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A Brighton Collaboration standardized template with key considerations for a benefit/risk assessment for the Moderna COVID-19 Vaccine (mRNA-1273)

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ABSTRACT

The Brighton Collaboration Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group has prepared standardized templates to describe the key considerations for the benefit-risk assessment of several vaccine platform technologies, including nucleic acid (RNA and DNA) vaccines. This paper uses the BRAVATO template to review the features of a vaccine employing a proprietary mRNA vaccine platform to develop Moderna COVID-19 Vaccine (mRNA-1273); a highly effective vaccine to prevent coronavirus disease 2019 (Covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In response to the pandemic the first in human studies began in March 2020 and the pivotal, placebo-controlled phase 3 efficacy study in over 30,000 adults began in July 2020. Based on demonstration of efficacy and safety at the time of interim analysis in November 2020 and at the time of trial unblinding in March 2021, the mRNA-1273 received Emergency Use Authorization in December 2020 and full FDA approval in January 2022.

1. Introduction

The Brighton Collaboration (www.brightoncollaboration.org) Viral Vector Vaccine Safety Working Group (V3SWG) was formed in 2008 in recognition of the increasing importance of viral vectors for the development of new vaccines and the need to understand their associated safety issues [1]. To better meet the needs of many other platform technologies used to develop vaccines to prevent COVID-19 beyond just vaccines using viral vectors, the V3SWG was renamed to Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group in July 2020. The BRAVATO WG has developed standardized templates to describe the key characteristics of several major vaccine platform technologies, including nucleic acid vaccines [90]. When completed (usually in a partnership between BRAVATO WG and the vaccine developer), the BRAVATO template helps answer key questions related to the essential safety and benefit-risk issues relevant for the intrinsic properties of the candidate vaccine to facilitate scientific discourse among key stakeholders [2]. The World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) has endorsed the use of the template "as it is a structured approach to vaccine safety" [91,92].

This paper uses a BRAVATO nucleic acid template to review the features of Moderna's rapid-response proprietary vaccine platform based on an mRNA delivery system used to develop the Moderna COVID-19 Vaccine (mRNA-1273). Moderna and the National Institute of Allergy and Infectious Disease (NIAID) within the National Institutes of Health (NIH) collaborated on the pre-clinical and early clinical development of the vaccine. The Moderna COVID-19 vaccine has a labelled indication to prevent coronavirus disease 2019 (Covid-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (see Table 1).

2. Background

While DNA vaccines have been under development since the early 1990s, RNA vaccines have reached clinical stage only in the past decade [3]. The scientific advances which enables the applica-

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tion of this technology for vaccines were initially reported in the 1990s [4]. An RNA vaccine is typically a synthetic messenger RNA molecule that encodes the immunogen of interest. In contrast to a DNA vaccine, an RNA vaccine is translated directly within the cytoplasm of the cell without the need to be transported into the nucleus for transcription; thus, there is no concern regarding insertional mutagenesis. Similar to a DNA vaccine, the de novo intracellular synthesis of the immunogen of an RNA vaccine stimulates both B- and T-cell responses. Due to the greater lability of RNA compared with DNA, more care has to be given to their formulation. RNA and DNA vaccines have, in theory, a distinct advantage of rapid development and deployment, especially in the context of emerging pandemics, because the manufacture of a specific vaccine is primarily dependent on the nucleic acid sequence of the antigen(s) of interest of the target pathogen, rather than growth of the pathogen. In December 2020, the Food and Drug Administration issued Emergency Use Authorizations for the Pfizer-BioNTech BNT162b2 and the mRNA 1273 COVID-19 vaccines. More recently, both vaccines were fully licensed for use (Comirnaty® on December 16, 2021, and SPIKEVAX® on January 31, 2022).

2.1. Moderna mRNA platform

Moderna used its rapid-response proprietary vaccine platform based on an mRNA delivery system, to rapidly develop a highly effective COVID-19 vaccine in 2020. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s) within intracellular or extracellular compartments. By specifying the relevant sequence, the mRNA can direct expression of the protein either

Table 1
Brighton Collaboration: Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid Vaccines.

