain fog' and fatigue.[18] Long Covid refers to a COVID-like illness lasting more than 12 weeks of yet to be defined pathogenesis and diagnostic criteria. Lung injury and neuronal injury contributing to Long Covid have been postulated and neurodegenerative disease also theorized as a future possibility.[19] Because the pandemic has been ongoing for less than 18 months, long term outcomes are uncertain. The possibility of COVID-19 disease being followed by pulmonary fibrosis and impaired lung function has been suggested by follow-up of SARS-CoV-1 patients from 2003, and might result from diffuse alveolar damage and diffuse thrombotic alveolar microvascular occlusion. Central and peripheral nervous systems might also show longer term neurological sequelae.[20] Coronaviruses SARS-CoV-1 and SARS-CoV-2 could enter the brain via alteration to the blood-brain barrier by the viral S protein. Concerns have also been raised about symptoms of Long Covid in children. The incidence is difficult to assess at this time. While one very small study suggests 30.9% of children had one to two persisting symptoms >120 days post COVID-19 infection,[21] a much larger study[22] of a randomly selected population based cohort, with 6 months follow up of over 1,350 of children and adolescents, found 4% of seropositive 6 to 16 year-olds reported one or more persisting symptoms, compared with 2% of seronegative children. This suggests a low prevalence of symptoms compatible with long COVID, the authors claim. While this Guidance focuses on adult vaccination for the reasons stated in methodology, early Italian experience[23] has suggested the incidence of multisystem inflammatory syndrome in children (MIS-C), which shows a significant overlap with other hyperinflammatory syndromes such as Kawasaki disease, may be 2.3%. However, this was a small study of 129 children. Consistency of diagnostic criteria is unclear. In a systematic review of MIS-C cases in children, by World Health Organization case definition, 68% required critical care.[24]

The Brighton Collaboration describes SARS-CoV-2 as an infection associated with a spectrum of disease that varies from asymptomatic infection to severe lung disease with acute respiratory distress syndrome and a fatal multi-organ disease with inflammatory, cardiovascular, hematologic and coagulation dysregulation. Post-infectious,

[18] 'COVID-19 Rapid Guideline: Managing the Long Term Effects of COVID-19', NICE Guideline [NG188] (Web Page, published 18 December 2020) <https://nice.org.uk/guideline/ng188>.

[19] F Wang, R Kream and G Stefano, 'Long -Term Respiratory and Neurological Sequelae of COVID-19' (2020) Medical Science Monitor (1 November 2020) <https://www.medscimonit.com/abstract/index/idArt/928996>.

[20] CMS Singal, P Jaiswal and P Seth, 'SARS-CoV-2, More Than a Respiratory Virus: Its Potential Role in Neuropathogenesis' (2020) 11(13) ACS Chemical Neuroscience 1887-99 <https://pubs.acs.org/doi/pdf/10.1021/acschemneuro.0c00251>.

[21] D Buonsenso et al, 'Preliminary Assessment on Long COVID in Children' Acta Paediatrica (2021) 110. doi: 1111/apa.15870 <https://onlinelibrary.wiley.com/doi/epdf/10.1111/apa.15870>.

[22] T Radke et al, 'Long-term Symptoms After SARS-CoV-2 Infection in School Children: Population-based Cohort with 6 Months Follow-up' MedRxiv doi: <https://doi.org/10.1101/2021.05.16.21257255>.

[23] D Buonsenso et al (n 21).

[24] T Radia et al, 'Multisystem Inflammatory Syndrome in Children and Adolescents (MIS-C): A Systematic Review of Clinical Features and Presentation' (2021) 38 Paediatric Respiratory Review 51-57 <https://pubmed.ncbi.nlm.nih.gov/32891582/>.

possibly immune-mediated systemic disease, has also been described, particularly the multi systemic inflammatory syndrome in children (MIS-C) and adults (MIS-A) which is of unclear pathogenesis at this time.[25]

In October 2020, the global COVID-19 infection fatality rate was estimated to be 0.15-0.20% (0.03-0.04% in those <70 years), with large variability across locations with different age-structure, institutionalization rates, socioeconomic inequalities, population-level clinical risk profile, public health measures, and health care.[26]

Case fatality data from January 25th to December 10th 2020 (encompassing two waves of COVID-19 cases) from Victoria, Australia, where there was ready access to standard care, give the observed case fatality risk of a confirmed COVID-19 infection to be: 0% to age 19, 0.02% in 20 to 29 year-olds, 0.06% in 30 to 39 year-olds, 0.04% in 40 to 49 year-olds. This increased to 0.63% in 50 to 59 year-olds and 2.16% in 60 to 69 year-olds. Thereafter, it increased more steeply to 14.41% in 70 to 79 year-olds, 31.90% in 80 to 89 year-olds, and 40.03% in those over 90[27] many of whom died in aged care facilities. This Victorian data of a completed outbreak is a valuable resource worldwide, since its data series ended on December 10th 2020, when the state had experienced 42 consecutive days with zero COVID-19 cases and COVID-19 was therefore officially eliminated.[28] These results therefore avoid right censoring of data as occurs from a population where cases are still active and accord with other Australian research.[29] The SARS-CoV-2 Delta variant was not present in Australia at this time.

3. b) The Proposed Approach to Management (Vaccination);

Vaccination has the potential to curb the SARS CoV2 pandemic. COVID-19 vaccines aim to prevent a person from becoming ill or dying from the SARS-Co-V2 virus.

Current anti-viral vaccines are essentially protein-based or gene-based. Gene-based vaccines are nucleic acid (mRNA and DNA) vaccines and viral vector vaccines. The provisionally licensed COVID-19 vaccines in Australia are both totally new, gene-

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[25] L I Jiang et al, 'COVID-19 and Multisystem Inflammatory Syndrome in Children and Adolescents (2020) 20 (11) Lancet Infectious Diseases doi.org/10.1016/51473-3099(20)30651-4.

See also, 'Covid-19 Symptom Checker', HealthDirect (Web Page) <https://www.healthdirect.gov.au/symptom-checker/tool/disposition/8768060/203/7>.

[26] John P A Ioannidis, 'Global Perspective of COVID-19 Epidemiology for a Full-Cycle Pandemic' (2020) European Journal of Clinical Information doi.org/10.1111/eci.13423 <https://onlinelibrary.wiley.com/doi/10.1111/eci.13423>.

[27] IC Marschner, 'Estimating Age-Specific COVID-19 Fatality Risk and Time to Death by Comparing Population Diagnosis and Death Patterns: Australian Data' (2021) 21 BMC Medical Research Methodology 126 (21 June 2021) <https://doi.org/10.1186/s12874-021-01314w>.

[28] T Blakely et al, 'The Probability of the 6 Week Lockdown in Victoria Achieving Elimination of Community Transmission of SARS-CoV-2' (2020) 213 Medical Journal of Australia 349-51. <https://www.mja.com.au/journal/2020/213/8/probability-6-week-lockdown-victoria-commencing-9-july-2020-achieving>.

[29] K Macartney, 'Thrombosis and Thrombocytopoenia Syndrome Associated with COVID-19 Vaccine AstraZeneca' (Presentation, Australian Health Protection Principal Committee, Australian Technical and Advisory Group on Immunization, 12 April 2021).

based vaccines, as is the pending Moderna vaccine.[30] They carry genetic instructions for the host cells to make antigen to induce an immune response.

The other vaccine accepted by the TGA to seek provisional registration is NVX-CoV2373 ('Novavax').[31] It is a protein-based vaccine. It differs from gene-based vaccines as it formulates the coronavirus spike protein as nanoparticles which stimulate the immune system.

The AstraZeneca vaccine is a chimpanzee adenovirus which enters host cells but has been modified to prevent replication. It is a double strand DNA vaccine carrying a gene encoding the SARS Co-V-2 spike protein surface glycoprotein. The product contains genetically modified organisms.[32]

The Pfizer vaccine contains single strand messenger RNA (mRNA) encoding the SARS-CoV-2 spike protein antigen which, after administration, is delivered into host cells. The spike protein is subsequently expressed, stimulating neutralising antibody and cellular immune responses.[33] Moderna mRNA vaccine works similarly, encapsulated in a lipid nanoparticle and encoding the spike glycoprotein.[34]

3. c) What the Proposed Approach Entails;

Vaccination with the AstraZeneca COVID-19 vaccine requires an intramuscular injection of 0.5 mls into the upper arm. It consists of two doses given 4 to 12 weeks apart. In Australia a 12 week interval is recommended.[35]

Vaccination with the Pfizer vaccine requires an intramuscular injection through a needle in the arm. It consists of two doses (30 microg, 0.3 mL each) administered intramuscularly, three weeks apart.[36]

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[30] LR Baden et al, 'Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine' (2021) 384 New England Journal of Medicine 403-416 <https://www.nejm.org/doi/full/10.1056/nejmoa2035389>.

[31] 'TGA Grants Additional Provisional Determination for a COVID-19 Vaccine' Australian Government, Department of Health, Therapeutic Goods Administration (Web Page, 20 January 2021) <https://www.tga.gov.au/tga-grants-additional-provisional-determination-covid-19-vaccine>.

[32] See, Australian Product Information Covid-19 Vaccine AstraZeneca, Australian Government, Department of Health, Therapeutic Goods Administration (Web Page) <https://www.tga.gov.au/sites/default/files/auspar-chadox1-s-covid-19-vaccine-astrazeneca-210215-pi.pdf>.

[33] Information for Healthcare Professionals on Pfizer BioNTech Covid-19 Vaccine', Government of the United Kingdom, Medicines and Healthcare Products Regulatory Authority (Web Page, 31 March 2021) <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/information-for-healthcare-professionals-on-pfizerbiontech-covid-19-vaccine>.

[34] LR Baden (n 30).

[35] COVID-19 vaccine: AstraZeneca ChAdOx1-S', Australian Government, Department of Health, Therapeutic Goods Administration (Web Page, 26 March 2021) <https://www.tga.gov.au/covid-19-vaccine-astrazeneca-chadox1-s>.

[36] See, Australian Product Information COMIRNATY™ (BNT162b2 [mRNA]) Covid-19 Vaccine Australian Government, Department of Health, Therapeutic Goods Administration (Web Page) <https://www.tga.gov.au/sites/default/files/auspar-bnt162b2-mrna-210125-pi.pdf>.

3. d) The Expected Benefits i.e. Protection Against Infection.

Re Oxford/AstraZeneca Vaccine ChAdOx1-S (AZD1222)

There is currently limited data available for the efficacy and safety in individuals over 65 years of age. Only 12% of those assessed for efficacy were over 55 years. However, the vaccine has been shown to create an immune response in this group and can be used based on the efficacy and safety demonstrated in the general clinical trial population.[37]

Vaccine effectiveness against primary symptomatic COVID-19 was 62.1% in the randomized controlled phase III trial tested group who received standard dosing, and 90.0% effective in those who received a half dosage (protocol error) followed by a standard dosage.[38] However, those who received this half dose were younger on average and vaccines are more effective in younger persons.

Emerging "real world" data from Scotland claimed the first dose of AstraZeneca vaccine was 94% effective against hospitalization (95% CI 73-99).[39] It is noted however, that this is pre-print research without peer review. It does not define indications for hospitalization, and vaccine effects against other outcomes of interest (such as ICU admission, death etc) were not estimated. In other pre-print research, two doses of the AstraZeneca vaccine had only 10% effectiveness against mild to moderate infections due to the South African variant B.1.351 (known as Beta variant).[40] Effectiveness of two doses against illness from the Delta variant has been given as 67%.[41]

Re the Pfizer vaccine (BNT162b2)

The percentage of people who get protection from symptomatic infection after 2 doses of the Pfizer vaccine in a randomized controlled trial with 21,720 vaccinated individuals has been estimated at 95%.[42] The probability of >30% vaccine efficacy is 99.99%.[43] For comparison, the modern influenza vaccine reduces infections by 40-60%.[44]

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[37] Australian Government, Department of Health, Therapeutic Goods Administration (n 32).

[38] Mervyn Voysey et al (n 3).

[39] E Vasileiou et al, 'Effectiveness of First Dose of COVID-19 Vaccines against Hospital Admissions in Scotland: National Prospective Cohort Study of 5.4 million People', (advance, Lancet, posted 19 February 2021 <https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264>.

[40] S A Madhi et al, 'Safety and Efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 Vaccine Against the B.1.351 Variant in South Africa' Posted February 12, 2021, MedRxiv doi: <https://doi.org/10.1101/2021.02.10.21251247>. Pre-print. Not peer reviewed. WHO Target Product Profile, World Health Organization (Web Page, 9 April 2020).

[41] JL Bernal et al, 'Effectiveness of Covid-19 Vaccines Against the B.1.617.2 (Delta) Variant' (2021) 385 New England Journal of Medicine 585-594 <https://www.nejm.org/doi/full/10.1056/NEJMoa2108891>.

[42] Fernando Polack (n 2).

[43] 'Australian Public Assessment Report for BNT162b2 (mRNA)' Australian Government, Department of Health, Therapeutic Goods Administration, (Web Page, January 2021) <https://www.tga.gov.au/sites/default/files/auspar-bnt162b2-mrna-210125.pdf>.

[44] 'Vaccine Effectiveness: How well do the Flu Vaccines Work?'Centers for Disease Control and Prevention (Web Page, last reviewed 16 December 2020) <https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm>.

Although vaccination is expected to reduce hospitalisations and deaths from COVID-19, the Pfizer phase III trial data albeit limited, does not confirm this.[45] The preprint Scottish study quoted above suggests an 85% reduction in hospitalisation following vaccination with the Pfizer vaccine (compared with a 94% reduction for the AstraZeneca vaccine).

A recent study of 596,000 vaccinated and matched unvaccinated persons gave similar results to the phase 3 trial quoted above.[46] It is noted that this study excluded health care workers and nursing home residents. 'Matched' vaccinated persons were therefore younger than the eligible population and had a lower prevalence of chronic conditions. Vaccines are known to be more effective in younger recipients.

More recent Israeli research showed adjusted estimates of vaccine effectiveness at 7 days or longer after the second dose to be 95·3% against SARS-CoV-2 infection (95% CI 94·9–95·7; incidence rate 91·5 per 100 000 person-days in unvaccinated *vs* 3·1 per 100 000 person-days in fully vaccinated individuals), 97·0% against symptomatic COVID-19 (95% CI 96·7–97·2; 32·5 *vs* 0·8 per 100 000 person-days), 97·2% against COVID-19-related hospitalisation (95% CI 96·8–97·5; 4·6 *vs* 0·3 per 100 000 person-days), 97·5% against severe or critical COVID-19-related hospitalisation (95% CI 97·1–97·8; 2·7 *vs* 0·2 per 100 000 person-days), and 96·7% against COVID-19-related death (95% CI 96·0–97·3; 0·6 *vs* 0·1 per 100 000 person-days).[47]

Vaccine effectiveness against asymptomatic infection, estimated at 91.5% (95% CI 90.7-92.2; 40.9 vs 1.8 per 100,000 person-days), could not be reliably calculated. The authors identified four factors which could have over-estimated vaccine effectiveness against asymptomatic infection: differing national testing protocols for vaccinated and unvaccinated study arms; vaccinated persons were exempt from the testing required of unvaccinated persons at times of risk such as re-entry to the country from abroad or after contact with a confirmed case; possible inclusion of pre-symptomatic vaccinated individuals with asymptomatic vaccinated individuals at the point of interview; possible concealment of symptoms at interview for fear of being blamed for infecting others. The authors noted that further studies were needed to confirm the magnitude of vaccine effectiveness against asymptomatic infection.

A vaccinated person may develop asymptomatic infection and still be infectious for the virus i.e. the vaccine may not prevent a person from contracting and transmitting COVID-19. This could be of concern since it has been estimated that 50% of transmis-

[45] See, Sara E Oliver et al, 'The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine—United States, December 2020' (2020) 69 (50) Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Reports 1922 <https://www.cdc.gov/mmwr/volumes/69/wr/mm6950e2.htm?s_cid=mm6950e2_w>.

[46] Noa Dagan et al, 'BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting' (2021) New England Journal of Medicine DOI: 10.1056/NEJMoa2101765. <https://www.nejm.org/doi/10.1056/NEJMoa2101765>.

[47] EJ Haas et al, 'Impact and Effectiveness of mRNA BNT262b2 Vaccine Against SARS-CoV-2 Infections and COVID-19 Cases, Hospitalizations and Deaths Following a Nationwide Vaccination Campaign in Israel: An observational study using national surveillance data (2021) 397 Lancet 1819.

sion of SARS CoV2 occurs from people who do not have symptoms.[48] Other research, however, suggests vaccinated carriers do have a reduced viral load.[49]

Duration of protection from the Pfizer vaccine is unknown. There is incomplete data on Pfizer vaccine effectiveness against emerging variants or strains. However, it appears to be reduced.[50] The effectiveness of two doses of the Pfizer vaccine against illness from the Delta variant is given as 88%.[51]

Comment:

Both vaccines exceed the minimum efficacy of 50% in their target product profile, as required by the WHO.[52] New variants are continually emerging and will require testing to confirm effective immunity and protection.[53] Moderna was estimated to be 94% effective against COVID-19 illness, including severe disease.[54]

COVID-19 vaccination has been recommended in previously infected individuals based on a large 2020 Danish study which did not directly compare vaccinated and unvaccinated individuals.[55] By contrast, a Cleveland Clinic preprint study dated June 5, 2021, which found that vaccination was associated with a significantly lowered risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI 0.015 to 0.061) but not among those previously infected (HR 0.313, 95% CI 0 to infinity), has provided evidence that vaccination with up to 5 months of follow-up does not add protection to those who were previously infected.[56] This is consistent with earlier observational studies which found very low rates of reinfection over several months among

[48] Michael A Johannson et al, 'SARS-CoV-2 Transmission from People without COVID-19 Symptoms' (2021) 4(1) JAMA Network Open e2035057. doi:10.1001/jamanetworkopen.2020.35057 <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2774707>.

[49] N K Jone et al, 'Single Dose BNT162b2 Vaccine Protects Against Asymptomatic SARS-CoV-2 Infection' eLife; 8 April 2021; DOI: 10.7554/eLife. 68808.

[50] See e.g. 'About the Pfizer/BioNTech COVID-19 Vaccine', Australian Government, Department of Health (Web Page, last updated 18 March 2021) <https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/about-covid-19-vaccines/about-the-pfizerbiontech-covid-19-vaccine>; See also, Noa Dagan et al (n 42).

[51] JL Bernal (n 41).

[52] WHO Target Product Profile, World Health Organization (Web Page, 9 April 2020) <https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines>.

[53] 'About the Pfizer BioNTech Covid-19 Vaccine,' Australian Government, Department of Health (Web Page, last updated 18 March 2021) <https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/about-covid-19-vaccines/about-the-pfizerbiontech-covid-19-vaccine>.

[54] LR Baden (n 30)

[55] C H Hansen, D Michlmayr, SM Gubbels et al. Assessment of protection against infection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet 2021;1204-12.

[56] K. Nabin et al. 'Necessity of Covid Vaccine in Previously Infected Individuals' Medrxiv (preprint, 5 June 2021) <https://www.medrxiv.org/content/10.1101/2021.06.01.21258176v2> Preprint. Not peer-reviewed.

survivors of COVID-19.[57] Cleveland Clinic authors conclude that previously infected individuals are unlikely to benefit from vaccination.

Since vaccines are not 100% effective, COVID-19 vaccines may not usher in the desired return to normal life. Social distancing, hand sanitizing, and masks may still be advised or required[58] on this basis by various health advisors and governments. Ultimately, requirements for social distancing will be determined by local governments and can be expected to change with alteration in the local incidence of infection.

3. e) Common Side Effects and Material Risks;

Re Oxford/AstraZeneca ChAdOx1 S (AZD1222)

The TGA states the side effects of the AstraZeneca vaccine to be headaches, fatigue (>50%), malaise (>40%), fever, chills, nausea and painful joints and muscles. Analgesics and anti-pyretic treatment may be required.[59]

Since those with severe cardiac, gastrointestinal, liver, renal, endocrine, metabolic and neurological illness were excluded from the vaccine trials, vaccine adverse effects in people with these conditions are unknown. As stated in the Product Information, there is limited data available for the efficacy and safety in individuals with significant co-morbidities.

Safety and efficacy in the frail, elderly, and immune suppressed is also unknown. Safety in those under 18 years has not been studied.

Very rare events of demyelinating disorders (transverse myelitis and multiple sclerosis) have been reported following vaccination with the AstraZeneca vaccines. A causal relationship has not been established.[60] ATAGI advises the first dose of COVID-19 vaccine has been found to be associated with Immune Thrombocytopoenic Purpura (ITP) and cautions about other serious but rare adverse events being reported, such as Guillane Barre Syndrome and capillary leak syndrome, [61] although a causal association has not been confirmed.

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[57] M M Sheehan et al, 'Reinfection Rates among Patients who Previously Tested Positive for Coronavirus Disease 2019: a Retrospective Cohort Study' (2021) Clinical Infectious Diseases (15 May 2021) <https://doi.org/10.1093/cid/ciab234>; S Pilz, et al, 'SARS-CoV-2 Re-infection Risk in Austria' (2021) European Journal of Clinical Investigation 51:e13520; S F Lumley et al, 'Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers' (2021) 384 New England Journal of Medicine 533.

[58] See, 'Continue to Wear a Face Mask, Practice Social Distancing After Being Vaccinated for Covid-19' News Network Mayo Clinic (Web Page, 2 February 2021) <https://newsnetwork.mayoclinic.org/discussion/continue-to-wear-a-mask-practice-social-distancing-after-being-vaccinated-for-covid-19/>; 'Good Hygiene for Coronavirus (COVID-19)' Australian Government Department of Health (Web Page, 29 April 2021) <https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/how-to-protect-yourself-and-others-from-coronavirus-covid-19/good-hygiene-for-coronavirus-covid-19>.

[59] Australian Government, Department of Health, Therapeutic Goods Administration (n 32).

[60] Ibid.

[61] 'Covid-19 Vaccination Training Program', Australian Government, Department of Health (Web Page, Updated 6 August 2021) <https://www.health.gov.au/covid-19-vaccination-training-program>.

Thrombosis with Thrombocytopoenia Syndrome (TTS):[62] The AstraZeneca vaccine has been suspended in many European and Scandinavian countries and, although re-instated in Germany, Italy, Philippines and Spain, it remains discontinued in Denmark due to coagulation disorder diagnoses. Features of this phenomenon have also included Disseminated Intravascular Coagulation (DIC) and Central Venous Sinus Thrombosis (CVST) with fatalities. While venous thromboembolic disorder (VTE) has been reported with COVID-19 disease, this is a different diagnostic entity to TTS. Among hospitalized and ICU patients with COVID-19 the incidence of VTE is 17.3%, with two thirds being deep vein thromboses (DVTs).[63] TTS has not to date been associated with COVID-19 disease.

The European Medicines Agency ('EMA') states most of these occurred in those under 55 and mostly in women.[64] The EMA reports that, based on pre-COVID figures, less than one reported case of DIC might have been expected by 16th March 2021, among people under 50 within 14 days of receiving the vaccine whereas, 5 cases had been reported. Similarly, on average, one case of CVST might have been expected among this age group whereas, by the same cut-off date, 12 cases had been reported. The EMA has advised physicians about cases of thrombosis and thrombocytopoenia, presenting as venous or arterial clotting, splanchnic/mesenteric vessels and cerebral vein/cerebral venous sinus thrombosis in persons who had recently received this vaccine, mostly within 14 days after vaccination.

ATAGI suggests a *TTS* rate of 2.6 per 100,000 persons vaccinated under age 50 and 1.6 per 100,000 over age 50.[65] Patients should be aware of the remote possibility of such syndromes and vaccine recipients who develop symptoms of these conditions should seek immediate medical attention. These symptoms are listed as dyspnoea, chest pain, stomach pain, swelling or coldness in an arm or leg, severe or worsening headache or blurred vision after vaccination, persistent bleeding, multiple small bruises, reddish or purplish spots, or blood blisters under the skin. Information on these cases is to be added to the Product Information.

The EMA has not, however, identified an overall association with this vaccine and thromboembolic disorders. It has meanwhile revised the summary of product character-

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[62] See, 'ATAGI, Statement on AstraZeneca Vaccine in Response to New Vaccine Safety Concerns' Australian Government, Department of Health (Web Page, 8 April 2021) <https://www.health.gov.au/news/atagi-statement-on-astrazeneca-vaccine-in-response-to-new-vaccine-safety-concerns>.

[63] D Jimenez et al, 'Incidence of VTE ad Bleeding Among Hospitalized Patients with Coronavirus Disease 2019 A Systematic Review and Meta-analysis' (2021) 159(3) CHEST 1182-1196 <https://doi.org/10.1016/j.chest.2020.11.005>.

[64] See, 'AstraZeneca's COVID-19 Vaccine: EMA Finds Possible Link to Very Rare Cases of Unusual Blood Clots With Low Blood Platelets' European Medicines Agency, (Web Page, 7 April 2021) <https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood>.

[65] 'ATAGI Update Following Weekly COVID-19 Meeting—26 May 202', Australian Government, Department of Health (Webpage, 21 May 2021) <https://health.gov.au/news/atagi-update-following-weekly-covid-19-meeting-26-may-2021>.

istics and listed thrombocytopenia as a 'common' side effect (i.e. 1 in 100 to 1 in 10) of AstraZeneca.[66] The EMA still advocates the benefits of this vaccine outweigh the risks.[67]

Interactions with other medications have not been studied and are unknown. No carcinogenicity or genotoxicity (mutagenicity) studies were performed. Genotoxicity tests are in vitro and in vivo tests designed to detect compounds that induce genetic damage by various mechanisms. These tests enable hazard identification with respect to damage to DNA and its fixation.[68] While not routinely done for vaccines, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, International Council for Harmonization (ICH) Guideline S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals 6.4, 18th February 2020, suggests additional testing strategies where there are novel active ingredients. This becomes more important as novel nucleic acid vaccines are introduced. The risk of integration or infection into host cell DNA is thought to be negligible, despite the absence of genotoxicity studies.

Dosages of excipients e.g. polysorbate have been omitted from the Product Information. The Australian Public Assessment Report for ChAdOx1-S-COVID-19 Vaccine AstraZeneca states:

> …one of the major limitations in the phase 3 study is the short and variable duration of follow up. The duration of follow up, and reasons for missing data in follow up, are important in determining efficacy. Lower duration of follow up may be from drop outs, but may also arise due to censoring of cases. Longer duration of follow up increases the time of exposure and increases the opportunity for true effectiveness (or non-effectiveness) to be demonstrated.[69]

Fertility, pregnancy and the newborn (also see section (3.j below): Developmental And Reproductive Toxicology study was published in July 2021.[70] This study concluded that AZD1222 has no adverse effects on female fertility, embryofetal development or postnatal development in mice.

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[66] See, Hamid Merchant, 'CoVID-19 Post-Vaccine Menorrhagia, Metrorrhagia or Postmenopausal Bleeding and Potential Risk of Vaccine-induced Thrombocytopoenia in Women (2021), 373 BMJ 373:n958, doi://doi.org/10.1136/bmj.n958 (published 14 April 2021).

[67] 'COVID-19 Vaccine AstraZeneca: Benefits Still Outweigh the Risks Despite Possible Link to Rare Blood Clots with Low Blood Platelets' European Medicines Agency (Web Page, 18 March 2021) <https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots>.

[68] 'Guidance for Industry S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, June 2021', U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (June 2021) <https://www.fda.gov/media/71980/download#:~:text=Genotoxicity%20tests%20can%20be%20defined,to%20DNA%20and%20its%20fixation>.

[69] 'Australian Public Assessment Report for CgAdOx1-S-COVID-19 Vaccine Astra Zeneca' Australian Government, Department of Health, Therapeutic Goods Administration, (Web Page, February 2021) <https://www.tga.gov.au/sites/default/files/auspar-chadox1-s-covid-19-vaccine-astrazeneca-210215.pdf>.

[70] R Stebbings et al, 'Developmental and Reproductive Safety of AZD1222 (ChAdOx1 ncoV-10)' (2021) 104 Reproductive Toxicology 134-142 <https://doi.org/10.1016/j.reprotox.2021.07.010>.

Increasing reports of new onset menstrual irregularities are being notified in the UK Medicines and Health Care products Regulatory Agency (MHRA) adverse event reports following COVID-19 vaccinations. As of April 5, there were 958 cases notified, with twice as many notifications following AstraZeneca than Pfizer vaccine. As a British Medical Journal Editorial response states,

> It is anticipated that the actual numbers of cases are much higher than the numbers recorded in the pharmacovigilance systems as many women in different cultural contexts may have felt uncomfortable to talk about it, may not have thought it was vaccine related, or may not have been encouraged by their clinician to make an official report into the adverse events reporting system.[71]

Platelet counts would need to be extremely deficient to be associated with spontaneous bleeding disorders.[72] Injected polysorbate 80 vaccine excipient has a proven association with ovarian toxicity and uterine vascular anomalies in rats. A safe dose is not established, as all parenteral doses tested showed equal toxicity[73] and its effects resembled that of the diethylstilboestrol arm of the study.