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines		
1. Authorship	**Information**	
1.1 Author(s) and affiliation(s)	Brett Leav, Walter Straus, Phil White, Alison Leav, Tashawnee Gaines, Grace Maggiacomo	
1.2. Date completed/updated	May 24, 2022 (The data lock point for this review is February 15, 2022)	
2. Basic Vaccine information	**Information**	**Comments/Concerns**
2.1 Vaccine name	Moderna COVID-19 Vaccine, 0.20 mg/mL dispersion for injection (COVID-19 mRNA Vaccine [nucleoside modified]) SPIKEVAX® (Brand name approved in US and Europe) [78].	
2.2 Nucleic Acid Type: DNA, RNA, self-amplifying RNA	Messenger RNA (mRNA) [26]	
2.3 Adjuvant (if applicable)	n/a	
2.4 Final vaccine formulation components that may impact delivery into cells, stability, and safety (e.g. complexing with polymers, encapsulation within microparticles, liposomes)	This vaccine contains polyethylene glycol/macrogol (PEG) as part of PEG2000-DMG, ionizable amino lipid heptadecan-9-yl 8 ((2 hydroxyethyl) (6 oxo 6-(undecyloxy)hexyl)amino)octanoate lipid, Cholesterol, (1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC)), (1,2-Dimyristoyl-*rac*-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG)), trometamol, trometamol hydrochloride, acetic acid, sodium acetate trihydrate, sucrose, and water for injections [26,27].	
2.5 Route and method of delivery (e.g. intramuscular injection, gene gun, electroporation)	0.10 mg mRNA (embedded in lipid nanoparticles) by intramuscular (IM) injection [26].	
3. Target Pathogen and Population	**Information**	**Comments/Concerns**
3.1 What is the target pathogen?	SARS-CoV-2	It is believed that SARS-CoV-2 has zoonotic origins, and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the betacoronaviruses. SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause. The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus). SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~ 50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV)" [53].
3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:		
• In healthy people	There is a broad spectrum of symptomatic infection, including mild (81%), severe (e.g. with dyspnea/hypoxia, 14%), critical (e.g. with respiratory failure, shock, or multiorgan dysfunction, 5%), and resulting in death (2.3% overall case fatality rate). Asymptomatic infections have been reported between 30% and 40%. Pneumonia is the most frequent serious manifestation, characterized by fever, cough, dyspnea, and abnormal chest imaging. Upper respiratory tract symptoms, myalgias, diarrhea, and smell or taste disorders, are also common.	

Table 1 (*continued*)