It is present in the AstraZeneca vaccine and is chemically related to polyethylene glycol present in the Pfizer vaccine. Attention has previously been drawn to its possible association with notified cases of premature ovarian insufficiency following human papillomavirus vaccination (HPV) Gardasil ®.[74] Increased new onset menstrual irregularities have been reported following HPV vaccination.[75] What data on reproductive toxicity studies of COVID vaccines is currently submitted was not released by the TGA when requested by general practitioner vaccine providers. The TGA replied to practitioners' written request stating in an email that a Freedom of Information request was needed before it would consider release of information sought for patients of reproductive age who are considering vaccination with a novel investigational vaccine. Arguably, creating barriers for obtaining this data is inconsistent with respecting informed consent.

This vaccine is not routinely recommended in pregnancy in Australia due to its TTS risk in those under 60 years of age.[76] All available COVID-19 vaccines are now

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[71] Hamid Merchant (n 66).

[72] Sruthi Jinna and PB Khandhar, Thrombocytopoenia (National Centre for Biotechnology Information NCBI Resources COVID-19 Information, July 10th 2020). <https://www.ncbi.nlm.nih.gov/books/NBK542208/#:~:text=Spontaneous%20bleeding%20can%20occur%20with,with%20counts%20below%2050000%2FmicroL>.

[73] M Gajdova et al, 'Delayed Effects of Neonatal Exposure to Tween 80 on Female Reproductive Organs in Rats' (1993) 31 Food Chemical Toxicology 183.

[74] D Little and H Ward, 'Adolescent Premature Ovarian Insufficiency Following Human Papillomavirus Vaccination: A Case Series Seen in General Practice' (2014) 2 Journal of Investigative Medicine High Impact Case Reports doi: 10.1177/2324709614556129>.

[75] Li Gong et al, 'Human Papillomavirus Vaccine Associated Premature Ovarian Insufficiency and Related Adverse Events: Data Mining of Vaccine Adverse Event Reporting System' (2020) 10 (10762) Scientific Reports <https://doi.org/10.1038/s41598-020-67668-1>.

[76] 'ATAGI Statement on Revised Recommendations on the Use of COVID-19 Vaccine AstraZeneca, 17 June 2010, Australian Government, Department of Health (Web Page, 17 June 2021) <https://www.

available for pregnant women in Great Britain but noting exclusion of AstraZeneca vaccine from pregnancy safety studies underway in the USA.[77,78]

A risk to breastfed newborns and infants cannot be excluded. The duration of vaccine effectiveness is unknown.

The Pfizer vaccine (BNT162b2)

The most frequent adverse reactions in participants 16 years of age and older were injection site pain (>80%), fatigue (>60%), headache (>50%), myalgia and chills (>30%), arthralgia (>20%), pyrexia and injection site swelling (>10%). These were usually mild or moderate in intensity and resolved within a few days after vaccination.[79] Severe local and systemic adverse reactions (grade ≥3, defined as interfering with daily activity) occur in 8.8% of vaccine recipients, more commonly after the second dose than the first, and are less prevalent in those >50 years. Serious adverse events are observed in 0.6%.[80] Safety in the frail elderly over 85 has not been assessed. Safety in children >16 years was not assessed in the original phase three trials. Publication of further research is awaited. Meanwhile, seven cases of acute myocarditis arising in newly vaccinated adolescents within 4 days of dose two of the Pfizer vaccine have been described and published.[81] Guillane-Barre occurring post the Pfizer vaccine has been notified and published.[82]

The occurrence of 'paroxysmal ventricular arrythmia' and 'cardiac arrest' in separate vaccine recipients in the phase 3 trial has not been fully researched. Furthermore, Israel Ministry for Health reports notifications of new onset myocarditis in young adults following Pfizer vaccination.[83] Most reported cases have occurred in men (55 out of 62). There had reportedly been two deaths of recipients aged 22 years (female) and 35 years (male). A causative link is not established. Myocarditis has also occurred with

health.gov.au/news/atagi-statement-on-revised-recommendations-on-the-use-of-covid-19-vaccine-astrazeneca-17-june-2021#:~:text=Home-,ATAGI%20statement%20on%20revised%20recommendations%20on%20the%20use%20of%20COVID,to%20new%20vaccine%20safety%20concerns>.

[77] Royal College of Obstetricians and Gynaecologists, 'Information Sheet and Decision Aid' (Web Page, Updated 20 July 2021) <https://www.rcog.org.uk/globalassets/documents/guidelines/2021-02-24-combined-info-sheet-and-decision-aid.pdf>.

[78] TT Shimabukuro et al, 'Preliminary Findings of mRNA COVID-19 Vaccine Safety in Pregnant Persons' (2021) 384(34) New England Journal of Medicine (published on line 21 April 2021) <https://pubmed.ncbi.nlm.nih.gov/33882218/>.

[79] Australian Government, Department of Health, Therapeutic Goods Administration (n 32).

[80] Sara E Oliver et al (n 45).

[81] M Marshall et al, 'Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination' Pediatrics doi: 10.1542/peds.2021-052478.

[82] Sadia Waheed et al, 'Neurological Complications of COVID-19: Guillain-Barre Syndrome Following Pfizer COVID-19 Vaccine' (2021) 13(2) Cureus e13426, doi:10.7759/cureus.13426 <https://www.cureus.com/articles/52295-neurological-complications-of-covid-19-guillain-barre-syndrome-following-pfizer-covid-19-vaccine>.

[83] 'Israel Assesses Myocarditis Cases Linked to Pfizer-BioNTech Covid-19 Vaccine', Pharmaceutical Technology News (Web Page, 26 April 2021) <https://www.pharmaceutical-technology.com/news/israel-myocarditis-pfizer-vaccine/>.

COVID-19 disease although it is reported as rare in COVID-19 autopsies,[84] performed at a median age of 75. Clinical myocarditis had a prevalence rate of 0.31% in 1597 athletes[85] after COVID-19 infection, and subclinical myocarditis a prevalence rate of 2.3% on routine cardiac MRI screening of the same group. Comparable routine cardiac MRI screening of a vaccinated cohort has not occurred. In one retrospective review of myocarditis post mRNA COVID-19 vaccination in members of the US military,[86] 23 male patients (22 serving, 1 retiree, median age 25 years) with acute onset of chest pain post vaccination, met CDC case definitions for probable myocarditis. Eight of these 23 had MRI findings consistent with myocarditis. No other aetiologies were identified. Symptoms commenced 12 to 96 hours after 2nd dose of vaccine in 20 patients, and followed the first dose in 3 patients, each of whom had previous SARS-CoV-2 infection more than 2 months prior. Cardiac symptoms resolved within one week for 16 of 23. Seven remained symptomatic at the time of the report. During that time 436,000 2nd doses had been administered to male military service members. In comparison, nearly 1% of highly fit athletes with mild COVID-19 infection have myocarditis on Cardiac MRI.[87,88] Other case reports of myocarditis post COVID-19 vaccine also followed the 2nd dosage,[89,90] and a series of 7 adolescents[91] developed myocarditis or myopericarditis

[84] MK Halushka and RS Vander Heide, 'Myocarditis is Rare in COVID-19 Autopsies: Cardiovascular Findings Across 277 Postmortem Examinations (2021) 50 Cardiovascular Pathology 107300. doi: 10.1016/j.carpath.2020.107300 <https://www.sciencedirect.com/science/article/abs/pii/S1054880720301046>.

[85] CJ Daniela, S Rajpal and JT Greenshields, 'Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes with Recent SARS-CoV-2 Infection Results from the Big Ten COVID-19 Cardiac Registry' (2021) JAMA Cardiology (published on line, 27 May 2021) doi: 10.1001/jamacardio.2021.2065 <https://jamanetwork.com/journals/jamacardiology/fullarticle/2780548>

[86] J Montgomery et al, 'Myocarditis Following Immunization with mRNA COVID-19 Vaccines in members of the US Military' (2021) JAMA Cardiology (published online June 29, 2021) doi:10.1001/jamacardio.2021.2833 <https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601>.

[87] J Starekova et al, 'Evaluation for Myocarditis in Competitive Student Athletes Recovering from Coronavirus Disease 2019 with Cardiac Magnetic Resonance Imaging (2021) JAMA Cardiology (published online, 14 January 2021) doi:10.1001/jamacardio.2020.7444 <https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601>.

[88] MW Martinez et al, 'Prevalence of Inflammatory Heart Disease Among Professional Athletes with Prior COVID-19 Infection who Received Systematic Return-to -Play Cardiac Screening (2021) JAMA Cardiology (published online, 4 March 2021) doi: 10.1001/jamacardio.2021.0565 <https://jamanetwork.com/journals/jamacardiology/fullarticle/2777308>.

[89] GJ Bautista, OP Pena and FJA Bonilla, 'Acute Myocarditis After Administration of the BNT162b2 Vaccine Against COVID-19' (2021) Revista Espanola Cardiologia (Engl Ed) (published online, 20 March 2021) doi:10.1016/j.rec.2021.04.005

[90] E Albert et al, 'Myocarditis Following COVID 19 Vaccination' (2021) 16(8) Radiology Case Reports 2142-2145 doi:10.1016/j.radcr.2021.05.033 <https://pubmed.ncbi.nlm.nih.gov/34025885/>.

[91] M Marshall et al, 'Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer BioNTech COVID-19 Vaccination' Pediatrics doi:10.1542/peds2021-052478 (published 2 June 2021) <https://pediatrics.aappublications.org/content/pediatrics/early/2021/06/02/peds.2021-052478.full.pdf>.

within 4 days of Pfizer vaccination. Related JAMA editorials,[92,93] commenting on the myocarditis case series post COVID-19 vaccine, note that cardiac injury after SARS-CoV-2 infection also occurs and may result in severe outcomes. They also note that public vaccine confidence includes transparency, with careful critical review and publication of possible links between vaccines and rare adverse events. Myocarditis is not referred to as a possible side effect on Australian Government COVID-19 vaccine consent forms.

Fertility, pregnancy and the newborn (also see section 3.j below):

Rat DART fertility studies were published May 28th 2021.[94] Only macroscopic examination and numbering of corpora lutea and implantation sites is presented. Authors state 'the lack of female fertility effects is consistent with the lack of microscopic effects in female reproductive organs in non-pregnant rats administered BNT162b2 in prior general toxicology studies (data not shown)'. The 'data not shown' is neither referenced nor cited. Pre-clinical gonad histology reports are not shown in accessible licensing documentation.[95] Freedom of Information Request (FOI) 2183 response from the TGA has redactions of organ histopathology in section 5.3.1 of the BIONTECH Investigator's Brochure.[96] The Brochure elsewhere states that section 5.3.1 contains microscopic evaluations of male and female reproductive tissues from the repeat-dose toxicity study. However, no such report is visible. The Investigator's Brochure summary, however, states there were no reported changes in these tissues. An email request made by vaccine providers to the TGA for access to available reproductive data was declined by the TGA without a Freedom of Information Request, which has since been lodged and rejected. Product Information states there were no effects on fertility or offspring following vaccination of rats before and during gestation. However, there is limited completed data of use in pregnant women.[97] An uncompleted USA study of Pfizer vaccine in pregnancy[98] found no short term ill effects from Pfizer vaccine given in the third trimester. Éarlier pregnancy outcomes are awaited. The authors conclude: 'Preliminary findings did not show obvious safety signals among

[92] DK Shay, TT Shimabukuro and F DeStefano, 'Myocarditis Occurring After Immunization with COVID-19 Vaccines' Editorial, JAMA Cardiology (published online, 29 June 2021) <https://jamanetwork.com/journals/jamacardiology/fullarticle/2781600>.

[93] AM Navar et al, 'Temporal Associations Between Immunization With the COVID-19 mRNA Vaccines and Myocarditis The Vaccine Safety Surveillance System is Working' JAMA Cardiology (published online 29 June 2021) <https://jamanetwork.com/journals/jamacardiology/fullarticle/2781599>.

[94] CJ Bowman et al, 'Lack of Effects on Female Fertility and Prenatal and Postnatal Offspring Development in Rats with BNT162b2, a mRNA-based COVID-19 Vaccine' (2021) 103 Reproductive Toxicology 28-35 (published on line, 28 May 2021) <https://doi.org/10.1016/j.reprotox.2021.05.007>.

[95] A Phase 1/2/3 study to Evaluate the Safety, Tolerability, Immunogenicity and Efficacy of SARS-CoV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals. Study Intervention Number PF-07302048. US IND Number 19736. <https://cdn.pfizer.com/pfizercom/2020-11/C4591001_Clinical_Protocol_Nov2020.pdf>

[96] Investigator's Brochure BNT162/PF-07302048. 12 August 2020. <https://www.tga.gov.au/sites/default/files/foi-2183-09.pdf> Response to FOI 2183.

[97] Australian Government, Department of Health, Therapeutic Goods Administration (n 33).

[98] TT Shimabukuro (n 78).

pregnant persons who received mRNA Covid-19 vaccines. However, more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes.'

TGA labels Pfizer vaccine category B1. Nonetheless, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) did not recommend use in pregnancy prior to June 9, 2021.[99] A joint ATAGI/ RANZCOG statement released June 9, 2021 stated:

> RANZCOG and ATAGI recommend that pregnant women are routinely offered Pfizer mRNA vaccine (Cominarty) at any stage of pregnancy. This is because the risk of severe outcomes from COVID-19 is significantly higher for pregnant women and their unborn baby. Global surveillance data from large numbers of pregnant women have not identified any significant safety concerns with mRNA COVID-19 vaccines given at any stage of pregnancy. Furthermore, there is also evidence of antibody in cord blood and breastmilk, which may offer protection to infants through passive immunity. Pregnant women are encouraged to discuss the decision in relation to timing of vaccination with their health professional.[100]

Further to this, on August 6th 2021 RANZCOG states pregnant women are a priority group for COVID-19 vaccination, and should be routinely offered the Pfizer vaccine (Comirnaty) and advised to receive it at any stage of pregnancy.[101] Reasons given for the altered policy concern the increased COVID-19 morbidity during pregnancy as discussed in section 3.j(i). Pregnant women's eligibility for Pfizer vaccine has been increased.

Neither genotoxicity nor carcinogenicity studies were performed. The components of the Pfizer vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Research is needed regarding the effects of biodistribution of mRNA vaccines. Pre-clinical evaluation of distribution of vaccine lipid nanoparticles in the rat following administration of a single 50 ucg dose show: 'The concentration of radioactive lipid marker reached the peak level in plasma (8.9 µg lipid eqv/mL) between 1–4 h post-dose and distribution mainly into liver, adrenal glands, spleen and ovaries over 48h.'[102]

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[99] COVID-19 Vaccination in Pregnant and Breastfeeding Women', Royal Australian and New Zealand College of Obstetricians and Gynaecologists (Web Page, 2021) <https://mailchi.mp/ranzcog.edu.au/covid-19-vaccination-in-pregnant-and-breastfeeding-women?e=9674ffe0a4>.

[100] 'Joint Statement between RANZCOG and ATAGI about COVID-19 Vaccination for Pregnant Women', Australian Government, Department of Health <https://www.health.gov.au/news/joint-statement-between-ranzcog-and-atagi-about-covid-19-vaccination-for-pregnant-women>.

[101] Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 'Covid-19 Vaccination in Pregnant and Breastfeeding Women' Statements and Guidelines (Web Page, 6 August 2021) <https://ranzcog.edu.au/statements-guidelines/covid-19-statement/covid-19-vaccination-information>

[102] Australian Government, Department of Health, Therapeutic Goods Administration, 'Non-clinical Evaluation Report BNT162b2 [mRNA] COVID-19 Vaccine (ComirnatyTM) Jan 2021' FOI 2389 Document 6, Submission PM-2020-05461-1-2.

Accumulation in rat ovaries at 48 hours post dose is more than ten times the concentration exceeding that in most other organs, with the exception of liver, spleen and adrenals. It is not known if a similar biodistribution phenomenon occurs in the ovaries of human vaccinees, or if this could affect human ovarian function or possibly be related to the menstrual irregularities observed post vaccination.[103]

Regarding assessment of possible COVID-19 disease effects on fertility:

A prospective observational study[104] was performed on the semen of 30 men with SARS-CoV-2 infection, due to the known high ACE2 expression in the male genital system. Total sperm numbers in 83% (25/30) were below the 25th percentile 11 to 64 days after a positive PCR test. Semen parameters can expect to be impacted by acute illness with fever, and 29 subjects were symptomatic at the time of sample collection. While baseline sperm counts pre-infection were not known, five participants had progress assessment 3 months later which showed similar sperm counts to that during symptoms. The authors concluded long term follow up is necessary to evaluate the effect of SARS-CoV-2 infection on spermatogenesis.

Ovarian function was also investigated after COVID-19 disease.[105]In a matched control group study of 78 women in Wuhan with COVID-19 disease, and a median age of 43 years, results indicate that although no obvious menstrual cycle change was observed, women affected by COVID-19 have a significantly lower serum anti-Mullerian hormone level and higher testosterone/prolactin level, suggesting a poor ovarian reserve and abnormal reproductive hormones compared to the age-matched healthy unaffected women. Authors concluded that COVID-19 disease may have a potential deleterious effect on ovarian reserve and endocrine function, but advised that more samples from younger women and long-term prospective cohorts are needed to further determine the effects of COVID-19 diseases on ovarian function. Dosages of most excipients are omitted from the Product Information.

Anaphylaxis, a severe allergic reaction, is very rare. For most vaccines the rate is less than one per million doses. According to the world allergy organization, the Pfizer vaccine has a rate approaching 1 per 200,000 doses.[106] A more recent report from the USA General Brigham Hospital Network found 2.7 anaphylaxes per 10,000

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[103] H. Merchant (n 66).

[104] JC Best et al, 'Evaluation of SARS-CoV-2 in Human Semen and Effect on Total Sperm Number: A Prospective Observational Study' (2021) 39(3) World Journal of Men's Health 489-495 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8255403/>.

[105] T Ding et al, 'Analysis of Ovarian Injury Associated with COVID-19 Disease in Reproductive-Aged Women in Wuhan, China, in an Observational Study' Frontiers in Medicine, 19 March 2021 <https://www.frontiersin.org/articles/10.3389/fmed.2021.635255/full>.

[106] PJ Turner et al, 'COVID-19 Vaccine-associated Anaphylaxis: A Statement of the World Allergy Organization Anaphylaxis Committee' (2021) 2 (14) World Allergy Organization Journal <http://doi.org/10.1016/j.waojou.2021.100517>. See also, COVID-19 Vaccine Safety Update, 27 January 2021.

doses, approximately 25 times higher than that reported by the Centers for Disease Control and Prevention.[107] Vaccination is a suggested contraindication in persons with a known (diagnosed) allergy to polyethylene glycol (PEG), or to other mRNA vaccine components.[108] Australian guidelines for COVID-19 vaccine providers limit this contraindication to a history of anaphylaxis to the vaccine or to its components, with special precautions to be taken for those with other allergy-related conditions as per administration guidelines in the Australian Immunization Handbook.[109] Facial paralysis (Bell's palsy) is listed as a possible side effect due to four cases occurring in vaccinated trial participants and none in placebo recipients.[110]

The safety, efficacy and immunogenicity of the Pfizer vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The effects of immunosuppressive medication, especially methotrexate and rituximab, on a COVID-19 vaccine response are yet to be determined and will need evaluation, especially given their effects on decreasing serological responses to other vaccines. Efficacy may be lower in immunosuppressed individuals.[111]

The Unknown Risks of COVID-19 Vaccination

The completion of safety analysis and ongoing safety observation is problematic due to vaccination of the placebo arms of COVID-19 vaccine trials.[112] For full license approval, two years of follow-up vaccine data are needed. The data will be contaminated as trials are being un-blinded.[113]

Nonetheless, the requirement for safety in modern prophylactic vaccines needs to be extremely stringent since vaccines are administered to healthy individuals.[114] The Brighton Collaboration publish regular 3-monthly lists of possible vaccine Adverse

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[107] Anthony Scholefield, 'Anaphylaxis after Pfizer COVID-19 Vaccine '25 Times Higher' Than Previously Reported' Australian Doctor, 9 March 2021 <https://www.ausdoc.com.au/news/anaphylaxis-after-pfizer-covid19-vaccine-25-times-higher-previously-reported?mkt_tok=MjE5LVNHSi02NTkAAAF7tDkbwGsH3Lgb92jpvlRqFrSL1zhtGe-fmpWV_WVfoWxljqOH_JwC4dExvHMo6BIjm39Nov9SKyZYO8STGdzyMpWxrjXHS2JhS5B2ot1RPJV26g>.

[108] 'Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States' Center for Diseases and Prevention Control (Web Page, page last reviewed 5 March 2021) <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fcovid-19%2Finfo-by-product%2Fpfizer%2Fclinical-considerations.html>.

[109] See, 'Clinical guidance on use of COVID-19 Vaccine in Australia in 2021 (v3.0)' Australian Technical Advisory Group on Immunization('ATAGI') (Web Page, 5 May 2021) <https://www.health.gov.au/sites/default/files/documents/2021/05/covid-19-vaccination-atagi-clinical-guidance-on-covid-19-vaccine-in-australia-in-2021_0.pdf>.

[110] Fernando P. Polack (n 1). See also, Food and Drug Administration, 'Vaccine and Related Biologic Products Advisory Committee Meeting December' Briefing Paper on Pfizer BioNTech COVID 19 Vaccine, 10 December 2020 <https:// www.fda.gov/media/144245/download>.

[111] B Sohani et al, 'Letter to the Editor' (2021) 40 Clinical Rheumatology 797.

[112] (2021) 27 Nature Medicine 569.

[113] J Lenzer, 'Should Vaccine Trials be Unblinded? (2020) BMJ 371 m4956, doi: <https://doi.org/10/1136/bmj.m4956>.

[114] Norbert Pardi et al, 'mRNA vaccines—A New Era in Vaccinology' (2018) 17 Nature Reviews Drug Discovery 261.

Events of Special Interest (AESI) to be alert to in the community, and case definitions, and requests their occurrences to be notified. The relevance of events is then assessed after cumulative analysis of clinical information. Brighton Collaboration updates are published quarterly. Recent items added to AESI are rhabdomyolysis, pancreatitis and subacute thyroiditis.[115] A draft case definition for thrombosis with thrombocytopoenia syndrome has been developed[116] and, more recently, for myocarditis.[117] Australian vaccine providers have been alerted to be aware of and report such cases of myocarditis and pericarditis.[118]

Post marketing, adverse event data gathering usually relies on a voluntary system which normally captures less than 10% of adverse pharmaceutical events. It is therefore imperative, and is indeed mandatory upon Australian vaccination providers, that all adverse events occurring after investigational COVID-19 vaccination be formally notified e.g. to the Database of Adverse Event Notifications.[119]

Unknown Risks Which Require Further Research Are:

1) Vaccine-Associated Enhanced Disease (VAED) sometimes called Antibody Dependent Enhancement, is a modified presentation of a clinical infection affecting individuals exposed to a wild-type virus after having received a prior vaccination for the same pathogen.[120] Past examples are atypical measles and enhanced respiratory syncytial virus (RSV) occurring after administration of inactivated vaccine for these pathogens. In this situation, severe disease has been documented resulting from infection in individuals primed with non-protective immune responses against the respective wild-type viruses. This was well documented in previous trials of corona vaccines and is acknowledged as a possible side effect for COVID-19 vaccines.[121] The risk of VAED cannot be calculated and assessed until further data is collected over time,[122] which will be more difficult by standard means after vaccination of the placebo arms of the safety trials.[123]

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[115] Barbara Law, 'SO2-D2.1.2 Priority List of COVID-19 Adverse events of special interest: Quarterly Update December 2020' 1(2) Safety Platform For Emergency Vaccines <https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020-review_final.pdf>.

[116] Ibid.

[117] 'Draft Myocarditis Case Definition (Version_1.4.2_30.May.2021)' Brighton Collaboration (Webpage, 30 May 2021) <https://brightoncollaboration.us/myocarditis-case-definition-update/>.

[118] 'Covid Vaccine Weekly Safety Report 27-05-21', Australian Government, Department of Health, Therapeutic Goods Administration (Web Page) <https://tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report-27-05-2021>.

[119] 'Report a Problem or Side Effect', Australian Government, Department of Health, Therapeutic Goods Administration (Web Page) <www.tga.gov.au/reporting-problems>.

[120] FM Munoz et el, 'Vaccine -associated Enhanced Disease: Case Definition and Guidelines for Data Collection Analysis and Presentation of Immunization Safety Data (2021) 39 Vaccine 3053-3056 (published on line, 23 February 2021) <https://doi.org/10.1016/j.vaccine.2021.01.055>.

[121] Fernando Polack et al (n 2).

[122] SB Halstead and L Katzelnick, 'COVID-19 Vaccines: Should We Fear ADE?'(2020) 222(12) Journal of Infectious Diseases 1946. <https://pubmed.ncbi.nlm.nih.gov/32785649/>.

[123] D Follman et al, 'A Deffered-Vaccination Design to Assess Durability of COVID-19 Vaccine Effect After the Placebo Group is Vaccinated' (2021) Annals of Internal Medicine M20-8149 (published on linem 13 April 2021) doi:10.7326/M20-8149 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8099035/>.

Pathogenic Priming[124] is another phenomenon, which has been described as immune priming that could involve an autoimmune reaction due to previous exposure to the spike protein, and occur via exposure, infection or injection.

2) Serious adverse events.

The occurrence of life threatening arrythmia following vaccination requires further research (See Pfizer section 3.e). The phase 3 trial of the Pfizer vaccine reported 'paroxysmal ventricular arrythmia' and another vaccine recipient's death due to 'cardiac arrest' of unknown cause, following vaccination in the observation period.[125] This requires further research. Older age group trial participants and vaccine recipients in the general population will have co-morbidities such as obesity and arteriosclerosis. In the absence of a causative diagnosis for these serious adverse events (e.g. 'myocardial infarct'), a link to the vaccine cannot be excluded. It could be misleading, in the absence of a causative diagnosis, to directly attribute life threatening arrythmia and cardiac arrest to obesity and arteriosclerosis common in these age groups.

While deaths in the placebo group were due to diagnosed myocardial infarct and cerebrovascular accident, these diagnoses were not present in the vaccine group's arrhythmic/dysrhythmic events. The risk is likely to be very small but requires researched clarification as to those who may be rendered more vulnerable to such events via pre-existing co-morbidities or drug interactions.

3) Deaths following vaccination.

In the U.K., whose vaccination programme since December 8th 2020 is ahead of Australia's, 24 million persons had been fully vaccinated by May 6th 2021. From January 4th to May 26th 2021, 1,253 post vaccination deaths had been notified to the Yellow Card adverse event reporting system and U.K. Medicines and Healthcare Products Regulatory Agency (MHRA).[126] Interpretation of this mortality data is not possible until the end of thorough investigation, and does not mean the vaccine caused these deaths. This is a limitation of pharmacovigilance upon which investigational vaccines rely heavily.

The pathophysiology of death in the elderly may require post-mortem evaluation since all elderly patients will likely have 'significant co-morbidities' to which death may be attributed.

4) Interactions with other medications are unknown.

5) Interactions with other vaccines are unknown.

Given the lack of safety and efficacy data for mRNA COVID-19 vaccines administered with other vaccines, the vaccine series should routinely be administered alone, with a minimum interval of 14 days before or after receiving any other vaccine.[127]

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[124] J Lyons-Weiler, 'Pathogenic Priming Likely Contributes to Serious and Critical Illness and Mortality in COVID-19 via Autoimmunity (2020) 3 (100051) Journal of Translational Autoimmunity doi: 10.1016/j.jtauto.2020.100051 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7142689/>.

[125] Fernando Polack et al (n 2).

[126] Letter to Dr. J Raine, the Chief Executive of the Medicines and Healthcare Products Regulatory Agency from Dr Tess Lawrie,Director, Evidence-based Medicine Consultancy Ltd. and EbMC Squared CiC, dated 9 June 2021 < https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/>.

[127] Centers for Disease Control and Prevention (n 72). See also, 'Covid-19 Vaccination Decision Guide for Women Who Are Pregnant, Breastfeeding of Planning Pregnancy' Australian Government,

6) Genotoxicity.

Since the possibility of incorporation of vaccine DNA and mRNA into host DNA is considered either negligible or non-existent, genotoxicity studies on vaccines currently available in Australia have not been performed. However, less certainty has been suggested regarding non-integration resulting from the adenovirus vector-based vaccine and mRNA vaccines.[128,129] Therefore, it would seem applicable to have genotoxicity studies on these novel gene vaccines to ensure safety and public confidence.

3.f) Whether the Intervention is Investigational (Experimental) or Conventional;

The TGA has provisionally approved COVID-19 vaccines for 2 years, subject to strict conditions, such as monitoring longer term efficacy and safety.[130]

As the vaccines are still under investigation, they are experimental or investigational. This is not mentioned in the Australian Government consent form for COVID-19 vaccination.[131] However, this knowledge underscores the importance of reporting adverse events post vaccinations. Notifications of adverse events that occur at these times can be made by health personnel, patients or their advocates. As such, they cannot themselves establish causality. Reports are used to assess possible safety signals which may generate an alert or a subsequent hypothesis for further research. Hence the need for vigorous case reporting and follow-up.

It is imperative that all post-vaccination adverse events are notified to the TGA Database of Adverse Events notifications to enable investigation, follow-up and analysis.

3. g) Other Options for Management;

These include exploring concerns about an individual's reluctance and obtaining specialist advice when a patient has a medical condition which may make COVID-19 vaccination more complex. An alternative should be offerable when there is a conscientious objection to vaccines developed or produced using cell lines derived from aborted babies. The NVX-CoV2373 'Novavax' vaccine, awaiting introduction to Australia (with a finalized purchase agreement of 51 million doses), utilized aborted fetal cell lines

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Department of Health (Web Page, 29 March 2021) <https://www.health.gov.au/resources/publications/covid-19-vaccination-covid-19-vaccination-decision-guide-for-women-who-are-pregnant-breastfeeding-or-planning-pregnancy>.

[128] W Doerfler. Adenoviral Vector DNA- and SARS-CoV-2 mRNA-Based Covid-19 Vaccines: Possible Integration into the Human Genome—Are Adenoviral Genes Expressed in Vector-based Vaccines? Virus Research Vol 302:198466. doi: 10.1016/j.virusres.2021.198466. Published online 1 June 2021. <https://pubmed.ncbi.nlm.nih.gov/34087261/>.

[129] N Cimolai, 'Do RNA Vaccines Obviate the Need for Genotoxicity Studies?' (2020) 35 Mutagenesis 509-510 (published 20 November 2020) doi: 10.1093/mutage/geaa028 <https://pubmed.ncbi.nlm.nih.gov/33216145/>.

[130] 'TGA provisionally approves Pfizer COVID-19 Vaccine', Australian Government, Department of Health, Therapeutic Goods Administration (Web Page, 25 January 2021) <https://www.tga.gov.au/media-release/tga-provisionally-approves-pfizer-covid-19-vaccine>.

[131] 'Consent Form for Covid Vaccination', Australian Government, Department of Health (Web Page) <https://www.health.gov.au/sites/default/files/documents/2021/02/covid-19-vaccination-consent-form-for-covid-19-vaccination_2.pdf>.

during testing, but not during development and production. In this regard, the Pfizer vaccine is equivalent.

As a protein-based vaccine, Novavax may be more acceptable to those who prefer not to have a genetically modified organism in the vaccine or who prefer not to use a gene-based vaccine. It has demonstrated suitable effectiveness.[132] There are both societal and medical reasons for vaccine choice. Dr Paul Griffin, the Infectious Disease physician and microbiologist who oversaw the Australian arm of phase 1/2 'Novavax' trials, reports of medical reasons:

> Even within our country, we're going to need a range of different vaccines that cater potentially for different populations or different comorbidities, for example, and different environments…another benefit for Australia in particular, is the fact that Novavax's candidate relies on a different mechanism to generate immunity than the Pfizer/BioNtech mRNA vaccine and AstraZeneca's viral vector candidate, AZD1222.[133]

Other viable ways of significantly reducing the risk of COVID-19 transmission such as physical distancing, cleaning, use of personal protective equipment, and minimising contact with others (working from home, shopping on-line etc.) should be explained.

There is significant clinical dissention in medical ranks and divergent models of research-based care which is consistent with a disease about which knowledge is accruing. It is therefore important to provide current, evidence-based research pertaining to the prevention and treatment of COVID-19 infection as patients may enquire about these alternatives to vaccinations. Government Treatment Guidelines are accessible and continuously updated eg the use of monoclonal antibodies in the outpatient setting.[134] Examples of treatments which have shown some benefit to treat early COVID-19 infection include Vitamin D[135] and Vitamin C.[136] Zinc has some evidence for recommendation since zinc deficiency is associated with poorer outcomes.[137] Further research is needed.

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[132] Elisabeth Mahase, 'Covid-19: Novavax Vaccine Efficacy is 86% Against UK Variant and 60% Against South African Variant' (2021) 372 British Medical Journal doi: <https://doi.org/10.1136/bmj.n296 <https://www.bmj.com/content/372/bmj.n296>.

[133] RACGP newsGP, 14 January 2021 interview Matt Woodley <https://www1.racgp.org.au/newsgp/clinical/novavax-candidate-may-prove-best-long-term-solution>.

[134] See 'Covid Treatment Guidelines' NIH (Web Page) <https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults—therapeutic-management/>.

[135] See, Petre Cristian Ilie, 'The Role of Vitamin D in the Prevention of Coronavirus Disease 2019 Infection and Mortality' Researchsqaure <https://www.researchsquare.com/article/rs-21211/v1>; Adrian R Martineau et al, 'Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systemic Review and Meta-Analysis of Individual Participant Data'(2017) 356 BMJ i6583 <https://www.bmj.com/content/356/bmj.i6583 https://doi.org/10.1136/bmj.i6583>.

[136] See, Luis Chiscano-Camon et al, 'Vitamin C Levels in Patients with SARS-Co-V-2 Associated Acute Respiratory Distress Syndrome' (2020) 24 BMC 522.

[137] Y Yasui et al, 'Analysis of the Predictive Factors for a Critical Illness of COVID-19 During Treatment—Relationship Between Serum Zinc Level and critical Illness of COVID-19 (2020) 100 International Journal of Infectious Diseases 230. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7476566/>.

However, Australian Guidelines for the Clinical Care of People with COVID-19 recommend no disease modifying treatments for mild cases having routine outpatient management.[138] They also have no outpatient management guidance to address intercurrent deficiencies in Vitamin D, Vitamin C and Zinc. All such treatments, if used, should be under medical supervision of dosage and contraindications (eg zinc may cause pancytopenia in those with a copper deficiency such as can occur following gastric bypass surgery) and to prevent toxicities. Coronavirus Disease 2019 Communicable Diseases Network Australia National Guidelines for Public Health Units (version 4.5, 25th May) also state:

> …readers should not rely solely on the information contained within these guidelines. Guideline information is not intended to be a substitute for advice from other relevant sources including, but not limited to, the advice from a public health specialist or other health professional. Clinical judgment and discretion may be required in the interpretation and application of these guidelines.[139]

Ivermectin, included in the WHO Essential Medicines list, is a common drug used to treat scabies and worms, and has been investigated with fourteen clinical trials of variable strength for treatment of COVID-19. These have been mostly clinician led, as opposed to having pharmaceutical sponsoring, and many are pre-print. Some trials have suggested Ivermectin as an adjunct reduced the rate of mortality, low O2 duration, and duration of hospitalisation in adult COVID-19 patients. The improvement of other clinical parameters suggested that Ivermectin, with a wide margin of safety, had a high therapeutic effect on COVID-19.[140] However, one systematic review of randomized controlled trials[141] (at this stage accepted for publication) evaluating ten RCTs of Ivermectin treatment for their risk of bias and quality of evidence, found three RCTs showing a significant reduction in all cause mortality were at high risk of bias. The authors recommended additional RCTs be completed to update their analysis, and that Ivermectin use should be confined to these trials. The following studies were referred to as having a high risk of bias with small numbers of participants, and their authors had called for more research:

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[138] Australian Guidelines for Clinical Care of Persons with COVID-19 Disease, 'Australian National COVID-19 Clinical Evidence Taskforce, section 6, version 40.1, 6/10/21' (Web Page) <https://files.magicapp.org/guideline/8b6f065b-814f-41f0-a1a5-70279b722e19/published_guideline_4346-12_0.pdf>.

[139] Coronavirus Disease 2019 Communicable Diseases Network Australia, National Guidelines for Public Health Units (version 4.5, 25th May) (Web Page) <https://www1.health.gov.au/internet/main/publishing.nsf/Content/7A8654A8CB144F5FCA2584F8001F91E2/$File/COVID-19-SoNG-v4.5.pdf>.

[140] S Ahmed et al, 'A Five Day Treatment with Ivermectin for the Treatment of Covid-19 May Reduce the Duration of Illness' (2021) 103 International Journal of Infectious Diseases 214: doi: 10.1016/j.ijid.2020.11.191.

[141] YM Roman et al, 'Ivermectin for the Treatment of COVID-19: A Systematic Review and Meta-analysis of Randomized Controlled Trials (Accepted manuscript), *Clinical Infectious Diseases*, ciab591, <https://doi.org/10.1093/cid/ciab591 Published by Oxford University Press for the Infectious Diseases Society of America <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab591/6310839>.

1) Iranian double-blind RCT hospital research, in pre-print and not peer reviewed, claimed reduced mortality, reduced duration of hypoxia and reduced duration of hospitalization, in a small study of 180 mild to severe COVID-19 hospitalized patients,[142] with confirmed PCR in 71% and confirmatory chest imaging.

2) A double-blind RCT in 72 persons claims evidence of the potential benefit of early intervention with Ivermectin for the treatment of adult patients diagnosed with mild COVID-19. Early intervention promoted faster viral clearance during disease onset, which authors suggest might have prevented significant immune system involvement and hastened recovery.[143]

Australian Guidelines for the Clinical Care of People with COVID-19 have not recommended Ivermectin due to the rate of side effects and perceived weakness of the evidence citing improvements across various parameters of reducing Intensive Care admissions, mortality, and the requirement for artificial ventilation.[144] Given the politicization and controversy around Ivermectin, and evidence of anti-SARS-CoV-2 infection in vivo benefit demonstrated by a most recent Pasteur Institute hamster study[145] which 'supports the use of immunomodulatory drugs such as Ivermectin to improve the clinical condition of SARS-CoV-2 -infected persons', its exclusion from the WHO Solidarity Trial for re-purposed drugs for COVID-19 is unfortunate.

Another controversial option, currently under use by some physicians for very early treatment of COVID-19, is the Zelenko protocol. This protocol was associated with reduced hospitalizations in a retrospective case series[146] study of COVID-19 outpatients. Controversy should not affect presentation and discussion of peer-reviewed, evidence-based medicine,[147] particularly around early outpatient care, where so little has been published. However, the need for close medical supervision including screening for contraindications is emphasized by the authors. For example, screening for QT intervals, retinopathy and glucose-6-phosphate dehydrogenase deficiency is required.

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[142] Morteza Shakhsi Niaee et al, 'Ivermectin as an Adjunct Treatment for Hospitalised Adult COVID-19 Patients: A Randomized Multi-Center Clinical Trial' doi: 10.21203/rs.3.rs-109670/v1 (pre-print).

[143] S Ahmed, MM Karim, AG Ross et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International Journal of Infectious Diseases. 103 (2021) 214-216. 26th November 2020. <https://doi.org/10.1016/jijid.2020.11.191>.

[144] Australian Guidelines for Clinical Care of Persons with COVID-19 Disease (n 138).

[145] GD de Melo et al, 'Attenuation of Clinical and Immunological Outcomes During SARS-CoV-2 Infection by Ivermectin' EMBO Molecular Medicine, June e14122 <https://research.pasteur.fr/en/publication/attenuation-of-clinical-and-immunological-outcomes-during-sars-cov-2-infection-by-ivermectin/>.

[146] R Derwand, M Scholz and V Zelenko, 'COVID-19 Outpatients: Early Risk-stratified Treatment with Zinc Plus Low-dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study, (2020) 56 International Journal of Antimicrobial Agents <https://doi.org/10.1016/j.ijantimicag.2020.106214>.

[147] R Bhopal and A Munro, 'Scholarly Communications Harmed by Covid-19 (2021) BMJ 372, doi: <https://doi.org/10.1136/bmj.n742>; I Torjesen, 'Covid-19: Sweden Vows Greater Protection for Academic as Researcher Quite After Aggressive Social Media Attack' (2021) BMJ 372, doi: <https/doi.org.10.1135.bmj.n489>.

A meta-analysis of RCTs[148] and of other studies of chloroquine and hydroxychloroquine has presented reports of COVID-19 treatments with significant dose variations of differing formulations of chloroquine and hydroxychloroquine, with differing initiation protocols at different stages of illness and target groups. These authors found inconsistent efficacy and concluded no improvement in clinical outcomes. In subsequent discussion, the same authors cite the retracted Lancet Surgisphere hydroxychloroquine data study,[149] which presented false Australian and other data and claimed increased hydroxychloroquine mortality. Its accompanying Lancet editorial was also removed and replaced. The meta-analysis authors wrongly claim the retraction was chiefly due to 'lack access to data [sic]..held by a private company'. These authors do conclude, however, that 'well designed randomized trials are required for assessing the efficacy and safety of hydroxychloroquine and chloroquine for COVID-19'.

Prophylaxis:

There is published evidence of some prophylactic benefit from use of Ivermectin,[150] which would also benefit from more research. Meta-analysis of three trials involving 738 participants evaluating Ivermectin for COVID-19 prophylaxis among health care workers and COVID-19 contacts found that 'Ivermectin prophylaxis among health care workers and COVID-19 contacts probably reduces the risk of COVID-19 infection' by an average of 86% (95% confidence interval, range 79%–91%). Five percent vs. 29.6% contracted COVID-19, respectively. This was assessed as low-certainty evidence and downgraded due to study design limitations and few included trials. No severe adverse events were recorded in two of the three trials involving a total of 538 participants.

3. h) The Degree of Uncertainty of the Outcome;

In relation to vaccine efficacy see discussion in previous section 3. d) above. The duration of vaccine effectiveness (immunity) is unknown.[151] The recent drive to vaccinate children who are themselves at low risk of severe COVID-19 disease, to reduce onward transmission in the community and achieve a level of herd immunity from an overall vaccination rate approaching 80%, exposes children to the known and un-

[148] A Elavarasi et al, 'Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: a Systematic Review and Meta-analysis' (2020) 35(11) Journal of General Internal Medicine 3308-14 <https://link.springer.com/article/10.1007/s11606-020-06146-w>.

[149] RETRACTED MR Mehra et al, 'Hydroxychloroquine or Chloroquine with or without a Macrolide for Treatment of COVID-19: A Multinational Registry Analysis, (2020) Lancet doi: <https://doi.org/10.1016/S0140-6736(20)3118-6> <https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31180-6/fulltext>.

[150] A Bryant et al, 'Ivermectin for Prevention and Treatment of COVID-19 Infection: A Systematic Review, Meta-analysis, and Trial Sequential Analysis to Inform Clinical Guidelines' (2021) 28(4) American Journal of Therapeutics, e434-e460 doi:10.1097/mjt.0000000000001402 <https://journals.lww.com/americantherapeutics/fulltext/2021/08000/ivermectin_for_prevention_and_treatment_of.7.aspx>.

[151] 'Coronavirus disease (COVID-19): Vaccines', World Health Organization (Web Page, 19 February 2021) <https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccines>.

known risks of gene based vaccines[152] with novel platforms for little gain to themselves, to protect vulnerable adults.[153] Health outcomes in children following mass childhood vaccination are uncertain.

3. i) The Likely Consequences of Not Choosing the Proposed Procedure, or of Not Having Any Procedure at All;

The consequences depend on the reason(s) for declining or deferring vaccination, the level of COVID-19 alert, the alternative anti-COVID measures adopted (as in point 3.g above), and the patient's risk of developing severe complications or death as a result of COVID-19 infection (see section 3.a). Declining or deferring vaccination avoids vaccine-related side effects at the expense of possibly suffering severe COVID-19 disease and its attendant risks (COVID-19 symptoms, hospitalisation, ventilation and death) during a subsequent community outbreak.

Other consequences may include Occupational Health and Safety considerations for health or aged care workers, and travel restrictions, should the Australian Government or other state/territory governments introduce border entry/re-entry requirements conditional on proof of vaccination or previous documented infection.[154]

There is also the potential social stigma of being inappropriately labelled an "antivaxxer."

3. j) Any Significant Long Term Physical, Emotional, Mental, Social, Sexual or Other Outcome That May Be Associated With the Proposed Procedure;

Because the development of these vaccines has been hastened, only short-term safety data is available and the long term safety of these vaccines is not established.

1) Vaccination of pregnant or breastfeeding women:

Observational data demonstrate that, while the absolute risk is low, pregnant women with COVID-19 have an increased risk of severe illness, hospitalization, intensive care admission and ventilation.[155] There is also increased risk of stillbirth. There is a possibility of vertical transmission of the COVID-19 virus and an increased incidence of third trimester premature birth due to medical intervention.[156] Pregnant women are

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[152] A Dionne et al, 'Association of Myocarditis with BNT162b2 Messenger RNA COVID-19 Vaccine in a case Series of Children' (2021) JAMA Cardiology Doi:10.1001/jamacardio.2021.3471 (published online, 10 August 2021) <https://jamanetwork.com/journals/jamacardiology/fullarticle/2783052>.

[153] E Abi-Jaoude, P Doshi and C Michal-Teitelbaum, 'Covid-19 Vaccines for Children: Hypothetical Benefits to Adults Do Not Outweigh Risks to Children, BMJ Opinion (Blog Post, 13 July 2021) <https://blogs.bmj.com/bmj/2021/07/13/covid-19-vaccines-for-children-hypothetical-benefits-to-adults-do-not-outweigh-risks-to-children/>.

[154] Australian Government, Australian Covid Vaccination Policy, 6 <https://www.health.gov.au/sites/default/files/documents/2020/12/covid-19-vaccination-australian-covid-19-vaccination-policy.pdf>.

[155] COVID-19 Vaccination in Pregnant and Breastfeeding Women. RANZCOG. Update August 6th. <https://ranzcog.edu.au/statements-guidelines/covid-19-statement/covid-19-vaccination-information>.

[156] Royal Australian and New Zealand College of Obstetricians and Gynaecologists (n 99).

now known to be at increased risk of other adverse pregnancy outcomes, such as pre-eclampsia, coagulopathy, and preterm birth that is not due to medical intervention.[157]

There are no phase III trial data on the safety of COVID-19 vaccines in pregnant or breastfeeding women.[158] Long term effects of gene-based COVID-19 vaccines on the fetus, breastfed infant or milk production/excretion are not known.[159] There is limited data on vaccine effectiveness during pregnancy and on subsequent pregnancy outcomes after vaccinations, and no long term outcome data. USA research into mRNA vaccine safety in pregnancy[160] is underway. A first dose of mRNA vaccine in the third trimester of pregnancy thus far reveals no short term safety signals of concern and the authors note transplacental transfer of antibodies after maternal vaccination may help protect the neonate. The authors mistakenly assess the spontaneous abortion rate as a fraction of total completed pregnancies rather than as a proportion of total vaccinated pregnancies per gestational trimester. AstraZeneca safety in pregnancy has not been researched.

The recently published reproductive toxicology research[161] on the Pfizer vaccine examined pre-implantation fetal loss, fetal abnormalities and other parameters. The study concluded vaccination caused no effects on embryo-fetal or postnatal survival, growth, or development in the offspring through to the end of lactation. Higher percentage pre-implantation loss in the vaccinated group compared with the control group ($p < 0.5$) was within the historical control data range and the authors attributed it due to a higher rate of ovulation in the vaccinated rat cohort. Of the rat pups examined from the maternally vaccinated cohort, there were 3 malformations (defined as 'structural defects rare in the control population and thought to be life-threatening or of major physiological consequence') compared with no malformations in the control group. These malformations were gastroschisis, agnathia with short and fused mandibles and a small mouth, and malformation of the right-sided aortic arch, in separate pups. These malformations, as well as minor abnormalities, were deemed within background historical control incidence.

RANZCOG's position changed from strongly considering, in June 2021 to 'routinely offering' mRNA COVID-19 vaccination to all pregnant women.[162] Women who

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[157] See, Vaccines and Immunizations, Centers for Disease Control and Prevention (Web Page, last updated 14 May 2021) <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html?CDC_AA_refVal+https%3A%2F%2Fwww.cdc.gov%Fvaccines%2Fcovid-10%2Finfo-by-product%2Fpfizer%2Fclinical-considerations.html>.

[158] 'Information and Decision Aid' Royal College of Obstetricians and Gynecologists (Web Page, updated 14 May 2021) <https://rcog.org.uk/globalassets/documents/guidelines/2021-02-24-combined-info-sheet-and-decison-aid.pdf>.

[159] Centers for Disease Control and Prevention (n 108).

[160] TT Shimabukuro et al, 'Preliminary findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons' (2021) 384 New England Journal of Medicine 2273-2282 <https://www.nejm.org/doi/full/10.1056/nejmoa2104983>.

[161] CJ Bowman et al (n 94).

[162] Joint Statement ATAGI and Royal Australian and New Zealand College of Obstetricians and Gynaecologists (n 100).

are classified as being extremely vulnerable to severe complications of COVID-19, it is advised, would especially benefit from vaccination.[163]

Significant inflammation on the maternal side of the placenta was observed at microscopy in a well-documented case of mid trimester foetal demise in COVID-19 disease in pregnancy.[164] This phenomenon has been seen in 40% of maternal infections with Middle East Respiratory Syndrome[165] and Severe Acute Respiratory Syndrome.[166] It has been speculated that the similarity between coronavirus spike protein antigens, either in the wild or in the vaccine, with a placental protein Syncytin-1 could theoretically establish an immune reaction to the placenta.[167] In the case of the vaccine, this would not be limited to the duration of a wild virus infection but could be permanent i.e. there is a theoretical possibility that the vaccine may, by a similar molecular mechanism, establish an immune reaction to the placenta which could endure. Pfizer state it is 'very unlikely our vaccine could harm the placenta.'[168] To date, this has not been fully investigated although it is considered that the section of the similar protein sequence in syncitin-1 does not share sufficient similarities and is covered under the surface of the protein, preventing binding by anti-spike antibodies. COVID-19 infected mothers' antibodies to the spike protein might also attack Syncitin-1 and have a similar risk of miscarriages. Ongoing pregnancy studies of entire pregnancies and subsequent pregnancies will clarify these issues.

Providing some level of reassurance, preliminary research of a single dose only of mRNA vaccine received from 30 weeks of gestation onwards in 75 women (plus 9 with unknown gestation) was not associated with placental inflammation.[169] However, the corresponding author stated 'we want to look at patients who are vaccinated in the pre-conception period as well, partially to look at if we see evidence of placental injury at delivery from women vaccinated at that point.'[170] Further research is still needed. The

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[163] Ibid.

[164] D Baud et al, 'Second Trimester Miscarriage in a Pregnant Woman with Sars-CoV-2 Infection' (2020) 323 (21) Journal of American Medical Association doi:10.1001/jama.2020.7233.

[165] G Favre et al, '2019-nCoV Epidemic: What about Pregnancies?'(2020)395(10224) E40 Lancet doi: 10.1016/S0140-6736(20)30311-1.

[166] SF Wong et al, 'Pregnancy and Perinatal Outcomes for Women with Severe Acute Respiratory Syndrome (2004) 19 (1) American Journal of Obstetrics and Gynecology 292, doi: 10.1016/j.ajog.2003.11.019.

[167] Giverse Vernon, 'Of HERVS and COVID-19: Questions for the Future' British Journal of General Practice (Post, 21 May 2020) <https://bjgplife.com/2020/05/21/of-hervs-and-covid-19-questions-for-the-future/>.

[168] 'The Facts about Pfizer and BioNTech's COVID-19 Vaccine', Pfizer, (Web Page, 6 January 2021) <https://www.pfizer.com/news/hot-topics/the_facts_about_pfizer_and_biontech_s_covid_19_vaccine>.

[169] E. Shanes et al, 'Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination in Pregnancy Measures of Immunity and Placental Histopathology' Research Letter, Obstetrics and Gynaecology (11 May 2021) doi: 10.1097/AOG.0000000000004457.

[170] JA Goldstein quoted in 'Clearing up a misconception: COVID-19 Vaccines and Infertility/Pregnancy Loss May 14th 2021. <https://www.biospace.com/article/no-known-link-between-covid-19-vaccines-and-infertility-pregnancy-loss-/>.

authors referenced observations made in mice in 2007 that changes at the feto-maternal interface, following similar immune processes as occur in the functioning of COVID-19 vaccines, included impaired spiral artery modification with increased fetal losses in the mid-gestation period.[171]

Concerns have been expressed about gaps in our knowledge of the effects of altered proportions of immune cells in pregnancy after COVID-19 vaccination.[172] Successful pregnancy outcomes are heavily dependent on heightened helper T cell type 2 (Th2) and regulatory T cell activity, with reduced helper T cell type 1 (Th1) responses. Disruption of the balance of T cell responses during pregnancy is associated with adverse perinatal outcomes including foetal loss and pre-term birth.[173] Data on two mRNA vaccine candidates indicate an altered balance of these cells in a broad immune response following vaccination.[174]

An accepted limitation of rat and mouse species for pre-clinical studies is their different placentation from humans. They are also less sensitive than humans to fertility perturbations.[175]

2) Conscientious objection

Deeply held convictions regarding vaccine derivation may be a source of tension personally and interpersonally. In relation to a patient considering vaccination but having a conscientious objection to vaccines which have used aborted foetal cell lines in their development, production or testing, such vaccines should be identified to patients where the doctor knows or suspects this information would affect the patient's decision to undergo vaccination, and an ethical alternative offered i.e. a vaccine which has been produced avoiding or, at the very least, minimising the use of cell lines derived from aborted babies.

For such patients, the Pfizer vaccine, which utilised aborted foetal cell lines only in its testing, is more likely to be acceptable than the AstraZeneca product, which used such cell lines in both its development and production. The Moderna vaccine is equivalent to AstraZeneca vaccine in this regard. Pending availability, the NVX-CoV2373

[171] Jianhong Zhang et al, 'Toll-like Receptor 3 Agonist Induces Impairment of Uterine Vascular Remodeling and Fetal Losses in CBAxDBA/2 Mice' (2007) June (1-2) Journal of Reproductive Immunology 2007 61. Doi:10.1016/j.jri.2006.10.005.

[172] SL Klein, P Creisher and I Burd, 'COVID-19 Vaccine Testing in Pregnant Females is Necessary' (2021) Journal of Clinical Investigation doi.org/10.1172/JCI147553.

[173] S Saito et al. 'Th1/Th2/Th17 and Regulatory T-cell Paradigm in pregnancy' (2010) 63(6) American Journal of Reproductive Immunology 601.

[174] EE Walsh et al, 'Safety and Immunogenicity of Two RNA-Based Vaccine Candidates' (2020) 383 (25) New England Journal of Medicine 2439; U Sahin et al, 'BNT162b2 induces SARS-Co-V-2-neutralizing Antibodies and T Cells in Humans' (2020) medRxiv <https://www.medrxiv.org/content/10.1101/2020.12.09.20245175v1>.

[175] 17 February 2020 EMA/CHMP/ICH/544278/1998 Committee for Medicinal Products for Human Use ICH S5 (R3) guideline on reproductive toxicology: Detection of Toxicity to Reproduction for Human Pharmaceuticals.

'Novavax' vaccine is an alternative to the Pfizer vaccine, as it also utilised aborted foetal cell lines only in the testing process.[176]

3.k) The Time Involved;

Eligible patients at each phase can book directly with a delivery hub, or accredited GP. There is no requirement for a referral for COVID-19 vaccination. There is no restriction on seeing only existing patients or patients in a particular area.

3. l) The Cost Involved, Including Out of Pocket Costs;

Cost varies from country to country. While vaccines for Australian citizens are government funded, those not eligible for this (some migrant workers and student visa holders) should be referred to a General Practitioner respiratory clinic or to state/territory immunisation centres.

Discussion

The COVID-19 pandemic is of great concern across the globe. COVID-19 morbidity, mortality and the transmissibility of the new Delta variant require effective management tools. Safe and effective vaccination is one such tool.

COVID-19 vaccination is a rapidly changing field with many emerging findings in different stages of publication and demonstration. There is much speculation in existing sources of literature which raise reasonable concerns about vaccination. However, given the rapid flux of new findings, both negative and positive, at the present time it is almost impossible to state this Guidance is complete.

This Guidance aims to address the important concern of ethical informed consent in an area of care delivery where there are many drivers, some unethical, for obtaining consent and use. Such drivers include the pressure for those obtaining consent to not exercise their duty to the consentee, but rather alter the consent process to achieve other laudable, but conflicting goals, such as herd immunity, public safety targets and protections, political mandates, etc.

We have provided an evidenced platform to deal with knowns and unknowns not covered in standard consent forms, from which to select issues to present to a greater or lesser extent, as relevant to the patient. The main challenges to address in our duty of care to the vaccinee are:

1) Ensuring the informed consent process for COVID-19 vaccination captures satisfactorily all the components deemed necessary for ethical informed consent without adding unnecessary obstacles to the vaccination process.
2) Informing consentees about a medical product when there are reasonable concerns about the product but no information yet to satisfactorily confirm or deny those concerns, and there is genuine concern about time to act on the reception of that product.

[176] T McGovern 'Vaccinated or Not: Answering Common Questions for Catholics' Federation Internationale des Associations de Medecins Catholiques (post 29 Dec 2020). <https://www.fiamc.org/covid-19/to-be-vaccinated-or-not-answering-common-questions-for-catholics/>.

3) Clarifying, in a timely manner, what constitutes substantive information to tell the proposed vaccine recipient, in the midst of a potentially life-threatening disease epidemic.
4) Defining any individuals/groups who may not benefit from vaccination or indeed may be harmed by it.
5) Advising a consentee with concerns on how long to wait for the data to collect when an epidemic is spreading.
6) Discussing alternative risk-reduction measures to vaccination and whether they can be used to assist in vaccine effectiveness.