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines	
	Complications of COVID-19 include respiratory failure; cardiac and cardiovascular; thromboembolic; neurologic; other inflammatory/autoimmune complications (e.g., Guillain-Barre syndrome, Multisystem Inflammatory Syndrome in Children [MIS-C]); and secondary infections. Prolonged symptoms and long-term sequelae of COVID-19 (aka "long COVID" or "Post-COVID Conditions"), including post-intensive care syndrome (persistent impairments in cognition, mental health, and/or physical function following survival of critical illness) are being reported with emerging data. Over the course of the pandemic the fatality rates of hospitalized patients have declined in high-income countries, but this may not be the case in countries with limited resources [28].
• In immunocompromised people	Certain underlying medical conditions characterized by impairments in the immune system appear to increase the risk of complications from COVID-19. These include cancer (solid organ and hematologic), solid organ transplantation, iatrogenic immune suppression, human immunodeficiency virus infection and other immune deficiencies. The strongest evidence supports cancer as an underlying risk (CDC medical conditions increasing risk of severe illness from COVID-19). Prolonged SARS-CoV-2 infection and shedding. There is evidence of viral evolution during infection and treatment (hospitalized patients) and low antibody/neutralization titers to SARS-CoV-2 variants [28,29,43,72-76].
• In neonates, infants, and children:	Children are at lower risk of symptomatic infection than adults. Most children with COVID-19 have mild symptoms or are asymptomatic. However, infants under 1 year old and children with certain medical conditions might be at increased risk of severe illness: asthma or chronic lung disease; diabetes; genetic, neurologic, or metabolic conditions; congenital heart disease; immunosuppression; multiple complexity; and obesity. MIS-C, a Kawasaki-like inflammatory condition involving the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs, has been observed in healthy children with COVID-19 [28,30,31].
• During pregnancy and in the fetus	Limited data to date indicates that pregnant women might be at increased risk for severe illness from SARS-CoV-2 infection. Pregnant women have disproportionately higher rates of COVID-19-associated hospitalizations compared to nonpregnant women. Severe illness (intensive care 15%, mechanical ventilation 8%, and death 1%) and pregnancy losses occur for 2% of hospitalized women; the later are experienced by both symptomatic and asymptomatic women [32,68]. Pregnant women with symptomatic COVID-19 compared to non-pregnant people are at higher risk of ICU admission, invasive ventilation, extracorporeal membrane oxygenation and death [32,83].
• **In** elderly	The risk for severe illness from COVID-19 increases with age, with older adults at highest risk. In the United States 80% of COVID-19 deaths reported in the U.S. have been in adults 65 years and older (16% of COVID-19 cases). The risk increases for people in their fifties and increases in sixties, seventies, and eighties. People 85 and older are the most likely to experience severe COVID-19 disease [33].
• In any other special populations	People with the following conditions are at increased risk of severe illness from COVID-19: cancer (solid organ and hematologic), chronic kidney disease, chronic obstructive pulmonary disease, immunocompromised state from solid organ transplant, obesity (BMI of 30 or higher), serious heart conditions, sickle cell disease, asthma (moderate to severe), cerebrovascular disease, hypertension, immunocompromised state from blood or bone

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Table 1 (*continued*)

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines		
	marrow transplant, immune deficiencies, HIV, steroid use or other immunomodulators, neurologic conditions, liver disease, pulmonary fibrosis, smoking, thalassemia, and type 1 and 2 diabetes mellitus. In an analysis by Stokes et al. of approximately 300,000 COVID-19 cases in the US, the mortality rate was 12 times as high among patients with reported co-morbidities compared to patients with none [34,35,81,84].	
3.3 Briefly, what are the key epidemiologic characteristics of the disease caused by the target pathogen (e.g. incubation period, communicable period, route/s of transmission, case fatality rate, transmissibility characteristics such as basic reproductive ratio (R_0), and spontaneous mutation)?	The incubation period is on average 4 to 5 days but can be as long as 14 days. Available data indicate that persons may be infectious 1–3 days before their symptom onset. Persons with mild to moderate COVID-19 remain infectious no longer than 10 days after symptom onset, whilst those with more severe to critical illness or severe immunocompromise likely remain infectious no longer than 20 days after symptom onset. Asymptomatic individuals might transmit the infection. Routes of transmission include contact and droplet (primary); airborne; fomite; mother-to-child, and other possible modes. A basic reproductive number (R0) for COVID-19 is estimated to be between 2 and 4. The crude global case fatality ratio is roughly 3% and varies widely between countries, from less than 0.1% to over 25% [28,36-40].	
3.4 What sections of the population are most affected by the target pathogen (e.g. pediatric, pregnant, lactating women (breast-feeding), adult, elderly)?	Data indicating that infants, older adults, pregnant women, and persons with certain medical conditions or with multi-morbidities (see 5.2) are at increased risk for severe illness from COVID-19. Men with COVID-19 have higher risk of all-cause death, severe infection, or ICU admission than women; the excess risk is not explained by age and comorbidities. Multiple large observation studies have concluded that HIV infection is associated with more severe COVID-19 disease, higher rates of hospitalization, and higher rates of mortality. Race and ethnicity are also risk factors for severe illness. In the United States the following racial and ethnic groups, American Indian, Alaska Natives, Asian, Black, or African American, and Hispanic or Latin-x, are at higher risk for illness, hospitalization, and death compared with White, Non-Hispanic Persons [28,41-44,81].	
3.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?	Challenge studies with other human coronavirus suggest that several immunological parameters (serum IgG, IgA, neutralizing titer, and mucosal IgA) may serve as correlates of protection. In animal models, elicitation of high titers of neutralizing antibodies targeting the receptor binding domain (RBD) of the spike (S) protein are protective against re-challenge with SARS-CoV-2. Correlates of protection, however, have not yet been established in humans [45,95]. While no clearly defined antibody titer threshold predictive of protection from SARS-CoV-2 has been defined, neutralizing antibody titers appear to be predictive of protection from symptomatic infection. The relative contribution of humoral and cellular immunity to prevention and resolution of SARS-CoV-2 infection is not currently known. Thus, it will be important to study other responses such as T cell responses or B cell memory responses as additional potential correlates of protection.	In an outbreak of SARS-CoV-2 on a fishing vessel with high (>85%) attack rate, neutralizing antibodies correlate with protection from SARS-CoV-2 [45].
3.6 Please describe any other key information about the target pathogen or population that may inform benefit-risk	Serum chemistry, hematological, and immunological laboratory markers: Certain abnormal results have been associated with poor prognoses in COVID-19 disease, including lymphopenia, thrombocytopenia, elevated liver enzymes (AST and ALT), elevated lactate dehydrogenase (LDH), elevated inflammatory markers and inflammatory cytokines, elevated D-dimer, elevated prothrombin time (PT), elevated troponin, elevated creatine phosphokinase (CPK), and acute kidney injury [79]. Viral Factors: There have been conflicting studies published discussing a potential association between	