Pertinent examples of concerns in informed consent include fetal safety following maternal vaccination, long term reproductive and gonadal safety for younger men and women, and groups who are low risk for morbidity and mortality from COVID-19 infection and yet are being included in vaccination campaigns. The latter are primarily minors of different ages, who are at low risk for death and injury from COVID-19 disease as best we know, but are at risk for known[177] and unknown vaccine side effects and complications. However, vaccinating them may contribute to protecting older groups more at risk for death and morbidity, including those already vaccinated, due to incomplete vaccine protection. Thus, the very young are being asked to shoulder risks that may outweigh the benefit for themselves. If protection of at-risk groups is the main benefit then such should be stated in the informed consent document.

Conclusion

On the basis of the data presented, if a patient considering vaccination with Pfizer and AstraZeneca vaccines were to ask about the chance of their protection against severe COVID-19 disease improving, one could answer confidently that protection against the original strain is very high in the short term, and against emerging strains relies on evolving information but appears reduced.

Obtaining informed consent for COVID-19 vaccination, however, goes well beyond this important question, and we therefore encourage vaccinators to raise the 12 guidance points in a patient-specific manner for everyone considering vaccination. The key point is that all considerations, including personal, family and societal ones, need to be counterbalanced against an individual's risk of developing severe disease when exposure to the SARS-CoV-2 virus occurs.

Nothing is known about the long term effects of the disease or of any COVID-19 vaccine. Absence of evidence of long term vaccine side effects is not evidence of safety, and further vaccine safety assessment will be more difficult to achieve without an unvaccinated comparator cohort to complete safety trials, due to vaccination of the control arms. There will be crucial reliance on recognition and notifications of post-vaccination adverse events by patients as well as practitioners. Some of these will require heightened public awareness for reporting, such as occurrences of new onset menstrual abnormalities which could be relevant to gonadal health. Failure to alert vaccinees to significant

[177] E Abi-Jaoude (n 153).

cluster reports associated with COVID-19 vaccination jeopardizes awareness and recognition of adverse event reporting, thereby reducing pharmacovigilance effectiveness.

Therefore, the combination of significant unknowns makes it difficult to assess, but necessary to discuss, the risk-benefit issues for any individual getting the infection and recovering or, possibly suffering long term COVID-19 sequelae, versus receiving an investigational vaccine and developing its side effects and complications. Each vaccine recipient will need to make their own judgement and the informed consent process will include concerns with no concrete science to deny or support the concerns as yet.

As should be apparent from this Guidance document, obtaining consent for vaccines still under investigation in the midst of a global pandemic, is a more complex task than obtaining consent for conventional vaccines. Doctors have an obligation to act in the best interests of their patients. This involves being aware of information on the risks, benefits and alternatives to the COVID-19 vaccines available in Australia, tailoring the advice and information they give to their patients to ensure that fully informed consent is achieved, and enquiring about adverse events and reporting them. It is hoped that this Guidance will provide Australian doctors with more comprehensive information to achieve these ends.

Liability in the Time of Coronavirus: The Ethical Necessity of Expanding the Legal Protections Afforded to Healthcare Workers During the COVID-19 Pandemic

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ABSTRACT: Although discussions have begun regarding the ways in which healthcare providers and individuals in fields adjacent to healthcare might be exposed to legal sanctions involving COVID-19, the complete scope of the legal risks is still largely unknown. This essay explores how current laws in the United States fail to offer adequate protections: (1) to healthcare workers (HCW) practicing under significantly altered standards of care, and (2) to individuals involved in the allocation of scarce resource decision-making

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process. Using research on Second Victim Syndrome and Medical Malpractice Stress Syndrome, legal protections are presented to provide HCW a form of "moral buffering" to help prevent further traumatizing them for shouldering extraordinary burdens during the COVID-19 pandemic. In so doing, this article advocates for the passage of appropriate legal protection as not merely a legal issue, but also an ethical one.

It now seems the height of cliché to say that we do not understand, nor can we foresee, all the repercussions of COVID-19. That the future looks uncertain for almost everyone, that persons of all walks of life cannot yet see how their lives will be impacted is one of the few certainties in this crisis. We are all forced to live in a liminal space—the time between the start of this pandemic and its end.

Nowhere is this liminality more apparent, however, than in the lives of those who work to see that healthcare is provided to those who need it and distributed justly when there are not enough resources to satisfy demand. The painful reality, though, is that people are going to die, despite the heroic efforts of healthcare workers (HCW) who battle to mitigate the damage.[1] While numerous HCW are acting outside of their comfort zones to keep us alive, what can be done to protect them? Shielding HCW with appropriate personal protective equipment (PPE) is a necessary first step, but as necessary is providing them legal protection to prevent harm in the aftermath of this disaster. When we ask healthcare providers to shoulder enormous risk, like we do when crisis standards of care (CSC) are invoked, we owe them basic legal protections commensurate with the amount of risk we have asked them to bear. Basic considerations of fairness require as much. What remains to be explored is why these legal protections are of such moral importance, to whom else we owe them, and what practices these protections should cover.

In our capacities as co-chairs of a county Disaster Clinical Advisory Committee and a Crisis Standards of Care Clinical Regional Triage Team, we have been alerted to the anxieties healthcare providers, triage team volunteers, and ethicists have regarding their legal liability during this crisis. Many people are pressed into service during times of crisis, and we ask these persons to shoulder the responsibility of making life-or-death decisions that may bring with them legal, ethical, and psychological consequences. We are asking them to take these risks without adequate support from their professional organizations (Grimaldi, 2007) and without adequate promises that they will be protected from legal repercussions (Hoffman, 2008; Cohen et al., 2020).

In this article we will explain what legal protections currently exist for HCW in the wake of the COVID-19 pandemic. We will advocate for enacting more liberal protec-

[1] We will be referring to this collection of persons as "healthcare workers" from here on out for the sake of simplicity, but we will include those whose work is adjacent to healthcare in our discussion of legal protections.

tions for all HCW, as well as for the individuals making scarce resource triage decisions that HCW are then asked to follow. Extending these protections not only serves a legal purpose, but also a moral one. Using research on Second Victim Syndrome and Medical Malpractice Stress Syndrome, we will advocate those legal protections can offer a form of "moral buffering" and help prevent further traumatization of those asked to shoulder extraordinary burdens.

Medical Context: Surge Capacity and the Standard of Care

HCW find themselves at increased legal risk largely due to shifting patient volumes and shortages of resources throughout this pandemic. Hospitals find themselves navigating between levels of surge capacity categorized by the Institute of Medicine (IOM) as conventional capacity, contingency capacity, and crisis capacity. At first glance, the distinctions between these different surge capacity levels seem somewhat clear. Conventional capacity is the capacity at which hospitals usually operate. There are enough resources for every patient, there is enough staff to deal with the demand, and the hospital infrastructure is sound (Institute of Medicine, 2012). Elective surgeries might be canceled and staff from different parts of a hospital might be reassigned to deal with any small surge, but standard protocols and conventional standards of care are practiced. Then, contingency capacity is invoked when spaces in a hospital are utilized differently and/or when supplies are rationed in a way that adjusts normal practices, even if standards of care remain functionally equivalent. For example, contingency capacity may require some types of hospital rooms to be used for purposes other than their normal designations (e.g., using post-anesthesia care rooms as temporary intensive care unit (ICU) rooms (Stroud, 2010)). At the end of this continuum is crisis capacity. Crisis capacity involves major changes to standard protocols and standards of care (Institute of Medicine, 2012). Healthcare practitioners may be asked to practice outside the scope of their expertise and equipment may need to be rationed and reused. Most significantly, healthcare practitioners must shift from a focus on making decisions that are in the best interest of individual patients to "public-focused" care that looks "to promote equality of person and equity in distribution of risks and benefits in society" (Berlinger et al., 2020, 1).[2]

The IOM documents make it clear that capacities and the corresponding standards of treatment exist along a continuum.

[2] This shift is one potential cause of the sort of moral burdening to HCW that we discuss later in this paper. In crisis and triage, we ask clinicians to fundamentally shift the way they reason about ethical decisions involving their patients, and this is not an uncontroversial ask. For many, the ethical call to shift from providing patient focused care to doing the most good for the greatest number is extremely troubling, even when using triage guidelines that apply utilitarian ethics. This fundamental shift in healthcare delivery can cause grave moral distress and moral injury to clinicians who need to think in utilitarian ways during crisis when their customary practice is to advocate for patient autonomy and to meet each patient's needs. Although it is outside of the scope of our paper to speak to this shift in ethical framing of medical practice necessitated by crisis and the potential harm it may cause, this insight animates our paper and concern for HCW during this time.

> These categories [of capacity]…represent a corresponding continuum of patient care delivered during a disaster. As the imbalance increases between resource availability and demand, healthcare—emblematic of the healthcare system as a whole—maximizes conventional capacity; then moves into contingency; and, once that capacity is maximized, moves finally into crisis capacity (Dan Hanfling, et al., 2012, 1-6).

Although the IOM provided a taxonomy meant to guide states and regions in determining when conventional capacity, and thus conventional standards of care, were surpassed, this taxonomy was meant to cover all kinds of events that would cause surges. However, this taxonomy can only be but so precise in delimiting exactly how the movement between different levels of capacity might happen and how standards of care might shift in any particular surge. As Hodge and colleagues note, "Moving from abstract principles and norms to the concrete world of healthcare delivery presents translational challenges" (Hodge et al., 2012, 52). For example, in a region struck by an acute natural disaster, such as New Orleans during Hurricane Katrina in 2005, area hospitals clearly operated under CSC. However, here, with on-going COVID-19 challenges fluctuating over the course of several months, shifts between levels of capacity often lack clear delineation. Additionally, in some instances, even when it is clear that crisis capacity has been reached, local and state governments have been reluctant to declare a crisis.

While many facilities have been operating somewhere between conventional capacity and contingency capacity during COVID-19, some have at times been in crisis. State and local health districts have periodically asked doctors to shift their focus from the usual standard of care in treating individual patients to preserving PPE and resources to prepare to meet the needs of a community. The lack of clear federal and/or state guidelines outlining specific "triggers" of CSC, in addition to a lack of guidance on whom has the authority to invoke CSC, makes the surge level at a particular hospital at a particular moment difficult to determine.[3] As a result, papers were published at the beginning of this pandemic that tried to elucidate how and when to move to CSC (*c.f.*, Hick et al., 2020 and Berlinger et al., 2020).

This unclarity exists in part because of the nature of problems facing HCW during this particular pandemic. Initially, the most pressing issue involved an inadequate supply of PPE. That there was a lack of appropriate PPE across the country was clear, but how that deficiency impacted a particular region of the country, or hospital system, or HCW was harder to determine. This lack of PPE was initially what forced many hospitals to move along the surge continuum closer to crisis capacity. It raised questions about

[3] For example, in a triage team meeting that the authors attended near the onset of the pandemic, healthcare practitioners were under the belief that CSC had been invoked in their hospitals, while public health officials refuted this and verbalized that part of the job of the triage team was to help clarify when crisis standards should be invoked, and went on to state that no hospital in our region had yet invoked CSC. Discussions that day, and in the weeks and months that followed, made it clear that any movement to CSC should be coordinated between health systems in the region, as well as public health officials, and the state. However, this was not clear before the initial triage team meeting, and still remains a point of discussion, even at the time of this publication over a year later.

whether to give universal do-not-resuscitate (DNR) orders to all critically ill COVID-19 patients, regardless of patient or family wishes. It also led to bypassing the normal stages of respiratory assistance—patients were going from nasal cannulas to intubation because of fears of aerosolizing the virus when HCW lacked an adequate supply of N95 masks. In order to conserve PPE, ICU beds, and ventilators, non-emergency procedures all over the country were being canceled. This has led to great concern about the repercussions of delaying procedures that, under conventional standards of care, are considered crucial to long-term survival and improved health (*c.f.*, Shrag et al., 2020 and Bochove & Court, 2020). Although cancelations of elective procedures may fall within "conventional capacity" when it is only one hospital or region requiring such cancelations, since this involves multiple healthcare systems all over the country, this might be more indicative of contingency capacity. Most importantly, in all of these examples, healthcare practitioners have been asked to shift their focus from doing what is in the best interest of each individual patient to "doing the greatest good for the greatest number of people" (Walsh, B., & Chakravarti, A., 2021, 1).[4] This lack of certainty regarding which surge capacity healthcare practitioners are operating under, in addition to which standard of care they are being held, may lead to legal, moral, and psychological distress.[5,6]

Even more concerning than this ambiguity is the reluctance on the part of some local and state governments to declare a crisis where a crisis exists. Los Angeles County is the clearest example of this. In late 2020 and early 2021, Los Angeles County hospitals were overwhelmed with patients. Patients were housed wherever there was room in the hospitals, including cafeterias and on gurneys in the hallways. Ambulances were lined up for hours outside of emergency departments. (Lin et al., 2021). The Emergency Medical Services Agency of Los Angeles County issued a memorandum in early January 2021 requiring EMS drivers to leave patients who experienced cardiac arrest that could not be resuscitated in the field (Gausche-Hill, 2021). Although standards of practice had clearly changed, no declaration of crisis from the county or state was issued. This failure to declare a crisis potentially left HCW legally unprotected for doing the best work they could during a crisis situation. If states and counties will not declare a crisis even when hospitals are clearly at a breaking point and in-field triage decisions are being made, HCW risk being left unshielded from liability, and potentially even criminal charges, in ways that should be reconciled by legislative bodies.

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[4] While it is beyond the scope of this article to argue about the ethics of the specifics of how standards of care shift during crisis situations, others have offered admirable attempts to just such thinking during this pandemic (*See*, for instance, Emanuel et al., 2020; Peterson, et al., 2020).

[5] Although it is possible that enhanced legal protection might not reduce stress for a particular HCW, it is reasonably foreseeable that avoiding malpractice claims could help mitigate HCW stress (*See* discussion of Medical Malpractice Stress Syndrome below).

[6] It is important to note that the authors are not providing legal advice. This article is meant to educate on apparent deficiencies in the current law and to advocate for additional and/or amended laws to improve the legal protection available to HCW, ethicists, and those involved in decision-making regarding the allocation of scarce resources.

Legal Context: Medical-Legal Liability in Uncertain Times

Legally acknowledging the plaguing uncertainty—medically and ethically—of how to allocate limited resources during a pandemic, most notably during periods of crisis, is crucial to preventing unreasonable inferences of negligence. Historically, laws involving negligence and medical malpractice have been available to impute liability on providers who have failed to meet the standard of care (61 Am. Jur. 2d Physicians, Surgeons, Etc. § 331; Restatement (Second) of Torts § 328A). Yet, a mere bad result does not infer liability (57A Am. Jur. 2d. Negligence § 28; 61 Am. Jur. 2d Physicians, Surgeons, Etc. § 331). Currently, given unstandardized and at times even unknown standards of care during the COVID-19 pandemic, inferring liability for negligence based on typical standards of care is likely not reasonable. However, traditional standards remain intact in many states, left to be applied on a case-by-case basis by panels of jurors who likely have no medical background. Due to unique complexities involving pandemic standards of care, this unduly burdens juries to answer questions that the medical profession itself struggles to answer.

Legislators should send a clear message that COVID-19's alterations to the standard of care are not the fault of an individual provider, hospital, or healthcare system. While civil negligence medical malpractice laws generally seek to accomplish two main goals: (1) to deter a healthcare provider from injuring patients, and (2) to compensate a patient for injuries sustained by a negligent caregiver (Tappan, 2005), there are two significant issues with this framework during a pandemic. First, deterrence in this context may carry unforeseen consequences. HCW may be deterred from working in hospitals that are short-staffed or without adequate resources, further contributing to understaffing and the inability to meet the needs of patients. Second, this framework is intended to trigger compensation for patients only involving a provider's breach to the standard of care (61 Am. Jur. 2d Physicians, Surgeons, Etc. § 331), a standard which is somewhat uncertain and fluctuant during the pandemic.[7] If certain states continue to enforce unclear standards of care during the COVID-19 pandemic, the standard for justice also remains vague and unclear, and legislators should proactively address this.

Current Laws and Suggested Changes

Early in the pandemic, Secretary of Health and Human Services (HHS) Alex Azar asked all state governors to help shield healthcare professionals from medical liability. Azar went so far as to state, "For health care professionals to feel comfortable serving in expanded capacities on the frontlines of the COVID-19 emergency, it is imperative that

[7] Generally, the standard of care to which a healthcare provider is held is determined by state law. The following is an example of a state statute from the State of Washington that describes the traditional standard in that state: "that degree of care, skill, and learning expected of a reasonably prudent health care provider at that time in the profession or class to which he or she belongs, in the state …, acting in the same or similar circumstances" (RCWA § 7.70.040). Note, that this particular statute has recently been amended, effective May 10, 2021, to add language recognizing an altered evidentiary standard involving the standard of care during the COVID-19 pandemic which is discussed further in footnote 16 below.

they feel shielded from medical tort liability" (Azar, 2020, 3). Azar called upon all states to "issue guidance summarizing the statutory scope of protections offered under their laws" and to clearly outline "the available liability protections during the COVID-19 emergency" (Azar, 2020, 3). We agree wholeheartedly and advocate that state governments should clarify what legal protections exist for HCW during the pandemic and pursue establishing further liability protections if current liability protections seem inadequate.

Current Civil Laws and Suggested Changes

Federal laws do provide certain protections for HCW during the COVID-19 pandemic against civil liability, but these do not go far enough, and state laws on this issue are inconsistent and often inadequate. While federal law does provide some protection to healthcare volunteers, it fails to protect the vast majority of HCW who are acting in the capacity of their jobs.[8] This inconsistency is troubling. What follows is a review of applicable federal civil legal protections and suggested legal improvements.

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 extends to volunteer health professionals certain protections from civil liability, but these protections are limited (HIPAA 1996; AMA, 2020). Further, HIPAA protection only applies at certain free clinics, and it is difficult to qualify for this protection (HIPAA, 1996; AMA, 2020). Thus, HIPAA's application is too narrow to provide liability protection to the majority of HCW.

Similarly, the Uniform Emergency Volunteer Health Practitioners Act (UEVHPA), which has only been enacted by a minority of states, is too narrow in scope to be protective for the vast majority of HCW. While the UEVHPA helps grant immunity from civil liability during a declared disaster, it only does so for out-of-state volunteer health professionals, and certain exceptions apply (Uniform Law Commission, 2020; AMA, 2020). Thus, UEVHPA's application is too narrow to provide liability protection to the majority of HCW.

Somewhat similarly, the Volunteer Protection Act (VPA) of 1997 applies too narrowly to offer much protection as it generally only benefits nonprofit organizations and/or government volunteers. While the VPA is protective in that it does preempt state laws, the VPA fails to provide liability protection to individuals being paid for their time. Additionally, the VPA does not cover acts or omissions deemed "willful or criminal misconduct, gross negligence, reckless misconduct, or a conscious, flagrant indifference

[8] While the sudden-emergency doctrine does potentially provide some protection to some HCW, its application would be quite narrow. This doctrine provides civil liability protection involving any "prudent person", facing an "unexpected danger", and making rapid choices (Am Jur Negligence § 200, 1). However, its application is not to include situations which occur "over a period of time" (Am Jur Negligence § 203, 2), which seemingly contradicts the essence of CSC which involves "crisis operations [that] will be in effect for a sustained period" (Institute of Medicine (2012)). Therefore, the sudden-emergency doctrine should not be relied on to reduce the number of negligence claims against HCW during the pandemic to any significant degree.

to the rights or safety of the individual harmed by the volunteer" (42 U.S.C. § 14503(a) (2000)). While these exceptions are usually reasonable, during this pandemic they may create unintended windows of liability for "willful" actions related to the allocation of scarce resources. For example, removing a ventilator from one patient to use on a more salvageable patient, an action sometimes required to do "the greatest good for the greatest number of people" (Walsh, B., & Chakravarti. A. 2021, 1), may be deemed a willful act that caused the death of a patient, opening a door to potential civil liability. Thus, while the VPA is protective in preempting state civil liability laws, it is unlikely to provide liability protection to the majority of HCW and may be deficient when involving the allocation of scarce resources.[9]

Therefore, we suggest that HCW should generally not expect to receive liability protection from either HIPAA, UEVHPA, or VPA and we encourage lawmakers to focus on amending other federal statutes contained herein, such as the Public Readiness and Emergency Preparedness (PREP) Act and/or the Coronavirus Aid, Relief and Economic Security (CARES) Act.

In contrast to statutes limited in scope to apply only to healthcare volunteers, the PREP Act does offer some protection from civil liability to paid healthcare providers. While this statute seemingly provides broad immunity to "Covered Persons", it only does so involving "Covered Countermeasures" (Department of Health and Human Services, 2020, 15199). While "Covered Persons" generally include healthcare providers and individuals dealing with "public health and medical emergency response of the [a]uthority [h]aving [j]urisdiction" (Department of Health and Human Services 2020, 15201), the language of the PREP Act fails to make clear whether Covered Persons are offered protection if the activities they perform fall outside the activities specifically listed as "Covered Countermeasures". Such measures do include such things as vaccines, treatments, testing and devices involving COVID-19 (42 U.S.C. §§ 247 d-6d (2005); Department of Health and Human Services, 2020). However, the statute does not address activities involving the triaging of scarce resources, which is problematic. A notice of declaration was issued by Secretary Azar in March 2020, and was later printed in the Federal Register, to add clarity to the "Covered Countermeasures" definition. Unfortunately, Secretary Azar did not address this specific issue. We recommend that the definition of "Covered Countermeasures" be expanded to specifically include the allocation of scarce resources, and that liability protection is extended to all individuals involved in that process.[10]

[9] State laws providing greater protection from liability are not preempted by the VPA, and we encourage states to pass laws providing such protection if alternative protections are not enacted.

[10] Congress may consider an alternative means of providing financial compensation to injured patients impacted by substandard care delivered during the pandemic (specifically involving care that does not meet traditional standards of care yet does not rise to the level of gross negligence). For example, Congress may consider extending access to compensation to patients affected by these protections thru the "Covered Countermeasure Process Fund" (*See* 42 U.S.C. §§ 247 d-6e (2005)). This fund has created the Countermeasures Injury Compensation Program (CICP) to provide compensation for patients injured by Covered Countermeasures (*See* Department of Health and Human Services, 2020), which Congress could expand upon should they so choose. Somewhat similarly, Congress previously passed the National

Additionally, Congress enacted a coronavirus-era act that, to some extent, attempts to address the lack of liability protection available to HCW during the pandemic, but this too falls short. The CARES Act became law spring of 2020 and, beyond providing economic relief for individuals and businesses, the CARES Act, using Good Samaritan verbiage (AMA, 2020), federally protects healthcare volunteers from liability during the COVID-19 pandemic by preempting state medical malpractice laws. The CARES Act extends federal protection to individuals providing medical services in response to COVID-19 in a volunteer capacity (AMA, 2020) but does not protect healthcare professionals performing the same or similar duties as a part of their actual jobs (H.R. 748). Yet, compensating patients for injuries caused by HCW but not volunteers, fails to honor the second goal of medical malpractice laws, which is to compensate injured patients for injuries sustained by negligent caregivers (*c.f.,* Tappan, 2005). This failure seemingly treats injured patients, for example two hospital roommates, differently under the law by providing certain legal recourse to the roommate treated by an employee but not to the roommate treated under otherwise similar conditions by a volunteer. Options for legal recourse for an injured plaintiff/patient would be dependent on the employment status of the providers, rather than the egregiousness of their care. Thus, it may be reasonable to amend the CARES Act to provide similar legal protections during the pandemic for both paid and volunteer healthcare professionals, as both are otherwise subject to liability for situations beyond their control during this crisis.[11]

Like HCW, ethicists and other individuals who offer guidance on triage committees involving scarce resource allocation should also be extended liability protections. Besides passing laws to protect doctors, nurses, and others involved in direct patient care, more must be done to protect those working and/or volunteering in adjacent fields. COVID-19 has greatly impacted public health districts and departments in ways that require the help of certain adjunct fields, for example academic ethicists; thus, it is essential to provide adequate legal protections to individuals who serve in these roles.

Childhood Vaccine Injury Act of 1986 in response to vaccination injuries. That injury program provides a no-fault avenue of recovery for individuals with vaccination-related injuries, allowing compensation for those injured, which seemingly decreases lawsuits against HCW while providing a means for compensation for patient injuries (*See* Health Resources & Services Administration National Vaccine Injury Compensation Program).

[11] Whether Congress has authority to create such broad civil liability protection for HCW during the pandemic involving state medical malpractice laws remains debatable. Yet, the U.S. Constitution does grant Congress authority to legislate on matters necessary and proper to regulate commerce or to spend (U.S. Const. art. I, § 8; *See* Bakera, 2014)). As such, Congress can likely financially incentivize states to enact liability protections to promote "the general welfare" if they "unambiguously" give states the opportunity to choose whether to participate (*See S. Dakota v. Dole*, 483 U.S. 203, 207 (1987)), and the incentives can be linked to a new or expanded federally funded healthcare program (*c.f., Nat'l Fed'n of Indep. Bus. v. Sebelius,* 567 U.S. 519, 574–81 (2012)). Alternatively, since Congress has "the power to regulate commerce" (*Id. at* 521), medical malpractice insurance impacts interstate commerce, and liability shields are likely to impact medical malpractice insurance rates, authority for such legislation may potentially exist through the Commerce Clause. Also, Congress has previously exercised use of constitutional authority to create civil liability protection for certain healthcare providers in the PREP Act for "Covered Persons" and "Covered Countermeasures", which does support, but does not confirm, congressional authority here.

While the Public Health Service (PHS) Act provides civil liability protection to public health officers and employees, these protections are limited (*See* Public Health Service Act, 42 U.S.C. § 247d-6d (2005)). The PHS Act does not on its face include protection for CSC triage committee members who allocate scarce resources using state approved CSC guidelines and function to support state or local health departments. Thus, individuals on triage committees may be unprotected from civil liability by the PHS Act, and we recommend amending this act to specifically extend legal protection to CSC triage committee members.

An amendment of the CARES Act could remedy this. Currently, the CARES Act likely does not extend legal protection to ethicists and others serving on committees involving the allocation of scarce resources, as these individuals do not fit nicely within the statutory definition of healthcare professionals providing healthcare. However, their function on these committees does indirectly, and significantly, affect the delivery of healthcare; hence, these committee members may face the possibility of being named as defendants in negligence lawsuits unless they are proactively protected by legislation. Ultimately, whether a triage committee member is a volunteer healthcare professional, ethicist, or other individual, the potential for being the "cause" of a plaintiff/patient's damages is similar, so the law should similarly protect them. Thus, in addition to consideration of amendment to the CARES Act that would extend protection from liability during the pandemic to all HCW, whether serving in a volunteer capacity or not, we also advocate to expand the list of professionals protected to include not only HCW but also individuals offering CSC triage recommendations.

The following is a summary of the potential legal protections we have suggested thus far, which focus on amending the CARES, VPA, PREP, and/or PHS acts.

First, the CARES Act could be expanded to include non-volunteer healthcare providers, as they are often performing the same role as employed providers, and it is neither ethical nor just that a patients' legal recourse is contingent on the employment status of their caregiver. Further, this act could be amended to specifically include protections for all individuals offering guidance related to scarce resource allocation due to COVID-19, such as ethicists and triage committee volunteers.

Second, if the CARES Act is not amended as described above, the VPA could be amended to provide liability protection beyond nonprofit and government volunteers to include those individuals being paid for their time. Further, it could be clearly state that activities related to the allocation of scarce resources are NOT acts consistent with willful or criminal misconduct, gross negligence, or reckless misconduct, and thus are not grounds for civil or criminal liability.

Third, if the above amendments are not adopted, the PREP Act could be amended to clearly include civil liability protection related to the allocation of scarce resources by adding this action as a recognized countermeasure.

Fourth, if the above suggestions are not adopted, the PHS Act could be amended to include liability protection for committee members, including ethicists, who are involved in state departments of health or local health districts CSC response efforts.

Certainly, committee members involved in decisions and/or actions regarding the allocation of scarce resource, which may lead to the death of a patient to benefit another, are deserving of protection.

If Congress is reluctant to enact the above suggestions, state legislatures should respond quickly to protect all of their HCW, not just their volunteers. They should do so by enacting legislation, if they have not done so already,[12] that clearly recognizes that the standard of care during the COVID-19 pandemic has been disrupted and providers are not to be held to a conventional standard of care; further, lawmakers should consider whether justice during the pandemic would be better served using a threshold which would require gross negligence,[13] willful misconduct, or intoxication. Generally, proving negligence in medical malpractice merely requires a "preponderance of evidence" that the defendant "deviated from good and accepted standards of medical practice" (61 Am. Jur. 2d Physicians, Surgeons, Etc. § 331). However, that may be an unreasonably low bar during a pandemic when transient shortages of space, staff, and stuff have been ongoing. Broad liability shields could resemble those set forth in the CARES Act involving healthcare volunteers (*See* H.R. 748 § 3215), if they are extended to include all HCW. Arguably, such extensions may seem overly defense-friendly, as some HCW have been practicing under conventional capacity and traditional standards of care during portions of the pandemic. Yet, there is no perfect solution and broad liability shields would serve to heighten the degree of deviation from the standard of care needed to prove malpractice, which under the circumstances is likely appropriate.[14]

Finally, should Congress and state legislatures fail to act, governors may be able to respond by issuing executive orders to help temporarily protect HCW and those involved in scarce resource triage from civil liability.[15] During the beginning of the pandemic, New York Governor Andrew Cuomo quickly issued an executive order to temporarily authorize civil liability protection for all HCW in the state, barring acts or omissions involving gross negligence (Executive Order, 2020). Similarly, since then other governors, most notably in the eastern United States, have extended immunity to

[12] By the time of this publication, most, but not all, states have enacted civil liability protections for HCW during the pandemic; these protections generally exclude gross negligence and willful misconduct, in addition to bad faith and intoxication (*See* Ferragamo, 2020).

[13] In contrast to negligence, gross negligence requires a more significant deviation from the standard of care. According to Black's Law Dictionary, gross negligence "differs from ordinary negligence only in degree" and generally does not require "a reckless disregard of the consequences" (NEGLIGENCE, 2019, *citing* W. Page Keeton et al., *Prosser and Keeton on the Law of Torts* § 34, at 211–12 (5th ed. 1984)).

[14] While medical malpractice is not a criminal claim, it may feel as such to HCW, especially those who may have been forced to practice medicine under crisis conditions. Shifting the law to require a near-criminal evidentiary standard of gross negligence and presuming innocence unless clearly proven otherwise may be reasonable under these circumstances.

[15] While governors issuing executive orders are often effective in providing temporary liability protection to HCW, not all state constitutions authorize executive orders to serve this function. For example, the Michigan Supreme Court determined on October 2, 2020, that multiple executive orders issued during the pandemic were unconstitutional. However, the Michigan legislature then passed legislation which basically retroactively enacted many of those provisions (*See* Ferragamo, 2020).

HCW by executive orders (Ferragamo, 2020). A Connecticut executive order includes immunity involving scarce resources.

> The Connecticut executive order…goes beyond the scope of the law passed in Massachusetts by protecting covered medical professionals and facilities from acts or omissions undertaken due to a lack of resources caused by the COVID-19 pandemic. In theory, this could provide immunity for acts or omissions involving a patient whose care was impacted by a lack of resources regardless of whether that patient was diagnosed with COVID-19 (Blei, 2020, 1).

In contrast, some states have ineffectively utilized executive orders in this arena. For example, the executive order by Pennsylvania Governor Tom Wolf has been reported as being "one of the weakest in the nation" by Curt Schroder, executive director of the Pennsylvania Coalition for Civil Justice Reform (Santoni, 2020, 3). There, the executive order fails to protect against claims of malpractice involving forced delays in elective procedures to conserve scarce resources, and the allocation of scarce resources, among other deficiencies. This example should be avoided in the future.

Therefore, if federal and state legislators fail to act, and if their state constitutions allow, governors should consider issuing executive orders similar to Connecticut's which helps ensure that HCW and those involved in scarce resource decision-making are shielded from liability to prevent further traumatization.

Addressing Opposition to the Suggested Civil Law Changes

Ralph Nader and others have argued that blanket liability protection against coronavirus liability represents a problematic extension of the law. They argue that offering broad liability protection to "institutions and personnel…for casualties caused in 'good faith,' is not necessary, and actually a potential 'legal contagion'" (Nader et al., 2020). We disagree and will handle both claims in turn.

The belief that these protections are unnecessary is incorrect for four reasons. First, Nader and coauthors fail to consider the potential harms caused by unnecessary lawsuits. While the authors claim "medical professionals are already insured against claims and losses" and "existing judicial and legal structures can and do already handle claims of this sort" as long as physicians are operating under the appropriate standards of care (Nader et al., 2020), such statements overlook that lawsuits often cause detrimental emotional distress, even when insured against losses. Doctor Curtis Miyamoto, Chair of Radiation Oncology at Temple Health in Philadelphia, stated, "A lot of us are being expected to do things we don't normally do," and the fear of malpractice is "a significant deal" (Bryan, 2020, 3-4). Pre-pandemic, results from a Medscape survey, as reported by Patricia Salber, MD, MBA, already noted that medical malpractice "take[s] a heavy toll on doctors" (Salber, 2015, 3). Many doctors acknowledged some form of long-term emotional injury (e.g., anxiety and/or depression) and over half became preoccupied with being sued again (Salber, 2015). Sadly, 30% stated they "no longer trust patients; I treat them differently" (Salber, 2015, 4). More will be said about the toll

of malpractice lawsuits on HCW below, but these are not insignificant findings, for both doctors and the patients they treat.

Second, it is an inaccurate assumption that all HCW serving during this crisis have adequate or any individual liability protection. Nader and coauthors do not consider non-physician HCW at all in their argument, but consideration of non-physician HCW is necessary. As Wayne Guglielmo explains, often nurses do not have such protection (Guglielmo, 2020). Similarly, it remains unclear what percentage of medical ethicists have liability insurance, especially those acting in the capacity of volunteers. Furthermore, Guglielmo argues that even doctors with liability protection are in a precarious situation. Many medical malpractice liability plans have clauses that exclude doctors from coverage when they are not practicing in the facility by which they are employed or are doing procedures for which they are not normally covered (which can be necessary for doctors practicing under CSC). Thus, Nader and coauthors' claim that doctors are adequately protected by current tort law is unsupported by facts.

Third, Nader and coauthors claim incorrectly that since standards of care will be altered by the facilities and systems in which physicians practice, these physicians will not be legally held to conventional standards of care.

> To the extent then, that medical/legal/ethical committees draw up new standards, new guidelines for appropriate medical decision-making, even when it comes to rationing or allocating ventilators, physicians who follow those guidelines would be within the standard of care, and not liable for malpractice (Nader et al., 2020).

However, that statement cannot be counted as true, as there is no master medical/legal/ethical committee that has declared what "the" standard of care is for each state and/or the nation during contingency or CSC. Additionally, there is confusion and a lack of clarity about how and when the shift to CSC is activated, as well as who has the authority to declare CSC standards. HCW may well be operating under CSC *de facto* before the institutions and communities they are serving have acknowledged the shift. Bureaucratic systems move more slowly than emergencies. Further, there is no national standard on how courts use clinical practice guidelines in determining the standard of care (*See* Moffett & Moore, 2011); thus, it is unlikely that CSC guidelines would universally offer liability protection to HCW. Some lawmakers are taking notice of this deficiency in the law and taking action, as demonstrated by the State of Washington recently enacting SSB 5271[16] which has amended the description of the standard of

[16] This recently enacted statute in the State of Washington recognizes alterations to the standard of care during the COVID-19 pandemic and clarifies that to determine "whether the health care provider followed the standard of care" considers good faith and "guidance, direction, or recommendations, including in interim or preliminary form, published by the federal government, the state of Washington or departments, divisions, agencies, or agents thereof, or local governments in the state of Washington or departments, divisions, agencies, or agents thereof, in response to the COVID-19 pandemic and applicable to such health care provider"; additionally, the standard of care during the COVID-19 pandemic is altered if there is "a lack of resources including, but not limited to, available facility capacity, staff, and supplies, directly attributable to the COVID-19 pandemic" (State of Washington SSB 5271 § 2 (2021)).

care in RCW 7.70.040. Other lawmakers should be moved to address this deficiency as well.

Fourth, Nader and coauthors likely overstate reality when they write that "a judge or jury *would* make significant allowances for health care providers" (Nader et al., 2020, emphasis added). Our belief that our current legal system is inadequate to deal with the claims that may come out of this pandemic is conjectural, but so are Nader and his coauthors' claims. There is no evidence that their claim is true, as there is no way to determine in advance that judges and juries would indeed make such allowances. Moreover, if Nader and coauthors are suggesting that significant allowances in courtrooms are justified for HCW during contingency and crisis capacity, and that judges and juries would indeed make these allowances, it is logical to put such allowances into statutes. Besides promoting justice by setting a clear standard on this issue, this would help decrease the number of HCW being named as defendants, enduring emotional trauma, and awaiting leniency years later at trial.

In response to Nader and coauthors' second argument, the legal contagion claim against extending legal protections to HCW, is a slippery slope argument and thus, fallacious. While industries and special interest groups outside of medicine may similarly appeal for liability protection, fear of future requests of this sort is not a valid reason to deny protection where it is warranted. Moreover, there is a morally significant difference between the healthcare industry and other industries in this crisis. If any industry deserves liability protection during the pandemic, it is the healthcare field. Society has asked HCW to take on special risks, not only to their physical health, but also to their emotional well-being, by practicing under situations that are unfamiliar and unconventional to save lives and protect public health. No such ask has been made of the industries that Nader and coauthors fear will seek liability protection (specifically, airlines, cruise companies, and restaurants). This difference creates the most significant defense against the statement those authors claim.

Criminal Protections Should Be Considered

Criminal laws generally create consequences for unreasonable behaviors deemed immoral against society (Samah, 2017, 9), yet providing healthcare in good faith during the COVID-19 pandemic, even if there is a poor outcome, should likely not be criminalized by society. As such, criminal protections are reasonable involving two issues: CSC guidelines and medical errors.

First, CSC guidelines exist to benefit society during a dire healthcare situation which has been created by the pandemic itself, not by a lack of morality of HCW. Almost by definition CSC involve patients unable to get the care that they need due to a scarcity of resources (*See* Institute of Medicine 2012). This is a function of the crisis at hand, irrespective of fault. As such, HCW should not fear criminal liability for attempting to follow CSC guidelines, when done in good faith, even though lives are likely to be lost. For example, during CSC an insufficient supply of life-sustaining resources may lead to HCW removing ventilators from certain patients to use on patients with a

higher likelihood of survival. The removal of the ventilators may lead to death. Death may open the door to prosecution for crimes such as manslaughter for the HCW. This foreseeable risk to HCW, especially those involved in scarce resource triage, needs to be addressed proactively. Shields from criminal prosecution under such circumstances would not devalue the lives lost. Rather, liability shields should help incentivize HCW to utilize rather than fear CSC guidelines, which by their very nature seek to equitably and fairly do the greatest good for the greatest number of people at a time when there is not enough space, staff, or stuff to meet the healthcare needs of patients.

Second, while criminal charges involving medical errors resulting in patient harm may be rare, they are becoming "less unusual every year" (Gordon 2019, 3), and should be addressed. According to Kirstin Manges, a University of Pennsylvania nurse and researcher on patient safety, prosecution of nurses related to medical errors tend to involve systemic problems during "busy, unpredictable circumstances" (Gordon 2019, 3). During the pandemic, HCW are often experiencing system-wide busy and unpredictable work conditions (Roth 2020; Begun & Jiang 2020), which foreseeably increase the risk of medical errors and resultant patient harm (*c.f.,* Gordon 2019). This increase in risk supports the need for consideration of criminal liability shields for HCW during the pandemic. "Doubts have [already] been raised about the fairness of criminalizing errors that are made in the course of executing normal professional duties with no criminal intent and the capriciousness of criminal prosecution" (Dekker 2017, 92). Specifically, nurses have been noted as being at risk for medical errors that lead to prosecution (Gordon 2019; Dekker 2017). With understaffing and busy work conditions during the pandemic, this foreseeable risk, especially to nurses, needs to be addressed.

Yet, at the time of this publication, only three states (Maryland, New York, and New Jersey) have enacted laws that largely provide criminal immunity for HCW during the pandemic (*See* MD Public Safety Code section 14-3A-06, New York Emergency or Disaster Treatment Protection Act, New Jersey SB 2333).[17] It is reasonable that the remaining 47 states consider protecting HCW from criminal prosecution when HCW are acting in good faith. Good faith is by no means a perfect standard even during the pandemic public health emergency, as it does have certain limitations; however, it is a reasonable standard to apply. One limitation may be the appearance of a somewhat blanket defense. Such a blanket defense may be inappropriate in situations involving "battlefield euthanasia", which in war has been found to violate the Geneva Convention (Neuhaus, 2011). However, scarce resource triage or the occurrence of medical errors leading to death do not equate to euthanasia.

> Euthanasia, particularly in a military setting, must be distinguished from "triage", which provides an ethical framework for deciding on priorities of care in resource-limited (predominantly mass-casualty) environments. There is no doubt that in these situations, patients with overwhelming injuries may be triaged to "expectant care". The overriding priority in all such cases is care, compassion and respect for

[17] Exceptions to these protections include such things as intoxication and/or intentional harm.

> human dignity and human life. The patient is provided with comfort until he or she either dies or the situation changes and resources become available to provide treatment. (Neuhaus, 2011).

Unlike euthanasia, where an action is taken with the purpose of ending life, scarce resource triage involves the allocation of scarce resources to certain patients with the purpose of saving the most lives. HCW do not intend any patients' deaths when they allocate resources to those who are most salvageable, although these deaths might be the consequence of not being the chosen recipient of a scarce resource. Unlike soldiers during war, HCW in the pandemic are forced to take on a role which resembles Good Samaritan status. Good Samaritan status can carry certain legal protection to help encourage members of society to render care during an emergency. Here, even when acting in an employed role, HCW may be forced to render care under risky conditions without adequate resources within strained healthcare systems. If in the setting of the COVID-19 public health emergency HCW and/or individuals involved in scarce resource triage are acting in good faith, society should recognize the extreme conditions in which they have been called to provide services and help to protect them. If those rendering care have the mindset of good intentions, it is reasonable for society to extend to them immunity from criminal prosecution.

Such legal protections serve to protect HCW from further trauma for being called on to provide care during a time when medical errors and/or the allocation of scarce resources are foreseeable risks caused by strains on healthcare systems during the pandemic.

Moral Buffering: Reduction of Trauma and Retraumatization for Healthcare Workers

Although the legal risks we ask HCW to face at this time are significant, as concerning are the moral risks that are attached to these legal risks. What we are proposing are clear, reasonable protections from liability for those involved with healthcare work done in good faith during periods of crisis. This includes not only doctors and nurses, but also public health workers, applied ethicists, and others who make decisions crucial to functioning in a taxed healthcare system. These legal protections serve four primary purposes. Most obviously, these laws provide legal protection, as discussed above. Given the current circumstances, the potential risk to providers of civil, even criminal, liability seems unfathomable, yet the risk is real. Currently, we are requiring HCW to deal with shortages of equipment and surges of capacity with which almost none of them have previously dealt. Similarly, we are asking individuals working in fields adjacent to healthcare to help healthcare providers make ethical decisions about rationing resources during times of crisis. In allocating scarce resources, some patients will die, not because an individual provider caused their death, but because the taxed healthcare system could not save everyone. Generally, liability is based on fault. Here, fault lies with a virus that the world was ill-prepared to treat. Federal and state-level legislation should

recognize this and authorize legal protections for those doing necessary and difficult work under extraordinary circumstances.

The second purpose of the proposed laws is the enforcement of new societal norms. A change in the law can be understood as societal recognition of the responsibility that has been placed on healthcare providers and those in fields adjacent to healthcare. As Eric Posner argues, laws are critical to enhance social norms and to undermine bad norms (Posner 2002). By passing laws that clearly exempt those acting in good faith when making decisions about healthcare and healthcare rationing during contingency and crisis capacities, we enforce new norms that are only beginning to be part of the cultural consciousness. With the public decreeing the label of "hero" to those on the frontlines of healthcare and healthcare planning, we see the beginnings of this new norm. This label belies a widespread public recognition that what we are asking of those involved in healthcare falls outside of their normal duties. Passing laws which delineate the protections society owes them for taking on this work further reinforces and defines this new norm.

The third purpose of these laws is reciprocity. When we call HCW heroes, what we mean is that HCW are going above and beyond their normal duties in order to protect the health of the public (Cox, 2020). HCW are working longer hours, under more strenuous and dangerous conditions, in order to provide care to those who are sick. They are doing this even as many in our country deny the efficacy of masks, continue to gather in ways that spread the virus, and display vaccine hesitancy. HCW are taking on increased risk in many ways: they are at risk of contracting the virus and spreading it to their loved ones. They risk burnout as their working conditions deteriorate and they see their fellow HCW come down sick. They are shouldering moral burdens when they practice under conditions of shifting standards of care, especially in places like Los Angeles County where the crisis situation on the ground was not recognized by local or state government as being in crisis. The legal protections for which we argue are owed to HCW because of their willingness to shoulder burdens above and beyond their normal work.

The final purpose of the proposed laws is to help offer "moral buffering" to HCW, which might help reduce their incidence of traumatization and retraumatization. Laws are needed that acknowledge conventional standards of care are not expected during a crisis. Traditional standards of care during conventional capacity are consistent with high standards of patient-centered care, but they are not the primary focus during CSC in a pandemic. Thus, in such a setting, high standards of patient-centered care are not only impractical, but also potentially impossible. Laws acknowledging that what we expect of HCW in normal times is not what we expect during a crisis may help to mitigate some of the psychological and emotional burdens on HCW as well as prevent future retraumatization that would occur because of lawsuits.

Burdens to HCW related to an inability to provide high standards of patient-centered care during a pandemic are, to a certain extent, unavoidable; however, laws should help protect them from unnecessary secondary trauma. There are two significant ways

laws might protect from further trauma to HCW. First, these laws provide a level of protection against moral suffering during the crisis or at least a way to frame experiences when reflecting on them after the crisis subsides. These laws also will prevent reigniting the trauma post-incident that is sure to occur if complaints are brought against HCW, especially if they are sued. What follows is a brief overview of the psychological impacts of crisis medicine and how the new norms established by law might help providers navigate the moral suffering endured during this crisis, followed by an exploration of how avoiding lawsuits can help prevent the retraumatization of HCW.

Trauma and Crisis Medicine

The toll on the mental health of workers and first responders involved in emergency and crisis response is well-established. Stellman and colleagues found that the frequency of psychological distress and psychopathology among first responders was greatly above that of the general population even years after the incident and was comparable to rates seen in veterans returning from the war in Afghanistan (Stellman et al., 2008). Similar issues were seen in first responders to the Uttarakhand flood in India (Jain 2013) and in search and rescue workers after the Bingol earthquake in Turkey in 2003 (Ozen & Sir, 2004). In fact, dozens of studies have been conducted which outline the potential mental health risk to those who responded to the September 11th attacks (Bills et al. 2008) and to Hurricane Katrina (Osofsky et al., 2011).

Although the nature of the crises mentioned above differ from what HCW face during the COVID-19 pandemic, research currently being produced on the toll the COVID-19 pandemic is having highlights the potential for similar impacts despite the differing nature of the crises. A rise in anxiety in the general population has been documented (Lima et al., 2020), as has a rise in depressive symptoms and sleep issues (Huang and Zhao, 2020). Very recent studies out of China indicated adverse mental health outcomes for HCW, including symptoms of depression, anxiety, insomnia and distress (Lai et al., 2020; Li et al., 2020; Huang et al., 2020). The distress caused by seeing widespread suffering alone should inspire us to protect HCW in whatever ways possible, but there is an additional type of psychological wounding—moral suffering[18]—that makes protecting this population in the ways described above even more important.

Moral suffering occurs in many forms, but two are especially important here: moral distress and moral injury. Moral distress is a type of moral suffering first identified in the nursing literature and refers to negative feelings caused by the inability to translate one's moral choices into action (Volbrecht, 2002). There are many possible reasons for the inability to act on one's sense of morality, from time pressures, institutional protocols, etc., but ultimately the frustration of one's ability to act on one's moral intuitions and reasoning is central to this phenomenon. McCarthy and Deady (2008) extend moral distress to the experience of needing to make difficult moral judgments in complex

[18] We are adopting the term used by Papzoglou and Chopko (2017) here. We recognize that there are important differences between moral injury and moral distress, but for the purposes of this paper, we are considering these phenomena related.

situations without appropriate support. Moral distress is obviously of great concern during the COVID-19 crisis. During this crisis, there are decisions being made every day because of the lack of PPE and the desire to conserve resources that likely go against many HCW' moral intuitions. More than this, given the uncertainty noted above, and that it is rare that healthcare systems find themselves clearly in crisis capacity (with obvious exceptions), shifting from making treatment decisions based on the best interest of the patient to considerations of public welfare might cause increased moral distress.

Moral injury is a slightly different, though related, concept developed from work with soldiers and veterans (Shay, 1994). Moral injury occurs when a person is confronted with a catastrophic situation in which that person perpetrates, fails to prevent, or witnesses' actions that run counter to deeply held moral beliefs (Litz et al., 2009). While moral distress might occur at any point, moral injury is a phenomenon experienced during moments of catastrophe. Again, it is clear that moral injury is a concern during this crisis, especially in areas where conventional and contingency capacity have been surpassed and genuine triage decisions are being made.

Scholars are already raising concerns about moral distress and moral injury impacting HCW during COVID-19. Mazanec (2020) explains that nurses witnessing the triaging of equipment to patients, dealing with limited medical supplies, and watching patients die without visitors to comfort them might experience moral distress. Angelos (2020) writes that surgeons will likely experience moral distress when asked to shift from doing what is in the best interest of individual patients to acting in the interest of public health. This is clearly seen with surgeons canceling elective surgeries and being mandated to stay at home unless they are called in to offer care. Also, similar concerns have been raised in palliative care (Domenico et al., 2020; Wallace et al., 2020) and oncology (Shuman and Campbell, 2020). Greenberg and colleagues believe that for some working on the front lines, recognizing that they did what they could for their patients with the limited resources they had, rather than their customary ability to do everything possible for patients, is the potential "seed" of moral injury (Greenberg et al. 2020).

One important function of the laws we propose is to provide "moral buffering" from this psychological wounding by offering formal and public recognition of the fact that in certain situations, there are no good choices. Like the doctrine of double effect, these laws give credence to reduced moral responsibility in times when the moral landscape means our best moral efforts will still have bad effects. As applied in situations of war, the doctrine of double effect allows for the fact that sometimes the pursuit of some greater moral good leads to bad consequences. We offer legal protections to those who do things in situations of war that would otherwise be considered illegal or at least morally intolerable. More to the point, the Feres Doctrine protects military doctors from being sued for medical malpractice in a triage zone. The laws we are proposing might offer HCW the same sort of mitigation, not only legally, but in terms of the way in which healthcare providers reason through their own moral culpability. The doctrine of double effect does not leave the moral actor perfectly comfortable, but it does give her space to reframe her actions as morally necessary, even if not morally good. We may

not be able to save HCW from the emotional guilt that they carry, but we can give them socially recognized absolution in the form of these laws, and thus impact HCW's moral reasoning about their own culpability in the situations they face.

The Perfect Storm: Medical Malpractice Stress Syndrome and Second Victim Syndrome

Even if the hope that the laws we propose might offer "moral buffering" is simply that— a hope—there are other ways in which the passage of these laws will prevent further harm befalling HCW. While some have argued that the common law legal standard is adaptable enough to provide legal protections if HCW are acting in good faith, these authors fail to address the potential harm that complaints against HCW, whether civil or criminal, cause to HCW, even when HCW are ultimately cleared of wrongdoing (*c.f.*, Annas, 2010; Koch et al., 2020). In addition to the well-documented emotional and moral burdens experienced by HCW during crises, there are two other forms of distress faced by HCW that bear exploring here: Second Victim Syndrome (SVS) and Medical Malpractice Stress Syndrome (MMSS).

SVS was a concept originally introduced by Albert Wu (2000). In an article for the *British Medical Journal*, Wu argued that although patients were obviously the primary victims of medical error, "physicians, pharmacists, and other members of the healthcare team," were potential secondary victims. He argues that the hardships faced by HCW, even when they themselves caused the medical error in question, need to be recognized and acknowledged. Significant literature has developed to explore the contours of SVS and medical error (*c.f.*, Denham 2007; Wu 2012; Scott and McCoig 2016). The repercussions of SVS are numerous. Cognitive effects, including inability to concentrate, are common (Seys et al., 2013). Additionally, feelings of depression, shame, guilt, and loss of confidence are possible (White and Gallagher 2011). Further, second victims are at a much higher risk for burn-out (Schwappach & Boluarte, 2009).

Although SVS was originally restricted to medical error, there have been attempts in the literature to include as possible triggers of SVS any adverse patient events that traumatize HCW, even if there is no medical error involved (Scott et al., 2009). Lander and colleagues argue that a healthcare provider can be the secondary victims of:

> anything that has happened anywhere in your practice (office, hospital, operating room, emergency room, etc.) that was not anticipated, should not have happened, and makes you say 'I don't want this to happen again.' It can be small or large, administrative or clinical—anything that you feel could be avoided in the future (Lander et al., 2006).

The nature of the COVID-19 crisis makes it such that there is much happening in hospitals, doctors' offices, public health districts, and ethics committee meetings across the country that would undoubtedly make HCW say, "I don't want this to happen again." More than this, there is likely recognition that if we were better prepared at national,

state, and local levels, some of what is occurring need not have occurred. Although scholars have been warning of a coming pandemic for years, the political will to prepare for this by adequately stocking our Strategic National Stockpile, by the timely invocation and use of the Defense Production Act, and by proactively upgrading electronic medical systems to help with communication between facilities during disasters like these has been lacking (*c.f.*, Miri & O'Neill, 2020; Kulish et al., 2020). HCW who are asked to make decisions that adversely affect patient outcomes that may have been avoided with proper preparedness are at risk of SVS.

If HCW face legal scrutiny for actions that were necessitated by our current crisis, then they will face more than the threat of SVS. Evidence exists that there are significant emotional and cognitive impacts to HCW who have complaints lodged against them and/or are sued for malpractice. Large scale studies have found that doctors with recent or current complaints filed against them had significant risks of moderate or severe depression, anxiety, and suicidal ideation (*e.g.*, Bourne et al., 2014; Balch et al., 2011). The impact of these incidents is so well-documented that a term has been coined—Medical Malpractice Stress Syndrome (MMSS). MMSS has been identified as a "*forme fruste*" of post-traumatic stress disorder (Patel et al. 2017). Those with MMSS experience depression and feelings of hopelessness (Reyes & Reyes, 2017). It is linked to increased anxiety that manifests as restlessness, exhaustion, difficulty concentrating, and/or insomnia (Sanbar & Firestone, 2007). There have even been cardiac events linked to MMSS (Maroon 2019). Many publications are dedicated to identifying ways to help HCW live through this syndrome (*c.f.*, Ryll, 2015; Iacob & Majer, 2012; Fileni et al., 2007). However, in times such as these, where HCW are asked to make choices well outside the traditional standard of care that might result in adverse impacts on those workers, the best way to help HCW is to prevent the conditions that trigger MMSS at all. The legal protections outlined above do just that.

Conclusion

Without adequate protection, HCW are bearing many risks in the COVID-19 healthcare crisis. Given what we know about the profound burdens experienced by those working in crisis situations, it is clear that we should do what is reasonable to mitigate their trauma. Despite arguments to the contrary, current laws do not offer adequate protections to physicians, let alone to those HCW working in non-physician capacities. One relatively simple way to protect HCW is with legislation that stops legal actions from being taken against them for doing what has been forced on them: moving from treatment shaped by what is in the best interest of individual patients to treatment shaped by the desire to do the most good for the greatest number of people. Such a shift is already an emotionally and psychologically difficult undertaking. HCW should not risk being further traumatized by laws that largely fail to recognize the impact of this shift.

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Autonomous Care Pathway to Patient Opioid Abstinence: Should All Programs Offer this Approach?

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ABSTRACT:

Introduction: The opioid epidemic resulted in vast increase in neonatal opioid withdrawal syndrome (NOWS). To mitigate NOWS and opioid dependency among women, staff established a gender specific, patient driven, autonomy based, outpatient therapeutic substitution program.

Methods: Prospective observational study of obstetric patients receiving prenatal care 7/1/2016-12/31/2019. Patients underwent universal urine drug screens to identify illicit drug use with dependency and offered addiction counseling with voluntary outpatient therapeutic substitution in an obstetrical-addictions combined clinic to achieve abstinence with oral Buprenorphine tapering protocol. Urine substance screening and cord blood testing were obtained at delivery. Birth outcomes compared among groups who achieved abstinence at birth, were successful at tapering, or continued opioid use.

Results: Of 783 births, 165 (20.9%) demonstrated opioid use with 91 (55.2%) participating at some point in pregnancy in therapeutic substitution program. At birth, 14/94 (14.9%) patients completed the program and achieved opioid abstinence, 22/94 (23.4%) still enrolled

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and actively tapering. 57/94 (34.5%) patients were lost to follow-up, relapsed, or terminated due to non-compliance. Seventy-four of 67 (44.3%) opioid positive mothers chose not to enroll. Of 14 women who completed the program, 0 babies born with NOWS, compared to 11/22 (50%) still enrolled in program and actively tapering, 29/57 (50.9%) lost to follow-up, relapsed, or terminated due to non-compliance, and 28/74 (37.8%) never enrolled in program.

***Conclusion/Implications*: Outpatient therapeutic substitution with oral Buprenorphine with abstinence is possible in pregnant patients and results zero NOWS. More data are needed to confirm findings and explore methods for enhanced success in obtaining abstinence.**

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***Keywords:* Pregnancy, substance abuse, therapeutic substitution**

The number of newborns treated for neonatal opioid withdrawal syndrome (NOWS), formerly known as the neonatal abstinence syndrome (NAS), has increased dramatically in West Virginia. In data collected from the Cabell Huntington Hospital in Huntington, WV, the number of neonates treated for NOWS increased from 25 in 2003 to 70 in 2007.[1] The mean cost difference in the care of an otherwise healthy neonate with NAS was compared to the cost of a normal full-term healthy neonate of $3,934 in the Cabell-Huntington cohort. Because of the added costs associated with the increased risk of prematurity and NOWS, the average cost of all infants with NOWS was over $36,000 compared to $2,000 for a NOWS-free neonate.[1] Therefore, pregnant patients present a unique opportunity to prevent NOWS and realize significant financial savings by decreasing the costs for neonatal care.

The previous data from CAMC presented by Hensel et al, 2012, found with universal urine screening for illicit substances in the CAMC obstetric and gynecologic residency clinic, that, 32% of pregnant patients were positive for illicit substances including 11% positive for multiple substances.[2]

The national substance abuse rates have been estimated to be between 2.8-19%.[3-5] These reported rates vary based upon the population screened and the method of screening used. In our own clinic experience, prior to universal urine drug screening using only a self-reported screening tool, zero of our patients reported any illicit substance usage. The lowest number reported is in the study by Ebrahim and Gfroerer utilizing a population survey of the entire United States[3] while the highest rates were reported (19%) by Azadi and Dildy utilizing urine toxicology testing.[5] Chasnoff et al developed a self-reporting screening tool that estimated that 15% of the population studied continued to use substances of abuse after becoming aware of the pregnancy.[4]

Neonatal opioid withdrawal syndrome may be present in 60-90% of neonates exposed in-utero to opioids with up to 70% of affected neonates exhibiting central nervous system irritability which may progress to seizures.[6] Up to 50% of exposed neonates may experience respiratory issues, feeding problems, severe diarrhea, inconsolability, and failure to thrive.[7] A randomized controlled study of 175 pregnant patients (89 Methadone/86 Buprenorphine) comparing Methadone to Buprenorphine by Jones et al, 2010 found that 41/75 (57%) of neonates had NOWS with Methadone and 27/58 (47%) of neonates had NOWS with Buprenorphine.[8] The Buprenorphine cohort had shorter hospital stays (10.0 days versus 17.5 days $P<0.0091$) and shorter days of treatment for NOWS (4.1 days versus 9.9 days, $P<0.003125$)[8] Treatment of NOWS represents a substantial hospital cost and significant effect on newborns with accepted treatment modalities.

Due to the morbidity to neonates and families with NOWS, we developed a voluntary program to prevent NOWS. Further, our patients expressed a desire to prevent NOWS in their neonates and to become opiate abstinent. Outpatient weaning from opiates had previously been considered impossible. The American College of Obstetricians and Gynecologists (ACOG) and Substance Abuse and Mental Health Services Administration (SAMHSA) both support medication assisted treatment (MAT) as the standard of care and discourage abstinence due to concerns about relapse.[9,10] Their positions rest on papers such as Terplin et al 2018 which reported that MAT should be the standard of care base on their review of the literature. However, Terplin's review consisted of patients primarily in inpatient settings, those who did not undergo fetal monitoring, patients with poorly defined counseling/adherence in the papers reviewed, and studies involving involuntary patient participation.[11] ACOG and SAMHSA simply did not engage the concerns regarding cognitive and behavioral impact, including NOWS, on neonates exposed to opioids.

Methods and Materials

Patient Autonomy

The American College of Obstetricians and Gynecologists strongly supports patient autonomy and informed consent as consistent with ethical care of patients.[12] The acceptance by ACOG of Jonsen's four principles-"four box" model of ethics (autonomy, beneficence, non-maleficence, and justice) displaces more traditional normative ethical theories.

The traditional historical ethical theories are generally divided into the Consequentialist Framework; The Duty Framework; and the Virtue Framework. The Consequentialist Framework focuses on the future effects of the possible courses of action, considering the people who will be directly or indirectly affected. It is then asked about what outcomes are desirable in a given situation, and consider ethical conduct to be whatever will achieve the best consequences (i.e. lying to protect Jews from Nazis). The Duty Framework focuses on the duties and obligations that exist in a given situation, and consider what ethical obligations are inherent and what things should

never be done (i.e. murdering someone). Ethical conduct is defined by doing one's duties and doing the right thing, and the goal is performing the correct action. The Virtue Framework focuses on person rather than action based: it looks at the virtue or moral character of the person carrying out an action, rather than at ethical duties and rules, or the consequences of particular actions (i.e. the practice of honesty on all dealings). A good person is someone who lives virtuously—who possesses and lives the virtues. The ignoring by ACOG of alternative ethical theories presupposes that they speak as the only authoritative voice when dealing with complex clinical issues such as substance abuse disorder (SUD) in pregnancy.

We utilized both Jonsen's four box model of autonomy/beneficence and Duty Framework Ethics to develop our treatment program. In support of respecting patient autonomy with regard to treatment options, we developed a voluntary outpatient Office-Based Medication Assisted Treatment Program (OBMAT) to secure patient abstinence. The instigation of such an OBMAT program aligns with ACOG Committee Opinion #390 regarding patient autonomy as an important cornerstone of ethical care of our patients.[12] Without any "choice" for a patient, there can be no autonomy since autonomy presupposes a choice between options. If there is no option present except MAT without abstinence, there is no exercise of autonomy. This would violate ACOG's ethical positon in Committee Opinion #390 regarding patient autonomy. Therefore, our program sought to prevent NOWS by honoring patient autonomy. We sought to use a gender specific, voluntary patient-centered, autonomous therapeutic substitution OBMAT program to achieve patient abstinence, thereby avoiding the neonatal hospitalizations, and costs associated with the use of Methadone and Buprenorphine maintenance therapy without abstinence. With regard to beneficence, we sought to contribute to both the welfare of the patient and her fetus by preventing NOWS and rendering the patient abstinent. The Duty Framework allowed our program to focus on our goal of performing the right action: preventing NOWS and achieving patient abstinence while honoring patient autonomy.

The purpose of our study was to evaluate the impact of gender specific care with patient respecting autonomy on the voluntary enrollment in a program designed to utilize therapeutic substitution to achieve maternal abstinence and thereby avoid NOWS.

Enrollment

All obstetric patients screened in our clinic were offered an opportunity to enroll in our abstinence-based program. Those who declined continued in their present programs, or were referred to other maintenance programs.

All patients received the same obstetrical care regardless of their choice of substance program. Patients who elected to enroll in our voluntary therapeutic substitution program from 1 July 2016-31 December 2019 in the CAMC resident obstetrics clinic, participated in an intensive multidisciplinary approach to prenatal care. Our plan of care included: weekly and random urine drug screening, a double board certified-addictions medicine/maternal-fetal medicine physician, a certified substance abuse counselor, ob-

stetrical staff/resident physicians, trained nursing personnel, and a nursing educator. Key in the management of all of our obstetrical patients' care was routine screening of patients' initial urine for illicit and non-prescribed substances. All patients who tested positive for non-prescribed (including tobacco and marijuana), or illicit substances, were counseled for voluntary enrollment in our abstinence-based addictions program including our contingency management program for substance abuse staffed by a certified addictions specialist. Weekly combined obstetric and addiction visits to the high-risk obstetrical clinic were included throughout the pregnancy and thereafter as dictated by the patient's obstetric and recovery needs. Patients had weekly group therapy alongside other women with substance use disorder, as well as monthly individual therapy addressing the entirety of the patient's psychosocial well-being. Obstetric management for all patients, whether in our program or not, included thorough fetal anatomic surveys, as well as fetal echocardiograms, antenatal testing, serial growth ultrasounds, and fetal umbilical artery Doppler studies, all as clinically indicated. Delivery was generally performed at 39 weeks gestation, or, as clinically indicated for obstetrical reasons.

Testing of patients' urine weekly during the program and with random drug screens for illicit substances continued throughout their obstetrical care. Patients who took opiates, and were at risk for acute opiate withdrawal, received therapeutic substitution with Buprenorphine medication to obtain abstinence. Careful attention to the use of other illicit medications paralleled the substitution of Buprenorphine for illicit opioids. Significant interactions with other medications, including patient mortality, occur with buprenorphine with concurrent abuse/use of benzodiazepines, other opioids, SSRIs, Benadryl, cocaine, and methamphetamine. Patients with persistent use of these medications and/or elicit medications would be removed from the program. Patients failing to adhere to the OBMAT program guidelines were referred to other programs for addiction care but received ongoing obstetrical care in our clinic. Further, patients who tested positive for illicit substances, who provided care for minor children, and, were deemed to be a danger to their children, underwent state directed mandatory reporting to child protective services to prevent child endangerment.

The program utilized outpatient therapeutic substitution with decreasing dosages of Buprenorphine with weekly group meetings which focused on improving coping skills and increasing distress tolerance. (See Table 1). Patients' urines were screened weekly and confirmed with mass spectrometry testing to ensure compliance with care. Detailed tapering schedules were individualized based on patients' gestational age and opiate requirements. None of our patients underwent any form of acute "detoxification" from their opioid medications. Rather, patients' dosages were slowly adjusted by decreasing by 2 mg of Buprenorphine over several weeks (usually 3 weeks at a given dose) until they were abstinent at least 1 week prior to delivery. (See Attachment 1). We chose at least one week prior to the anticipated delivery date due to the long half-life of Buprenorphine of approximately 96 hours.

The therapy component of the program consists of both psycho-educational and cognitive-behavioral therapy. Patients were educated on the disease concept of

Table 1: Prenatal Positive Substance Screens (n=783)

	n (%)
Substance Screen Positive*	557 (71.1)
Cotinine	415 (53.0)
Marijuana	326 (41.6)
Buprenorphine	131 (16.7)
Norbuprenorphine	113 (14.4)
Amphetamine	95 (12.1)
Methamphetamine	95 (12.1)
Oxycodone	16 (2.0)
Oxymorphone	19 (2.4)
Methadone	8 (1.0)
Morphine	38 (4.8)
Cocaine	16 (2.0)
Benzodiazepines	66 (8.4)
Ecstasy	0
Barbiturates	0
Phencyclidine	0
Multiple Substances *	351 (44.8)

*These calculations do not include tobacco use

addiction, the recovery process, relapse prevention, and the effects of drugs on the baby. A contingency management program, an evidence based practice with roots in Motivational Interviewing, was utilized to keep patients engaged in their abstinence process. Contingency management therapies are a type of psychosocial intervention where clients receive rewards in the form of vouchers or prizes if they demonstrate changed behaviors. Data supports contingency management therapy in cocaine and opioid abuse.[13-16] It has also been shown to be effective in the vulnerable populations of co-occurring psychological disorders and in pregnant women.

Analysis of the delivery outcomes in patients screening positive for substance abuse in pregnancy was performed. The study was approved by the joint Charleston Area Medical Center-West Virginia University IRB.

Results

During the study time period, there were 783 births at our tertiary care medical center from mothers receiving prenatal care in our affiliated resident service clinic. The majority of these neonates (557; 71.2%) were exposed in utero to substances including, illicit drugs, alcohol, marijuana, and tobacco, and were assessed via universal substance screening throughout prenatal visits. Table 1 summarizes the percent of specific substance exposures, with very high rates of cotinine (tobacco) 52.6% and marijuana 41.4%.

Study groups were divided into four arms. The first group included those who successfully completed the program and were opioid abstinent at the time of childbirth (1). The second group included those who were enrolled in the program and compliant but were still tapering (2). The third group included patients who chose to voluntarily withdraw from the program, were terminated due to continued noncompliance (use of known dangerous substances listed above with buprenorphine), transferred to another program, or who completed tapering successfully and then continued to use opiates illicitly (3). The fourth group consisted of those patients who did not elect to participate in therapeutic substitution. (4). Women who did not test positive for opiates in prenatal care were not included in the study groups.

The number of neonates exposed to opioids during prenatal visits was 167/783 (21.3%), of these mothers of 94/167 (56.3%) neonates voluntarily participated in the therapeutic substitution program at some point in gestation. At time of birth, 14/94 (14.9%) neonates had mothers who completed the program and achieved opioid abstinence at the time of birth, 22/94 (23.4%) were still enrolled and actively tapering. Mothers of 57/94 (34.5%) neonates were either lost to follow-up, relapse, or termination due to non-compliance. Finally, of the 167 opioid positive mothers, 74/167 (44.3%) chose not to enroll in the program.

Of the 783 births, a total of 71 (9.1%) babies were born with NOWS. The majority of mothers were White, with a rate of over 10% having babies with NOWS, compared with 3.1% for Blacks/African Americans, $p=0.027$. Most mothers with NOWS affected neonates were multiparous and this rate was statistically significant at 76.1%, $p<0.001$. Associated tobacco use was statistically more likely in mothers with NOWS affected neonates at a high rate of 80.3%, as compared with 49.7% tobacco use in mothers of NOWS free babies, $p<0.001$. Conversely, marijuana use rates were higher among mothers with babies without NOWS, 42.3% versus 28.2% for those with NOWS, $p=0.014$. Other maternal characteristic comparisons are detailed in Table 2.

Of the 14 women who successfully completed the program, 0 babies were born with NOWS demonstrating the ability to successfully to achieve outpatient abstinence at patient's request and prevent NOWS. These findings of zero neonates born with NOWS validated the autonomous decisions of the patients to voluntarily enter the OBMAT program to achieve abstinence. Of those who did not achieve abstinence, 11/22 (50%) were still enrolled in the program and actively working toward tapering, 29/57 (50.9%) were either lost to follow-up, relapsed, or terminated due to non-compliance, and 28/74 (37.8%) were never enrolled in the program (see Figure 1). There is a statistically significant difference when comparing program status with rates of NOWS ($p=0.004$).

The goal of the program was to achieve opioid abstinence at birth per patients' request to avoid NOWS and validate patient autonomy. To measure the success of the program, a comparison was made between all four groups and the rate of negative illicit opiate drug screens at birth (see Figure 2). This excluded Buprenorphine prescribed as part of a Medication-Assisted Treatment program. This was a statistically significant comparison with regard to opioid positive testing in labor [$p<0.001$], with 1/14 (7.1%)

Table 2: Maternal Characteristics of Newborns and NOWS Status (n=783)

	No NOWS (n=712)	NOWS (n=71)	p value
	n (%)	n (%)	
Race/Ethnicity			0.027
White	581 (89.7)	67 (10.3)	
African American	124 (96.9)	4 (3.1)	
Asian American	5 (100.0)	0 (0.0%)	
Latino American	1 (100.0)	0 (0.0%	
Parity			<0.001
Nulliparous	206 (28.9)	17 (23.9)	
Multiparous	506 (71.1)	54 (76.1)	
Diabetes	58 (8.1)	1 (1.4)	1.00
Psychiatric Disorders	158 (22.2)	18 (25.4)	0.552
Cotinine	354 (49.7)	57 (80.3)	<0.001
Marijuana Use	301 (42.3)	20 (28.2)	0.023

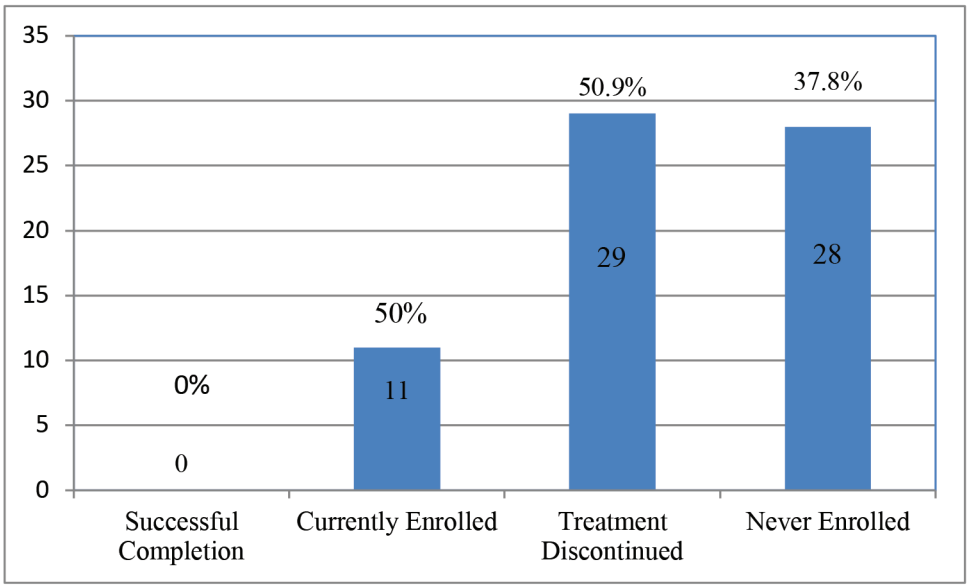

Figure 1: Neonates Free of NOWS by Program Status at Time of Delivery (p=0.004)

of mothers testing positive who completed the program, 2/22, (9%) testing positive of tapering mothers, 33/57, (57.9%) testing positive of terminated/transfer/lost to follow

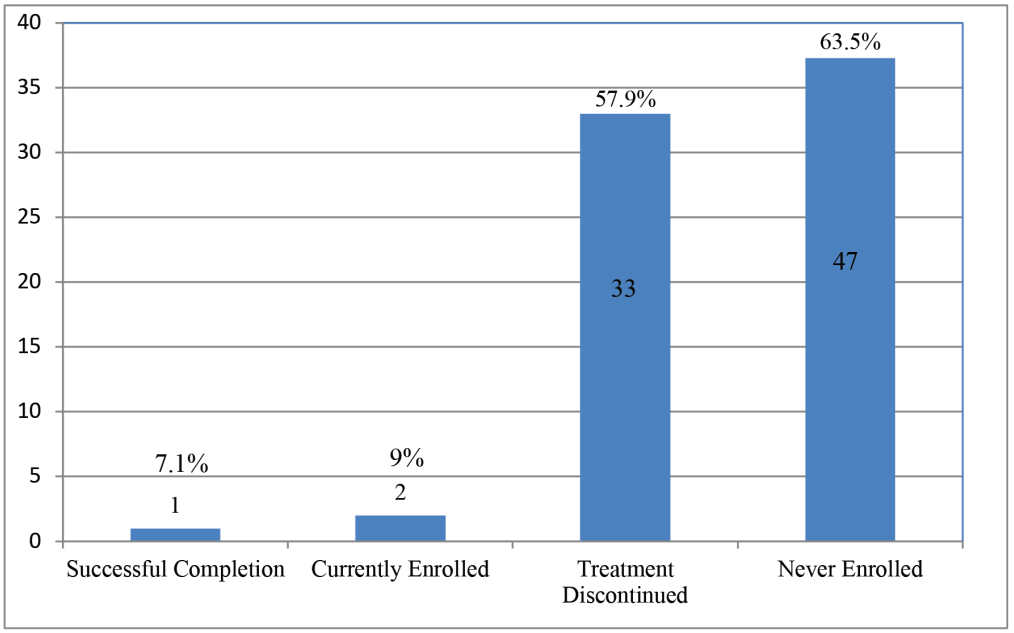

Figure 2: Positive Illicit Opioid Drug Screens at Birth by Program Status ($p<0.001$)

up, and 47/74, 63.5% of non-program mothers testing positive for illicit opiates at the time of delivery. Of note, the one mother who tested positive for illicit opiate use from the successful opioid treatment completion group (1/14), received morphine in labor for pain control, and therefore, tested positive due to opioid medication used for pain therapy during labor.

There were 3 neonates with NOWS born to women who tested negative at prenatal care and were therefore not eligible for enrollment in our OBMAT program. Women with negative opioid drug testing both during prenatal care and at birth had 0 births with NOWS. Conversely, women using substances throughout gestation with positive opioid drug tests both during prenatal care and at birth had the highest number 51/218 (23.4%) of babies with NOWS. Women who tested negative prenatally and then positive at birth had a 13.3% (4/30) NOWS rate. This is in comparison to women who tested positive prenatally and negative at time of birth with a 4.7% (16/344) NOWS rate, thus demonstrating the importance of abstinence at time of delivery. (See Table 3) No adverse outcomes were noted in any patients or neonates who entered and/or completed our program. If you take a rate of NOWS at 50% with opiate use then there would have been 7 neonates in the completed abstinence program group that should have had NOWS without therapeutic substitution. With the actual number at 0, this program prevented 7 additional babies with NOWS. Cost savings for the 7 neonates born abstinent is estimated at over $200,000 in hospital costs alone.[1] Detailed cost analysis for our program was not available but is an area to consider for further investigation.

Table 3: NOWS by Prenatal and Birth Test Results (Neg or Pos)

	Neg UDS at Initial Appointment & Neg UDS at Birth (n=197)	Pos UDS at Initial Appointment & Pos UDS at Birth (n=218)	Pos UDS at Initial Appointment & Neg UDS at Birth (n=344)	Neg UDS at Initial Appointment & Pos UDS at Birth (n=30)
	n (%)	n (%)	n (%)	n (%)
Instances of NOWS	0 (0.0)	51 (23.4)	16 (4.7)	4 (13.3)

There were no statistically significant differences in Neonatal Intensive Care Unit (NICU) admission, Pre-term birth (PTB) defined as birth before 37 weeks gestation, Intrauterine Growth Restriction (IUGR), Low Birth Weight (LBW) defined as <2500 gm, Pre-eclampsia, and Respiratory Distress Syndrome (RDS).

Discussion

In our obstetric population, we found a surprising 557; 71.2% of our patients with illicit or non-prescribed substances (including tobacco) in their urine at initial prenatal visit with utilization of universal screening. This is in contrast to the use of illicit or non-prescribed substances reported in previous studies in the general population of 3-19 %.[3-5] It is believed that our increased rates of substance use are partly explained by universal screening (including for marijuana) compared with the use of questionnaires in many studies. Using our novel approach of patient-requested, autonomous oral therapeutic substitution with Buprenorphine and contingency management in conjunction with a certified addictions counseling, we had 14 births to mothers who successfully completed the program and 0 of the neonates had NOWS. This low rate of abstinence (15%) among our program patients reflects the challenges faced with substance abuse disorder and other chronic illnesses. For example, only 20% of individuals who engaged in weight loss maintain their weight over time.[17] Chronic hypertension presents another example. A study by Vrijens et al 2008 using database information from Belgium found that 50% of patients stopped their antihypertensive by one year and that of patients who were taking medications, at least 10% were omitting single or multiple doses.[18] Diabetes care compliance appears similar to substance abuse with Koro et al 2013 finding only 11-18% of patients in their study maintaining their diabetes medication usage.[19]

Our success mirrors the previous experience of Luty, et al 2003 which studied 101 opiate dependent women who underwent a 21-day Methadone inpatient withdrawal with no adverse effects found.[20] However, only ten of the patients in Luty's sample were completely weaned off Methadone and only 1 was drug free at delivery.

Our data also replicates Stewart et al, 2013 who utilized a slow Methadone inpatient taper for pregnant inpatients without any associated morbidity or mortality.[13] Their group found that 53/96 (56%) of patients could successfully be detoxified as inpatients.

Finally, Bell et al, 2016 published on 301 pregnant patients who were fully detoxified using Buprenorphine in both inpatient and outpatient settings with no adverse maternal or neonatal outcomes.[21]

Our data is in contrast to a recent systematic review by Terplan et al 2018, which purported that "detoxification" as a treatment recommendation in pregnancy was not supported by their review.[11] Their review consisted of patients primarily in inpatient settings, who did not undergo fetal monitoring, poorly defined counseling/adherence in the papers reviewed, and some studies involved involuntary patient participation.[11] In contrast, our patients voluntarily participate in gender-specific, outpatient, autonomous therapeutic substitution with adjustment of medication to achieve abstinence, undergo weekly group addictions counseling sessions, at least monthly individual counseling, and participate in weekly and random urine drug screening. They also participate in weekly high-risk obstetrical prenatal visits and receive comprehensive prenatal diagnostic ultrasounds for anatomy/fetal echocardiograms, undergo serial growth ultrasounds, antepartum assessment by non-stress testing/AFIs/BPPs, and umbilical artery Doppler studies, all as indicated. Our patients are screened at delivery for substances, and neonates are screened at delivery. Further, all neonates were evaluated for NOWS by our neonatologists using the Finnegan scoring system.[22]

Radiologic and Behavioral Findings

MRI studies of postmortem and quantitative brain studies found smaller brains and decreased volumes including the cerebral cortex, amygdala, accumbens area, putamen, pallidum, brainstem, and cerebellum in neonates born to mothers exposed to heroin.[23] Sirnes et al 2017 compare volumes in 16 opioid exposed children ages 10-14 years to controls and found smaller brain volumes in the basal ganglia, thalamus, and cerebellar white matter.[24] Yuan et al echoed these findings documenting smaller whole brain and basal ganglia volumes compared to controls.[25] Monnelly et al 2017 compared 20 methadone exposed neonates to 20 non-exposed neonates via diffusion tensor imaging and found differences in white matter microstructure in the superior longitudinal fasiculus responsible for connecting the frontal, occipital, temporal and parietal lobes of the brain.[26] Altogether, this data validates serious concerns regarding fetal opioid exposure in utero (including buprenorphine) with regard to brain growth in utero and subsequent neurodevelopment after exposure. These concerns for adverse neurological outcomes appear inadequately addressed in the ACOG and SAMSHA position statements and care guidelines for MAT in pregnancy.

One study regarding mental development of 72 neonates (without other prenatal risk factors) found IQ differences at 1, 2, 3, 4.5 and 8.5 years of age.[27] Boys had lower IQ scores than girls. Cognitive functioning remained lower in all children exposed to opioids compared to controls even after accounting for socioeconomic status, adoption, foster care placement, gestational age at delivery, and birth weight.[27] Children diagnosed with NOWS after delivery exhibited twice the likelihood of conduct disorders; including attention-deficit/hyperactivity, adjustment, and intellectual disabilities.[28] These children

were also 1.5 times more likely to be diagnosed with developmental delays, anxiety, emotional disturbances, and autistic disorders compared to controls.[28] Buprenorphine, however, appears to be associated with a decreased risk of low birth weight and smaller head circumference, but, with more preterm births compared to methadone.[29] The effects of buprenorphine on both fetal brain development and behavior are not well studied.

ACOG and SAMSHA also appear to ignore the literature documenting increased risk of congenital heart defects, hydrocephalus, and neural tube defects in prenatal opioid exposure.[30]

Concerns for achieving abstinence appear unwarranted. A study by Luty, et al 2003 with 101 opiate dependent women tapered 21 pregnant patients off opiates without ill effects.[20] More recently Bell et al, 2016 reported more than 600 patients detoxified from opiates during pregnancy with no report of fetal harm related to the process.[21] We sought to build upon this literature with the development of our voluntary gender specific autonomy based program.

Most striking in our study was the financial analysis, which revealed over $200,000 estimated savings for the NICU hospital stays in our hospital associated with the 14 drug-free neonates based on the previous NICU cost data for neonates who did not require any withdrawal therapy or care for neonatal abstinence.[31] This does not include the substantial cost savings and decrease in morbidity associated with a neonate born drug free.

Comorbidities with multiple psychiatric disorders in patients with substance use disorder must also be considered. Many patients with substance use disorder have affective disorders including: depression, mania, schizoaffective disorders, schizophrenia, borderline personality, and bipolar disorders. Therefore, many authors suggest that detoxification must be linked with a combination of behavioral therapy with contingency management therapy with certified addictions counseling as in our patients.[23-26] Our behavioral therapy relies on counseling with certified addictions counselors, to assist patients in remaining drug and alcohol free.

Due to the large number of patients affected in the state of West Virginia and in our population at CAMC by substance abuse, we followed a patient centered, autonomous, programmatic, multidisciplinary approach with the use of outpatient abstinence therapy and therapeutic substitution with Buprenorphine when necessary. Inpatient therapy and stabilization was used when indicated in select patients. Therefore, in distinction to ACOG's recommendations,[9] and the findings of Terplan et al,[11] we demonstrate that gender-specific, patient centered outpatient treatment for opioid addiction should be considered in spite of the low completion rates and uncertain relapse rates. Further, since patient autonomy remains a cornerstone of women's healthcare today, patients ought to at least be offered an opportunity to deliver their infant completely drug-free and abstinent without NOWS.

Limitations to our study include low total enrollment rate of 56.3% (94), a relatively high dropout rate 34.5%, and a significant number of patients (16) transferring to other opioid maintenance programs for which we did not have any information on program compliance. We have not been able to demonstrate longer-term follow up post-partum, which is a limitation in assessing the long-term effectiveness of the program. Strengths include that despite low enrollment, over 10% (14.9%) of patients achieved complete abstinence, and hence, a decreased NOWS rate. Additionally, patients who did not comply with weekly drug testing were dismissed from the program with referral to outside programs, allowing the capture of more accurate drug usage data. Despite losing patients to failed compliance or transfer to other programs, many of the patients delivered at our hospital, thus allowing us to capture their birth outcomes and drug testing upon delivery. We also do not have detailed information regarding patient decisions process for enrollment other than to achieve abstinence. The participation in our program could be a surrogate for difficulty with other programs, desire to avoid child protective services, obviate possible legal actions/incarceration, and desires to please providers.

Patient requested-autonomous gender-specific outpatient therapeutic opioid substitution to obtain abstinence appears to be a reasonable and achievable approach alongside treatment of the psychological co-morbidities associated with substance use disorder. Multidisciplinary clinics with a single location for services would appear the ideal solution with the combination of excellent onsite medical care, antepartum fetal diagnostic services, antepartum fetal assessment, board certified addictions physicians/counselors, psychiatric support, and social support necessary to deliver drug-free mothers with healthy drug-free neonates. Increased compliance with outpatient programs may be enhanced by patients and families participating in long-term residential recovery programs, designed for restoration from addiction while undergoing therapeutic substitution.

Gender-specific treatment and public health-oriented approaches emphasizing, that, in spite of the chronic nature of addiction, women should be offered an opportunity at abstinence to prevent NOWS. In spite of the uncertain relapse rates associated with abstinence attempts, the dialogue involving opioid use disorder in women ought to be modified to elucidate that effective treatment for abstinence should be offered to prevent NOWS along with efforts to enhance comprehensive women-centered treatment availability and accessibility to improve maternal and neonatal outcomes within the perinatal period.

Finally, obvious significant financial savings (over $200,000 in NICU costs alone) may be realized from this programmatic approach to abstinence therapy, as well as providing an autonomy affirming choice to our pregnant patients. Such large savings may be actualized to enhance services with case management and increased support services for pregnant women with substance use disorder.

Further study is needed to evaluate if such outpatient programs help prevent relapse in patients postpartum.

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Attachment 1 Suggested Guidelines for Opioid Therapeutic Substitution*

1) Background
   a) 10-14% of women use illicit drugs in pregnancy.
   b) Neonatal abstinence syndrome (NAS) increases average cost of delivery from $2,000 to over $36,000 (18 times).
   c) 2009 Anonymous cord study at 8 hospitals found 115/759 (15%) positive for substances.[1]
2) Treatment
   a) Previous literature from 1970's and up to early 1990's suggested avoidance of detoxification.
   b) Recent literature does not substantiate these claims.
   c) Study by Luty, et al 2003 with 101 opiate dependent women, of which 21 underwent acute withdrawal without ill effects on pregnancy.[2]
   d) Our program also does not acutely withdraw patients, but rather offers slow therapeutic substitution which is not associated with acute withdrawal symptoms.
3) CAMC Women's & Children's Outline for Therapy
   a) Universal urine drug screening (UDS) with confirmatory testing for all new obstetrical patients.
   b) All patients testing positive for illicit substances are seen in high risk clinic. THC has a quantitative analysis.
   c) All patients with positive tests are offered a visit with our addictions counselor for evaluation for therapeutic substitution program and need for group therapy. If THC positive patient has a level < 150 ng/mL, they are placed in a routine clinic and re-screened with urine screens periodically.
   d) All other positive testing results are offered referral to our addictions counselor for for group sessions/therapy with our addictions counselor. Therapy sessions follow a DBT model and 12 step philosophy and incentives are given to patients to encourage and reward participation.
4) Therapeutic Substitution
   a) If patients are opiate dependent, found by our addictions counselor to be eligible for outpatient opiate therapy and request therapeutic substitution, they are offered therapeutic substitution with decreasing Buprenorphine (Subutex) dosing until abstinent.
   b) Patients on Methadone must be decreased to 30 mg or lower of Methadone and be off Methadone for approximately 36- 48 hours prior to attempting opiate therapeutic substitution due to significant adverse drug interactions.
   c) Patients on short-acting opiates may be started immediately on Buprenorphine (Subutex).

d) Patients on heroin generally need to be abstinent from heroin for approximately 12-24 hours prior to initiation of treatment due to interactions with Buprenorphine (Subutex).
e) The therapeutic protocol treatment dosage is gauged by amount of opiate the patients have been self-reporting for their use.
f) Patients generally start between 8-16 mg of Buprenorphine daily. We generally start at 8 mg as the induction dose and asses the patient's symptomatology.
g) After induction and stabilization, Buprenorphine (Subutex) dose is then decreased in 2 mg increments until patients are abstinent from Buprenorphine (Subutex).
h) Dose reduction is initiated no more than weekly, with timing individualized to the patient's motivation and time remaining until expected delivery.
i) We attempt to have patients weaned off Buprenorphine approximately 1 week prior to their estimated delivery date due to the long half-life of Buprenorphine of approximately 96 hours.
j) Patients are screened every week with stat UDS and random UDS done at the discretion of providers. Positive screens for illicit substances are sent for confirmatory testing with mass spectrometry. Positive testing triggers an intervention with the patient and potential for termination from program with referral to a maintenance based Buprenorphine program.
k) Every patient must attend weekly group addiction therapy sessions and at least one individual therapy session a month. Medications are dispensed only after attending group sessions.

5) Special Considerations
   a) Higher doses of opiates may necessitate starting at 16 mg of Buprenorphine (Subutex) per day.
   b) Patients must not be taking ***ANY*** other opiates, benzodiazepines, or other illicit drugs at induction of the Buprenorphine due to the severe interactions.

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The Reform of the Newborn Screening Policy: Spinal Muscular Atrophy

Blanka Bartos, Dr. Jur., LLM*

ABSTRACT: One in every 10,000 children is born with SMA and half of them will not even live two years. It is a hereditary genetic disorder, where the muscles die. If it is discovered just after birth, newborns can get the newest medicines to maintain their health. Unlike some other common genetic diseases (e.g. Down-Syndrome), SMA can be screened prior to pregnancy to determine whether the parents are carriers. In Hungary, people have urged reform, due to the baby Zente case, whose story has reached millions. Australia and Germany have also discovered the need for screenings. However, the US has already introduced newborn screening for SMA, far ahead of European countries. National policies should adhere to the same path to contribute to appropriate family planning and to make the treatment available as soon as needed to provide a longer and better life for sick infants.

Keywords: **newborn screening, SMA, family planning, national health policy, human rights**

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Introduction

Newborn screening has been available since the 1960s and has saved lives.[1] Countries have continuously expanded the range of screened diseases prior to a baby's birth including Spinal Muscular Atrophy or SMA. We could be optimistic and patient as health care policy and regulations constantly change in parallel with innovation, however, some countries need to take the first steps, which will motivate others. The USA and Australia have already changed their legislation to dedicate financial resources, technology, and administrative systems for this goal, and now, it is Europe's turn to follow this strategy.

About SMA

Spinal muscular atrophy is caused by a mutation or an absence of the survival motor neuron gene (SMN1). Normally, it produces a protein for the function of the nerves, which control the muscles. Without SMN1, the muscles become weak and eventually die. The disease becomes life-threatening when the basic life support organs (lungs, heart, the digestive system) shut down, nevertheless, the illness does not affect the ability to think, and the patient's mental health remains intact.[2]

We can distinguish SMA 1, 2, 3, 4, based on the age of onset and severity. SMA 1 is the most severe and common type, affecting ca. 60% of SMA patients. It has nine further sub-groups, patients with SMA 1/1 need intensive care to stay alive. The symptoms of SMA 1 appear before the age of six months and without appropriate treatment, the majority of these babies cannot celebrate their second birthday. In contrast to this, the signs of SMA 2 appear between the age of six months - two years and children can reach adulthood, but they will never walk without treatment. SMA 3 is diagnosed from the age of 18 months until the tail end of the teenage years. These children can walk initially, but they lose this ability as they get older. The rarest SMA 4 begins in adulthood. It can appear anywhere from the age of 18 up until 35. There are further mutations of the SMN1 gene which are common in all forms.

SMA can affect any race or gender. It is the number one genetic cause of death among infants in the USA. This illness affects 1 in 11,000 births, and about 1 in every 50 Americans is a genetic carrier. With a DNA test, people can find out whether they are a carrier. If they are thinking about starting a family and both of the partners are carriers, they have a 25% chance that their baby will have SMA. They have several options including no prenatal testing, prenatal testing, adoption, and pre-implantation genetic diagnosis (PGD[3]).

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[2] About SMA, Cure SMA https://www.curesma.org/about-sma/

[3] PGD screens embryos for genetic disorders and selects the unaffected embryos for implantation.

Zente Baby

It would be hard to find a person in Hungary who has not heard about Zente, a little boy, who suffered from SMA 1 (I/9) syndrome. In September 2019, the family needed to raise 2.1 million US dollars before the end of the year to buy the newest medicine, Zolgensma.[4] Fortunately, they succeeded in a matter of days. Hungarians donated a sufficient amount of money to order this American drug.[5] Zente was one of the first infants given the drug in Europe and the first one in Hungary.[6] Thanks to this campaign, people received further information regarding SMA disease and became more attentive to infants with this deadly condition.

Zente was born on February 28, 2018, weighing 3470g and measuring 47cm, just like a normal, healthy baby.[7] The delivery happened quickly and safely, the baby got a 9-10 Apgar score[8] (out of 10). Nevertheless, when the family arrived home, problems began to appear. Bowel movements were very difficult and the infant was not able to raise his head. Physiotherapy had positive results, but at the age of 4-5 months, his development plattoed and he was unable to turn onto his stomach. Although the physiotherapist recommended patience, the parents wanted to consult a specialist.[9] The neurologist performed a blood test on Zente, which, unfortunately, came back positive for SMA. The baby boy was fortunate because his genetic illness was revealed at an early stage, but it would not have happened if his mother, Krisztina Tóth, had been more "patient"—as was recommended. Neither the weekly visits by the midwife nor the medical examinations by the pediatrician were enough to recognize the possibility of a genetic disorder. Thanks to his mother's vigilance and consulting a physiotherapy specialist, Zente was diagnosed in time and received the proper treatments.

Nevertheless, the mother does not believe that this is the fault of the doctors, rather the fault of the system. Other mothers with SMA-positive children continue to urge reform by offering a blood test just after birth in order to receive an early diagnosis. The earlier the diagnosis, the greater chances there are to reduce the symptoms of this disease. In addition, there is also more time to collect the money for Zolgensma[10] or to

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[4] Génterápia—a 21. század gyógymódja, Gyógyszertechnológia.hu https://gyogyszertechnologia.hu/genterapia-a-21-szazad-gyogymodja/?fbclid=IwAR2bIBdbzhJzhDp4VJ8iNY4WOkY5VVOZt2WzwyitAtzkouHMIAHcKv8E-M9I

[5] A kétéves kisfiú, aki kis idöre jó hellyé varázsolta Magyarországot, hvg.hu, https://m.hvg.hu/itthon/20191231_A_keteves_aki_egy_kis_idore_jo_hellye_varazsolta_Magyarorszagot?fbclid=IwAR1tca7ANvC52oAva9tlqz15EpU2WV_3_DuS3t_4jRcmcV172QzX3TAoik4

[6] Mínusz 60 fokra lehütve érkezett Zente forradalmi gyógyszere, ö a negyedik európai, aki megkapta, hvg.hu https://hvg.hu/elet/20191029_zente_zolgensma_infzi_bethesda

[7] Zente SMA 1 Tiny Hero . Stronger than SMA, Personal blog, Facebook https://www.facebook.com/Zente-SMA-1-Tiny-Hero-Stronger-than-SMA-350892568989729

[8] Apgar score, MedlinePlus https://medlineplus.gov/ency/article/003402.htm

[9] Dévény, Anna http://www.deveny.hu/

[10] Zolgensma https://www.zolgensma.com/

apply for Spinraza[11] through the government. Although it is not possible to cure SMA, the symptoms can be reduced up to 90% with medication, thus the patient can have a full, long life.[12]

This family has already made a major appeal to the Hungarian state. The Parliament has voted for providing the drug Spinraza to every SMA child under 18 without exception.[13] At that time, Spinraza was the most modern registered medication in the EU[14] (since May 2020, it is Zolgensma[15]). At this time, 54 Hungarian patients may receive this treatment for free, instead of paying approximately 566,000 US dollars out of pocket. Before this decision, only those whose condition was justified received it. The others would have to pay this amount by themselves, however, none of them had sufficient funds to do that.[16] One month after Zente received Zolgensma, the Parliament changed the budget to include Spinraza.[17] If such a short time was enough to increase the budget of this cure, perhaps, the country could devote more sources to the prevention. In the USA, France,[18] and Australia, Spinraza is covered conditionally by health insurance, and unconditionally in Germany.[19] Therefore, we may conclude that Hungary is on a right track for taking better care of SMA patients.

Newborn Screening

In this case, if the parents wish to know prior to birth whether their future child has SMA, they can ask for either a blood test before pregnancy or a prenatal screening after conception.[20] Usually, they have these possibilities when both of the parents know that they are SMA carriers or they have a carrier or case in the family. If they do not have this information, generally, they need to wait until the first symptoms appear to

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[11] Spinraza https://www.spinraza.com/

[12] Danó, Anna: Nem csak a pénzen múlik Zente kezelése, Népszava, https://nepszava.hu/3051959_nem-csak-a-penzen-mulik-zente-kezelese

[13] Minden 18 év alatti gyermek részesülhet Magyarországon a Spinraza kezelésben, Euronews https://hu.euronews.com/2019/11/29/minden-18-ev-alatti-sma-s-beteg-reszesulhet-magyarorszagon-a-spinraza-kezelesben

[14] Ibid.

[15] Zolgensma, EMA , https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma

[16] A Magyarország 2019. évi központi költségvetéséről szóló 2018. évi L. törvénynek az SMA-betegség gyógyítására kifejlesztett gyógyszer támogatásához szükséges módosításáról szóló T/4668. számú törvényjavaslat (Döntés képviselöi önálló indítvány tárgysorozatba vételéröl), Jegyzökönyv az Országgyülés Költségvetési bizottságának 2019. március 12-én, kedden 10 óra 03 perckor az Országház Széll Kálmán termében (föemelet 64.) megtartott üléséröl, Ikt. sz.: KVB-41/16-8/2019., 15-21.

[17] Minden 18 év alatti SMA-s beteg megkaphatja a kezelést Magyarország Kormánya https://www.kormany.hu/hu/emberi-eroforrasok-miniszteriuma/hirek/minden-18-ev-alatti-sma-s-beteg-megkaphatja-a-kezelest

[18] Accord en France sur le prix du Spinraza, médicament pour une maladie génétique rare, Figaro, https://www.lefigaro.fr/flash-eco/accord-en-france-sur-le-prix-du-spinraza-medicament-pour-une-maladie-genetique-rare-20190418

[19] Reimbursement Information on Spinraza (nusinersen), TheSocialMedWork https://thesocialmedwork.com/blog/reimbursement-information-on-spinraza-nusinersen#:~:text=Reimbursement%20information%20on%20Spinraza%20(nusinersen),-Posted%3A%20January%2018&text=Spinraza%20(nusinersen)%20is%20indicated%20for,5ml%20vial%20for%20one%20treatment.

[20] Testing & Diagnosis, Cure SMA https://www.curesma.org/testing-diagnosis/#newbornscreening

conduct an SMA test.[21] However, if a blood test can be conducted immediately after birth, treatments have better outcomes, thus the baby has more chances to maintain the condition for survival.[22] In evidence that supports this theory, in 2018, 23 American states screened newborns for SMA—in addition to other genetic disorders including endocrine, metabolic, hearing loss, and critical congenital heart defects (CCHDs).[23] A further 13 states have already adopted the program and seek to activate it within two years. Another three states have trials in this field.[24] To succeed, the Advisory Committee must recommend these conditions to the Commissioner of Health, making arguments at the Public Health Council, where they will vote regarding this question.[25] According to the wish of the SMA community, all states will include the SMA test in newborn screening in the future. This test is quite easy to implement. In the baby's first days of life, a few drops of blood are taken onto a special filter paper (Guthrie cards) and then analyzed in a laboratory.[26]

In Australia, as in the USA, SMA testing began in 2018.[27] For the moment, it is only a two-year program, however, it may be continued into the future. According to the results, there have been more than 100,000 newborns screened and 10 of them were positive.[28]

In Germany, two federal states had a one-year pilot project regarding testing SMA on newborns.[29] Bavaria and North-Rhine Westphalia screened 165,525 newborns and 22 SMA cases were detected between January 2018 and February 2019. In conclusion, German officials recommend other countries where SMA treatment is available to do the same. Their motivation was the creation of a new drug for this genetic disease, Spinraza (nusinersen), which was released at the end of 2016.[30] It has historical importance because this drug was the first offered to maintain muscle condition with SMA. This one-year research was not financed by the German government, but by the German Cystinosis Foundation. This is the reason it will not be continued and will not automatically be included in every newborn screening.

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[21] Ibid.

[22] Ibid.

[23] Centers for Disease Control and Prevention, Newborn Screening Portal https://www.cdc.gov/newbornscreening/index.html

[24] Newborn Screening Programs, Cure SMA https://curesma.wpengine.com/newborn-screening-for-sma/#genetictesting State Fact Sheets, Cure SMA

[25] SMA State Fact Sheet, Massachusetts https://curesma.wpengine.com/wp-content/uploads/2020/02/SMA-State-Fact-Sheet_2020_MA_v4.pdf

[26] Guthrie test, Embryology https://embryology.med.unsw.edu.au/embryology/index.php/Guthrie_test

[27] Guthrie test—Australia, Embryology https://embryology.med.unsw.edu.au/embryology/index.php/Guthrie_test#Australia

[28] Kariyawasam, D.S.T., Russell, J.S., Wiley, V. et al. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Genet Med 22, 557–565 (2020) https://doi.org/10.1038/s41436-019-0673-0

[29] Journal of Neuromuscular Diseases, vol. 6, no. 4, pp. 503-515, 2019

[30] FDA approves first drug for spinal muscular atrophy, U:S: Food & Drug Administration, 23.12.2016. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-spinal-muscular-atrophy

In France, which is considered to have one of the best health care systems in the world,[31] 13 illnesses are tested automatically after birth and another 17 will be added by 2023. Unfortunately, SMA is not among them. In 2011, the French National Authority for Health recommended including[32] MCAD deficiency[33] in the screening, and it was finally accepted in 2020.[34] Taking into consideration the progress of this decision in the last nine years, we cannot expect a faster evaluation from the application of the SMA tests either.

In Hungary, newborn screening has been applied since the '70s and has been obligatory[35] since 2007. In 2020, up to 26 metabolic disorders can be tested.[36] This number is better than the majority of the European countries but less than the US where they can screen for more than 40 diseases. The Head of the Hungarian Metabolic Center, László Szönyi declared that it is essential to reveal these illnesses before the symptoms appear. In this regard, they can cure patients immediately without making them suffer irreversible damage to their mental or physical health. Especially since the cure for most of these illnesses is easy to apply, simple, and affordable. Even with dietary changes and taking particular vitamins, they can improve the patient's condition. He (Szonyi) added that a further test against cystic fibrosis would also be beneficial. According to their statistics, newborn screening can save lives, approximately 50 to 60,000 babies a year.[37]

Both Germany and Hungary have aimed to include cystic fibrosis (CF) in newborn screening shortly. It seems that the United States is ahead of them in this field, all 50 states screen for it after birth.[38] Cystic fibrosis is a genetic disease that causes lung infections and inappropriate digestion. There are more than 70,000 registered patients in the world, 30,000 of them being in the US. One thousand more new cases appear each year, 75% of them are diagnosed before the age of two. Although there is still no cure for this illness, treatments can improve the chances of greater longevity.[39]

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[31] Mark Rice-Oxley: Which country has world's best healthcare system? The Guardian, 09.02.2016 https://www.theguardian.com/society/2016/feb/09/which-country-has-worlds-best-healthcare-system-this-is-the-nhs

[32] Recommendations for the expansion of newborn screening to MCAD deficiency, Summary of Public Health Recommendations, HAS, June 2011, https://www.has-sante.fr/upload/docs/application/pdf/2011-07/fs_depistage_neonatal-en-v2.pdf

[33] MCAD deficiency is an inherited metabolic disorder characterised by the inability of the body to use fat. While children with MCAD do not have symptoms at birth, they may develop a metabolic crisis (e.g. during intercurrent illness), which may rapidly lead to coma or death.

[34] Dépistage Néonatal: Quelle maladies dépister? Haute Autorité de Santé (HAS), 03.02.2020. https://www.has-sante.fr/jcms/p_3149627/fr/depistage-neonatal-quelles-maladies-depister

[35] Decree of the Minister of Health in Hungary 44/2007. (IX. 29)

[36] Újszülöttkori szürövizsgálatok, László Szönyi, I.sz. Children's Clinic Budapest http://www.gyermekklinika.semmelweis.hu/upload/seaok1gyermek/document/2009.03.19.sz337nyilszl_jszlttkorisz369r337vizsglatok.pdf

[37] Czétényi, Rita: Évente 50-60 életet ment meg az újszülöttkori szürövizsgálat, Semmelweis Hírek, 28.02.2013 https://semmelweis.hu/hirek/2013/02/28/evente-50-60-eletet-ment-meg-az-ujszulottkori-szurovizsgalat/

[38] Newborn Screening for CF, Cystic Fibrosis Foundation https://www.cff.org/What-is-CF/Testing/Newborn-Screening-for-CF/

[39] About Cystic Fibrosis, Cystic Fibrosis Foundation https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/

We can see from the numbers, why countries are focused on cystic fibrosis rather than SMA. There are more than 40,000 CF cases in Europe, 560 in Hungary.[40] Although the registration of SMA patients does not have official statistics, there are approximately 10 to 25,000 American patients[41] and 120-300 cases in Hungary.[42]

Carrier Screening for SMA

Carrier screening would be more useful than newborn SMA testing, however, it is less utilized. If women who are planning to start a family could have the possibility for a blood test to discover whether they are carriers, they would have more choices. In the case where the woman discovers she is a carrier, her partner could be screened as well.[43] If both of them are carriers and they do not want to risk (25%) that their future child will suffer from SMA, they can choose either in vitro fertilization or intrauterine insemination.[44] If they prefer natural conception, they can also give up the plan of carrying a child and can choose adoption instead. If they opt for natural conception, doctors can test the fetus for SMA by amniocentesis or chorionic villus sampling.[45] The choice of the parents is more difficult in this case; they can prepare in advance for having a child with special needs for a lifetime or in the worst case, with a lower life expectancy. Nevertheless, some parents choose to terminate the pregnancy at an early stage or give up their newborn for adoption.[46]

The implementation of carrier screening would be temporary. If governments made newborn screening obligatory from 2020 forward, individuals would know by birth whether they are carriers. In 40 years, there would be no need for newborn testing, but for the moment, it is quite useful for young adults. Women should be informed about and offered this possibility without additional payment. Currently, in the US, only people with an SMA family history are offered testing.[47] However, it is already a good start as it identifies 2.6% of couples at risk.[48] Since every one in fifty people is a

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[40] European Cystic Fibrosis Society, Patient Registry https://www.ecfs.eu/sites/default/files/general-content-images/working-groups/ecfs-patient-registry/Hungary_Poster_ECFSPR.pdf

[41] SMA Overview, SMA Foundation http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf

[42] Joób Sándor: Van egy új szupergyógyszer, csak az állam nem adná oda Index, 04.05.2018. https://index.hu/belfold/2018/05/04/gyogyszer_neak_sma_gyogyszertamogatas_betegseg/

[43] Carrier Screening for Spinal Muscular Atrophy, The American College of Obstetricians and Gynecologists https://www.acog.org/patient-resources/faqs/pregnancy/carrier-screening-for-spinal-muscular-atrophy

[44] Norrgard, K. (2008) Medical ethics: genetic testing and spinal muscular atrophy. Nature Education 1(1):88

[45] Ibid.

[46] Prior, Thomas W, and Professional Practice and Guidelines Committee. "Carrier screening for spinal muscular atrophy." Genetics in medicine : official journal of the American College of Medical Genetics vol. 10,11 (2008): 840-2. doi:10.1097/GIM.0b013e318188d069

[47] Ibid.

[48] SMA Genetic Carrier Status Test Being Launched in Europe, Latin America, SMA News Today, April 27, 2017, https://smanewstoday.com/2017/04/27/synlab-and-counsyl-to-launch-sma-genetic-carrier-status-test-in-europe-latin-america/

carrier,[49] it makes sense to provide the test to everyone. In Europe, only Spain, Portugal, and Italy can perform these screenings.[50] In Germany, Austria, Netherlands, and Switzerland, future mothers may ask for a prenatal blood test to determine whether they are carriers.[51] Nevertheless, in this case, the mother is already pregnant, so her choices are more limited regarding the fetus.

Legal Issues

Public policy always needs time to catch up with technology, even when the standard of care is clear. In the case of newborn screening, this standard is evolving. The medical sector cannot only precisely determine the illness, but sometimes actually cure it. There are two parts for the legislation: diagnosis and treatment. Moreover, screening regulations may be complicated because screening before the pregnancy reveals only a possibility of SMA, screening during the pregnancy reveals the presence of SMA, and screening positive for SMA after birth requires treatment. The screening results are not always reliable. For example, if both of the parents are discovered to be SMA carriers during pre-pregnancy screening, they have only a 25% chance having a baby with SMA. Or, for example, when they calculate the possibility during the pregnancy having an infant with Down syndrome based on the blood test of the mother, her age, and the ultrasonography, it is the mother's choice to proceed with amniosynthesis to confirm the condition. Even if these predictions combine with issues of privacy or religious and cultural beliefs,[52] public policy needs to balance the interests around the protection of the health of mother and fetus. But, can public health justify making newborn screening obligatory for the entire population, even if it is a hereditary genetic disease? Or should it be only an option for the parents? Generally, most parents want to know whether their child has a genetic defect and whether there is an available treatment for it. If not, based on cultural reasons, these parents should have an opt-out possibility, where they could refuse these genetic tests. Or, with an opt-in provision, they could choose those tests which they think are appropriate. This kind of regulation would respect the right of an individual's choice as hereditary diseases are not infectious, it is rather a part of private than public health. The states could offer a choice for parents by making newborn screening available for as many diseases as technology allows. Public health agencies promote family planning programs focusing on the health of infants. They inform parents that through newborn screening-detected diseases can be treated with higher efficiency.[53]

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[49] Ibid.

[50] Ibid.

[51] Prenatal Blood Test for SMA Now Available in Four Countries in Europe, BillionToOne Announces, SMA News Today, November 8, 2019, https://smanewstoday.com/2019/11/08/prenatal-blood-test-sma-other-single-gene-diseases-now-available-four-countries-in-europe/

[52] Cooper, Todd: Blood test for newborns faces religious challenge, Omaha World-Herald/December 21, 2004

[53] Kraszewski, J., Burke, T., & Rosenbaum, S. (2006). Legal issues in newborn screening: implications for public health practice and policy. Public health reports (Washington, D.C. : 1974), 121(1), 92–94. https://doi.org/10.1177/003335490612100116

In the United States, newborn screening is mandatory and parental consent is not required. Based on two foundational laws, the states have the responsibility to protect their citizens. The police power protects "the health, safety, morals, and general welfare," the "parens patriae" power (i.e., the state acting as parent in certain circumstances) ensures the rights of children and vulnerable persons to health and well-being. The latter gives the right to the state to intervene against an abusive or negligent parent to protect the child. These state privileges and responsibilities are weighed against parents' rights to make decisions about their minor children's welfare. The parents can accept or refuse medical treatments according to their views.[54]

In the European Union, the establishment of a centralized screening committee would be reasonable as many different aspects can block the decision of whether or not to accept a new screening method in a country. A screening committee would have the necessary expertise to review scientific studies and analyze their advantages and disadvantages. However, a committee for evaluating cost-effectiveness and ethics would also be needed. Although some countries involve parent and patient groups in decisionmaking, in addition to federal and regional health authorities and medical professionals, the final word should be the state's, based on the funding and provisions made by the health care system. Eighteen EU countries already have a committee, laws, and regulations devoted to examining newborn screening. Some of them make it obligatory for parents to have their babies screened. Another group of states only inform them that they have a possibility for screening, and the parents can choose it or not. In the last five years, twenty-one EU member countries have changed the newborn screening policy.

A common mechanism would be desirable between them as national screening committees have to evaluate the same issues. The European Network for Health Technology Assessment (EUnetHTA) asks for collaboration because it can facilitate a transparent and effective health technology assessment.[55]

Public health authorities are responsible for offering newborn screening to their citizens.[56] A legal obligation ensures quality and accessibility. But, it would remain only an offer of screening, and should not be mandatory.[57] In the US and Hungary, newborn screenings are mandatory, under the rationale that parents have the obligation to protect the health of their child. But can a human right become an obligation? At a European Cystic Fibrosis Society's conference, a question was posed and remained unanswered: is

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[54] US Constitution, 14th Amendement

[55] EU Tender "Evaluation of population newborn screening practices for rare disorders in Member States of the European Union", Newborn screening in Europe, Expert Opinion Document, Final 28/08/2011 https://www.isns-neoscreening.org/wp-content/uploads/2018/11/Expert-opinion-document-on-NBS-FINAL.pdf

Kristensen FB, Mäkelä M, Neikter SA, Rehnqvist N, Håheim LL, Mørland B, Milne R, Nielsen CP, Busse R, Lee-Robin SH, Wild C, Espallargues M, Chamova J; European network for Health Technology Assessment (EUnetHTA). European network for health technology assessment, EUnetHTA: planning, development, and implementation of a sustainable European network for health technology assessment. Int J Technol Assess Health Care. 2009 Dec;25 Suppl 2:107-16. doi: 10.1017/S0266462309990754. PMID: 20030898.

[56] Charter of fundamental rights of the European Union, Art 24

[57] CoE additional Protocol, art 10

newborn screening a basic human right?[58] They based this theory on the concept that if doctors detect this genetic illness less than two months after birth, the child has better chances of survival. The same can be applied to SMA, but no one asked this question yet. It is an important question now that Zolgensma is accessible and should be given before the baby's second birthday.

To have a look at it from a broader perspective, is health care a basic human right? If so, then providing it is a duty of the state. From a narrower perspective, is early detection of a lethal genetic disease a basic human right? After several debates and studies, we can answer "yes" to this question if four conditions are present: 1) if the child is born in a region where the questioned disease is relatively common (at least 1:10,000 in the case of cystic fibrosis); 2) the newborn screening program exists there or can be created; 3) in case of a positive test, there is an available treatment; and 4) sustained funding is available. We must answer "no" to the question above if it causes more harm than good, when the regional readiness does not exist or when there is no available funding, service, or treatment.[59] Taking into consideration, that we have talked about newborn screening programs in developed countries above, of whom all of the four points are true, making newborn screening available for every parent would be a duty.

Summary

Prevention should always come first before treatment. It would be beneficial for the state as they would have less material expenditure for life aids, hospitalization, therapies, and medication for the patients. Paying for Spinraza through health insurance is expensive. Moreover, the mother of a sick child probably cannot continue her career because she will most likely need to stay at home to care for her son/daughter. It is a loss for the individual as she did not have a choice and also a loss for society regarding the labor market. Among the goals of the World Health Organization (WHO), we can find inter alia the prevention of non-communicable diseases, the promotion of mental health, the improvement of access to essential medicines and health products, and the improvement of monitoring, data, and information.[60] In this way, they could urge the development of newborn screening, provide mental support for the patients' families, negotiate the price of life-saving drugs, promote the invention of new treatments and methodize the registration of genetic disease. But there is also work to be done at the national level. For example, the Minister of Health in each country could focus more on the importance of the Guthrie test and increase the revenue sources for health services. Developed countries should find the financial sources to offer all technologically available newborn tests to the people. It is the state's responsibility to protect its citizens and this test can save lives. Making SMA screening available to parents as part of standard newborn screening ensures a basic human right.

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[58] Farrell PM. Is newborn screening for cystic fibrosis a basic human right? J Cyst Fibros. 2008 May;7(3):262-5. doi: 10.1016/j.jcf.2008.01.001. Epub 2008 Feb 11. PMID: 18262856; PMCID: PMC2504861.

[59] Ibid.

[60] What we do, WHO https://www.who.int/about/what-we-do

The Scientific Consensus on When a Human's Life Begins

Steven Andrew Jacobs, J.D., Ph.D.*

ABSTRACT: Peer-reviewed journals in the biological and life sciences literature have published articles that represent the biological view that a human's life begins at fertilization ("the fertilization view"). As those statements are typically offered without explanation or citation, the fertilization view seems to be uncontested by the editors, reviewers, and authors who contribute to scientific journals. However, Americans are split on whether the fertilization view is a "philosophical or religious belief" (45%) or a "biological and scientific fact" (46%), and only 38% of Americans view fertilization as the starting point of a human's life. In the two studies that explored experts' views on the matter, the fertilization view was the most popular perspective held by public health and IVF professionals. Since a recent study suggested that 80% of Americans view biologists as the group most qualified to determine when a human's life begins, experts in biology were surveyed to provide a new perspective to the literature on experts' views on this matter. Biologists from 1,058 academic institutions around the world assessed survey items on when a human's life begins and, overall, 96% (5337 out of 5577) affirmed the fertilization view. The founding principles of the field Science Communication suggest that scientists have an ethical and professional obligation to inform Americans, as well as people around the world, about scientific developments so members of the public can be empowered to make life decisions that are consistent with the best information available. Given that perspective—and a recent study's finding that a majority of Americans believe they deserve to know when a human's life begins in order to make informed reproductive decisions—science communicators should work to increase the level of science awareness on the fertilization view, as it

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stands alone as the leading biological perspective on when a human's life begins.

Keywords: **fertilization; when life begins; when a human's life begins; science communication; abortion; human rights; personhood; scientific consensus**

1. Introduction

A recent national poll suggested that 38% of Americans believe a human's life begins at fertilization ("the fertilization view").[1] Another recent national poll reported that 46% of Americans recognize the fertilization view as a "biological and scientific fact", and 45% view it as a "philosophical or religious belief".[2] While Americans' views on when a human's life begins have been assessed in numerous polls in recent years, there is scant evidence of experts' opinions on this matter. This form of inquiry—assessing a factual dispute by surveying those with the relevant expertise—has been prominent in the debate about anthropogenic climate change,[3,4] but it has yet to be used to assess a large sample of relevant experts' views on when a human's life begins.

Two small-scale studies have been conducted to assess experts' views on this matter: in 1967, researchers surveyed public health professionals,[5] and in 2008, researchers surveyed professionals working in the *in vitro* fertilization field.[6] In both studies, fertilization was the most common view held by the experts: 35% of public health professionals (27 out of 76) and 26% of IVF professionals (67 out of 255) affirmed the fertilization view. However, given the scientific literature's recognition of the fertilization view, it is surprising that it has been affirmed by a plurality of Americans and experts, rather than a majority.

A recent review of the abstracts of peer-reviewed journals in the biological and life sciences literature reported that dozens of journals have published articles containing statements that affirm the fertilization view.[7] Since journals publish these statements without explanation or citation, it suggests that researchers, reviewers, and journal editors seem to accept the fertilization view as a well-known and well-accepted biological observation. As previewed in Table 1 below, efforts to compile citations to peer-reviewed articles that contain such statements have continued[8]—these articles can be categorized based on how explicitly they represent the fertilization view.

Table 1. Peer-reviewed journals that represent the fertilization view.

A. Fertilization marks the beginning of a human's life

1. *California Medicine*: "[T]he scientific fact, which everyone really knows, that human life begins at conception."[9]
2. *Australian and New Zealand Journal of Obstetrics and Gynaecology*: "The time of our conception is when we are most vulnerable to survival and growing as a healthy human being."[10]

3. *Trends in Cell Biology*: "Most readers of this review originated from a sperm-egg fusion event."[11]
4. *Reproduction*: "Human life begins with sperm and oocyte fusion."[12]

B. Fertilization marks the beginning of a new individual

5. *Frontiers in Cell and Developmental Biology*: "Fertilization is a key process in biology to the extent that a new individual will be born from the fusion of two cells."[13]
6. *Journal of Assisted Reproduction and Genetics:* "[A] new individual is derived from the fusion of a single sperm and egg."[14]
7. *Cell and Tissue Research:* "[F]ertilization is the process by which male and female haploid gametes (sperm and egg) unite to produce a genetically distinct individual."[15]
8. *Nature Reviews Molecular Cell Biology:* "During fertilization of an egg with a sperm, the haploid genomes of each parent are unified to form the diploid genome of a new and unique individual."[16]

C. Fertilization marks the beginning of life

9. *Physiological Reviews*: "A proper dialogue between spermatozoa and the egg is essential for conception of a new individual in sexually reproducing animals. Ca(2+) is crucial in orchestrating this unique event leading to a new life."[17]
10. *Cell*: "Recognition between sperm and the egg surface marks the beginning of life in all sexually reproducing organisms."[18]
11. *Molecular & Cellular Proteomics*: "Sperm are remarkably complex cells with a singularly important mission: to deliver paternal DNA and its associated factors to the oocyte to start a new life."[19]
12. *Communicative & Integrative Biology*: "It is intuitive that fertilization-the start of life-involves communication between a sperm cell and an egg."[20]

D. Fertilization is the transmission of genes from parents to their children

13. *Science*: "Fertilization is the sum of the cellular mechanisms that pass the genome from one generation to the next and initiate development of a new organism."[21]
14. *Methods in Molecular Biology*: "As representatives of the 60 trillion cells that make a human body, a sperm and an egg meet, recognize each other, and fuse to create a new generation."[22]
15. *Animal Reproduction Science*: "In higher animals, the beginning of new life and transfer of genetic material to the next generation occurs in the oviduct when two distinct gametes cells unite resulting in the formation of a zygote."[23]
16. *Current Opinion in Genetics & Development*: "In mammals, a new generation begins when an oocyte is fertilized by a sperm to form a zygote."[24]

E. Fertilization marks the beginning of development and the life cycle

17. *Nature*: "The life cycle of mammals begins when a sperm enters an egg."[25]
18. *Molecular Neurobiology*: "Aging is a developmental process that begins with fertilization and ends up with death involving a lot of environmental and genetic factors."[26]
19. *Journal of Cellular Physiology*: "At the time of fertilization, an increase in the intracellular Ca(2+) concentration ([Ca(2+)](i)) underlies egg activation and initiation of development in all species studied to date."[27]
20. *Seminars in Cell and Developmental Biology*: "At fertilization, eggs unite with sperm to initiate developmental programs that give rise to development of the embryo. Defining the molecular mechanism of this fundamental process at the beginning of life has been a key question in cell and developmental biology."[28]

These statements vary in their framing of the fertilization view, as some specifically state that fertilization marks the beginning of a human's life and others generally state that fertilization marks the beginning of a new individual, a new life, or the life cycle

of an organism. Still, all of these statements represent the fertilization view since they directly or indirectly state that fertilization marks the point at which a male's spermatozoon (sperm) and a female's oocyte (egg) unite to form a genetically unique organism (zygote)—that a zygote with a human genome is a human since he or she would then be biologically classified as a member of the *Homo sapiens* species whose life has started on the developmental path that can continue through the zygotic, embryonic, fetal, infant, child, adolescent, and adult stages of the human life cycle. Thus, taken together, these statements suggest the fertilization view is common in the biological and life sciences literature.

In a recent study,[29] Americans were asked who among the following list of authorities is most qualified to determine when a human's life begins: biologists, philosophers, religious leaders, Supreme Court Justices, and voters. A large majority of the 4,107 Americans surveyed selected biologists (80%). When participants were asked why they selected biologists, 91% stated that they "view biologists as objective experts in the study of life". Thus, a study was designed to assess biologists' views on the ontogenetic starting point of a human's life.

2. Materials and Methods

Participation in the survey was sought from members of biology and life sciences departments of colleges, universities, and research institutes around the world. First, a list of academic institutions was generated from rankings of biology programs.[30, 31] Second, contact information for post-doctoral researchers, lecturers, professors, and professors *emeriti* was collected from the institutions' biology and life sciences departmental faculty webpages.

62,469 academic biologists were recruited through e-mail and 7,402 participated in the online survey (12% response rate). Of the participants, 5,577 biologists from 1,058 institutions provided analyzable data on operative questions. This response rate was comparable to a recent study that used professors' publicly available e-mail addresses to recruit them to participate in a survey on their views on controversial topics.[32] The demographics of the participants suggest the sample was representative of the population of academic biologists around the world.

A majority of the participants held a Ph.D. (95%), and most identified as male (63%) and non-religious (63%). Ideologically, a majority identified as liberal (89%) and pro-choice (85%). Previous studies have shown that 61% of biologists identify as atheist or agnostic[33] and that members of the academy are likely to hold liberal beliefs.[34] Thus, since there was no indication of non-response or self-selection bias, the sample's religious and ideological breakdowns suggest the sample was likely representative of the overall population of academic biologists. Overall, the sample comprised biologists from 86 countries.

2.1. Survey Questions

First, biologists were asked whether they view the question of when a human's life begins as a scientific matter. Participants were presented the question: "Which group

is most qualified to answer the question 'When does a human's life begin?'" They were then asked to select from the following five options: biologists, philosophers, religious leaders, Supreme Court Justices, and voters. The participants were also asked to assess Americans' selection of biologists as the most credible authority on the matter: "In a recent survey, a large majority of participants selected biologists as the group most qualified to answer the question 'When does a human's life begin?'. Do you agree that biologists are most qualified to define when a human's life begins?"

Since the fertilization view is the leading view among Americans,[1, 2] public health professionals,[5] and *in vitro* professionals[6]—and since it has been stated without explanation or citation in articles published in numerous peer-reviewed journals such as *Science*,[21] *Nature*,[25, 35, 36] and *Cell*[18]—survey items were designed to assess whether biologists affirm the fertilization view.

Participants were presented five statements (Q1-Q5) that represented various semantic framings of the fertilization view, and they were asked to affirm or reject the statements. Finally, they were presented an open-ended essay question on the biological perspective on when a human's life begins (Q6):

- **Question 1:** The end product of mammalian fertilization is a fertilized egg ('zygote'), a new mammalian organism in the first stage of its species' life cycle with its species' genome.
- **Question 2:** The development of a mammal begins with fertilization, a process by which the spermatozoon from the male and the oocyte from the female unite to give rise to a new organism, the zygote.
- **Question 3:** A mammal's life begins at fertilization, the process during which a male gamete unites with a female gamete to form a single cell called a zygote.
- **Question 4:** In developmental biology, fertilization marks the beginning of a human's life since that process produces an organism with a human genome that has begun to develop in the first stage of the human life cycle.
- **Question 5:** From a biological perspective, a zygote that has a human genome is a human because it is a human organism developing in the earliest stage of the human life cycle.
- **Question 6:** From a biological perspective, how would you answer the question "When does a human's life begin?"

As shown in Table 1 above, peer-reviewed journals' statements that represent the fertilization view vary in how explicitly they state that a human's life begins at fertilization. These statements (Q1-Q5) similarly varied in their explicitness. Q1 and Q2 reference the beginning of a new organism, Q3 references the beginning of a new life, and Q4 and Q5 explicitly reference the beginning of a human's life. Some statements focused on mammals (Q1-Q3) and others focused on humans (Q4-Q5); while some were in the form of a declarative statement (Q1-Q3), others took the form of an argument (Q4-Q5); however, all fundamentally represented the view that fertilization marks the beginning

of a human's physical existence as an organism with a human genome who is developing in the human life cycle.

3. Results

3.1. Assessments of Who is Most Qualified to Determine When a Human's Life Begins

As shown in Figure 1 below, 64% of participants (2395 out of 3773) selected biologists as the group most qualified to answer the question "When does a human's life begin?", 23% selected philosophers (865 out of 3773), 1% selected religious leaders (53 out of 3773), 4% selected Supreme Court Justices (135 out of 3773), and 9% selected voters (325 out of 3773). In a separate measure, 68% of participants (2365 out of 3457) agreed with Americans' selection of biologists as the group most qualified to determine when a human's life begins, and 32% disagreed (1092 out of 3457). These data suggest that biologists do not only view experts in biology as most qualified to make this determination—they primarily view the question of when a human's life begins as a matter of biology.

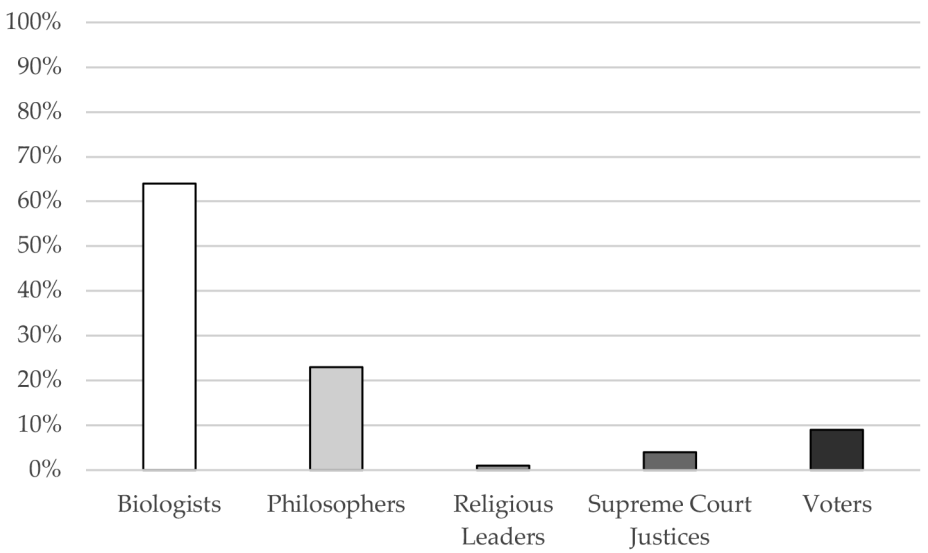

Figure 1. Percentage of biologists who selected different authorities in response to a question on who is most qualified to determine when a human's life begins.

3.2. Assessments of the Fertilization View

The statement in Q1 was affirmed by 91% of participants (4555 out of 4993). The statement in Q2 was affirmed by 88% of participants (3984 out of 4510). The statement in Q3 was affirmed by 77% of participants (3153 out of 4078). The statement in Q4 was affirmed by 75% of participants (2500 out of 3334). The statement in Q5 was affirmed by 69% of participants (2744 out of 3980). For a comparison of these affirmation rates, see Figure 2 below.

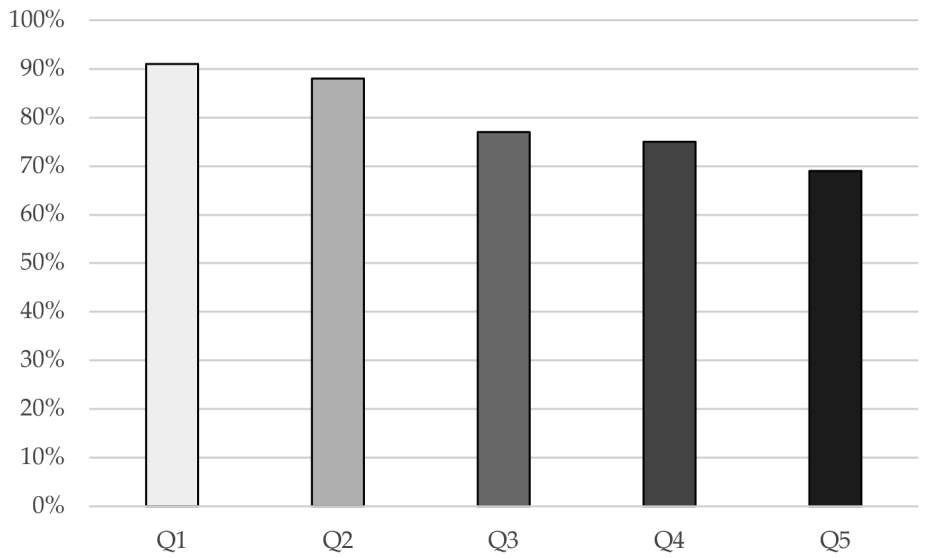

Figure 2. Percentage of biologists who assessed and affirmed the five statements that represented the fertilization view.

As shown in Figure 3 below, of those who assessed at least one of the five statements, 96% of participants affirmed at least one statement (5337 out of 5577) and 4% did not (240 out of 5577). Further, of those who assessed multiple statements, 96% affirmed at least one (4463 out of 4650) and 85% affirmed at least half of the statements they assessed (3936 out of 4650).

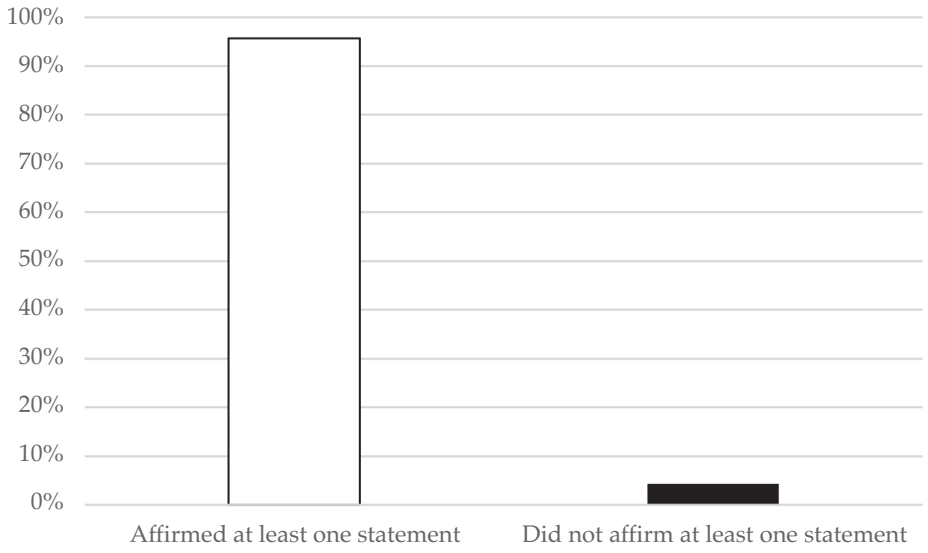

Figure 3. Percentage of biologists who assessed and affirmed at least one statement (Q1-Q5), and the percentage of biologists who assessed at least one statement but did not affirm any.

3.3. An Assessment of the Biological View on When a Human's Life Begins

Consistent with their affirmation rates of the fertilization view in Q1-Q5, Figure 4 below shows that 68% of biologists (1898 out of 2793) represented the fertilization view in response to Q6's open-ended essay question. Among the biologists who did not write about fertilization: 10% (268 out of 2793) represented some point between fertilization and viability (i.e., when a fetus can first survive outside of the womb), 10% (284 out of 2793) represented the viability view, and 12% (343 out of 2793) represented the view that a human's life begins at birth.

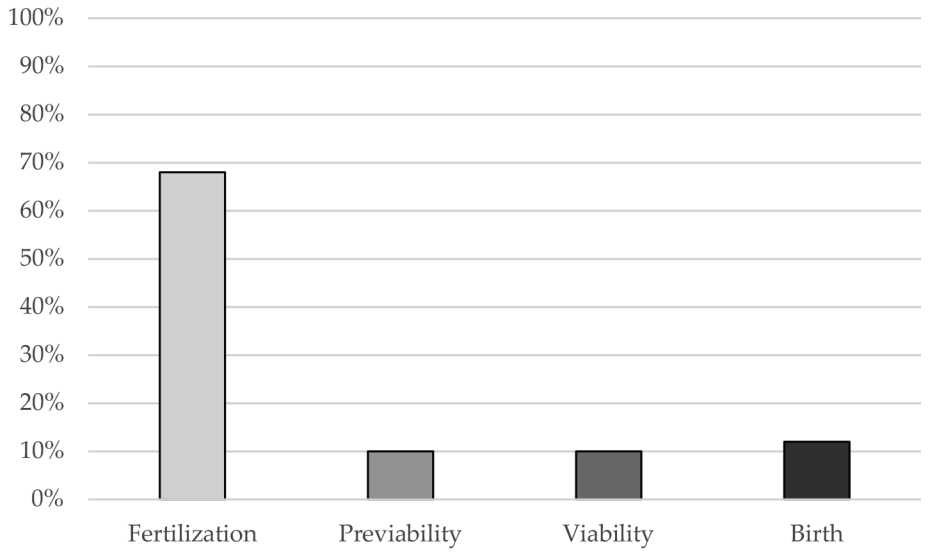

Figure 4. Percentage of biologists who represented different views in response to an open-ended essay question on the biological perspective on when a human's life begins.

The strictest measure of biologists' views assessed the responses of participants who answered each item consistently: (1) those who either affirmed each statement (Q1-Q5) and wrote about the fertilization view in response to the essay question (Q6), and (2) those who rejected each statement and wrote about some later point in development. As shown in Figure 5 below, there was a greater number of participants who consistently affirmed the fertilization view (97%; 1011 out of 1044) than those who consistently rejected the fertilization view (3%; 33 out of 1044).

4. Discussion

The use of the scientific method to assess experts' opinions on controversial topics has been effective in promoting science awareness of the effect of human behavior on climate change.[3, 4] Consensus cannot prove that the most commonly held view is true, but it can establish the leading view that can be recognized and relied upon as the best science available. However, a leading view can be most trusted if there is no reasonable

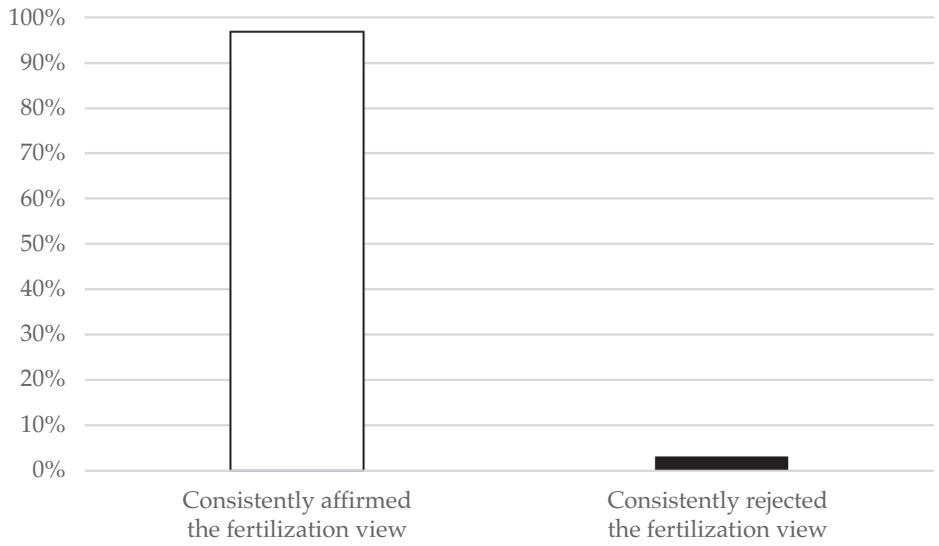

Figure 5. Percentage of biologists who responded consistently across all measures. Biologists who assessed and affirmed each statement (Q1-Q5) and represented the fertilization view in response to an open-ended essay question on when a human's life begins (Q6), and biologists who assessed and rejected each statement and represented some point other than fertilization in response to the essay question.

expectation that the consensus is driven by experts' financial, political, ideological, or personal motivations.

For instance, in the case of anthropogenic climate change, climate scientists might have financial incentives to affirm that human behavior is causing global warming[37] (e.g., increased grant funding, better speaking engagements, and even lucrative job opportunities in the corporate and finance sectors.)[38] They might also have personal motivations to affirm it; discussions of global warming have made climate science research more prominent, and climate scientists have never been more important or had more of an impact on policy, the economy, and politics. However, in the present study, since 85% of the sample identified as pro-choice and the fertilization view is typically associated with those who identify as pro-life,[1, 2] there is no indication that the present study's results were affected by such bias.

Based on the totality of the biological and life sciences literature's recognition of the fertilization view,[8] principles of the modern genetics-based method of biologically classifying organisms,[39] and the data reported in the present study, the fertilization view stands alone as the leading biological view on when a human's life begins. Thus, using the common meaning of "consensus" (i.e., general agreement), one can reasonably conclude that there is a scientific consensus on the view that a human's life begins at fertilization. Simply put, fertilization marks the point at which a human begins his or her physical existence as a human organism developing in the human life cycle, so he

or she is then properly biologically classified as a human and a member of the *Homo sapiens* species.

Given the high levels of agreement on the fertilization view in the scientific community, the low levels of agreement among the American public suggest an issue of low science awareness on when a human's life begins. Since 96% of biologists affirm the fertilization view but only 38% of Americans do,[1] there seems to not only be a large expert/public opinion gap but perhaps the largest gap on any contentious issue.

The *Pew Research Center* recently analyzed various knowledge gaps between the American public and experts, and it found that the largest gap (51 points) between Americans (37%) and scientists (88%) was on whether it is "[s]afe to eat genetically modified foods."[40] However, as suggested by the results of the present study, the expert/public opinion gap on when a human's life begins is even larger (58 points), as Americans are less likely to affirm the fertilization view (38%) than scientists (96%).

Since polls on Americans' views are typically conducted in the context of the abortion issue, it is possible that Americans' affirmation rate of the fertilization view would be higher, and the expert/public opinion gap would be smaller, if such questions are asked in isolation from discussions about abortion—Americans who support abortion rights might be more likely to affirm the fertilization view if they are not primed to think about abortion. Thus, researchers seeking to directly assess this expert/public opinion gap should consider asking both Americans and biologists their views in a non-abortive context. Indeed, it is important to understand and address this gap, as the question of when a human's life begins is no trivial or purely academic matter.

Americans were recently surveyed on the importance of this question, and 76% of participants suggested that Americans deserve to know when a human's life begins so they can make informed reproductive decisions.[29] The burgeoning field of Science Communication promotes the precept that scientists have a responsibility to communicate scientific findings to members of the public who can then base their life decisions on the best information available.[41, 42] The field's principles suggest that scientists are responsible for communicating the leading scientific view on when a human's life begins to the public, as it would enable Americans to make reproductive decisions informed by biological knowledge.

Given the size and breadth of the international sample of biologists in the present study, its results represent strong support for the claim that there is a scientific consensus on the view that a human's life begins at fertilization. However, as with any study, follow-up studies should be conducted to replicate these findings, to further assess biologists' stances on the fertilization view, and to perhaps assess why some biologists rejected the fertilization view by arguing that, from a biological perspective, a human's life begins at birth. If this study's findings are confirmed, then the fertilization view can be promoted by scientists and shared with members of the public to ensure they are informed on the biological perspective on when a human's life begins, as this would empower them to make informed reproductive decisions.

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Institutional Review Board Statement: The study was approved by The University of Chicago's Social and Behavioral Sciences Institutional Review Board (IRB16-1228-CR002 on 8/20/18).

Informed Consent Statement: Informed consent was obtained from all participants involved in the study.

Data Availability Statement: Any and all data can be made available before publication.

Conflicts of Interest: The author declares no conflict of interest.

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