Table 1 (*continued*)

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines		
	higher viral RNA levels in respiratory specimens and disease severity. Viral RNA detection in the blood has been associated with severe disease including outcomes such as organ damage, coagulopathy, and mortality. Genetic Factors: Host genetic factors are currently undergoing evaluation for associations with severe COVID-19 disease [28,46,47].	
4. Characteristics of Vaccine Transgene and Expression	**Information**	**Comments/ Concerns**
4.1 Nature of the nucleic acid platform (**DNA** - synthetic, bacterial, plasmid, linear, >1 type/molecule, other; **RNA-** messenger, self-replicating, other)	mRNA-1273 encodes for the prefusion stabilized spike (S)protein based on the sequence of the Wuhan strain of SARS-CoV-2. The starting materials are adenosine triphosphate, cytidine triphosphate, guanosine triphosphate, modified uridine triphosphate and the DNA template (linearized plasmid) from which the RNA is transcribed [26].	
4.2 Gene(s) incorporated into the vaccine (antigen, T-cell epitopes, antibiotic resistance factors, cytokines, other)	mRNA-1273 includes a 5′ cap, a 5′ untranslated region (UTR), an Open Reading Frame ORF), a3′ UTR, and a 3′ polyA tail. The S protein derived from the Wuhan strain of SARS-CoV-2 is stabilized in the so-called prefusion conformation by two amino acid mutations, K986P, V987P [26,48,49].	
4.3 Factors enhancing/controlling gene expression	To enable translation, the mRNA has a 5′-cap and a 3′-polyA tail [26].	
4.4 Non-expressed features impacting vaccine efficacy (CpG sequences, other)	mRNA-1273 lipid nanoparticle (LNP) is a mRNA-lipid complex [lipid nanoparticle (LNP)] mixture that contains an mRNA that encodes for the pre-fusion stabilized Spike (S) protein of SARS-CoV-2. mRNA-1273 LNP is prepared in a multi-step process incorporating the mRNA and the lipids to form LNPs. The LNPs comprise 4 lipids to encapsulate and protect the mRNA: ionizable amino lipid heptadecan-9-yl 8 ((2 hydroxyethyl)(6 oxo 6-(undecyloxy)hexyl)amino) octanoate lipid (the custom-manufactured ionizable lipid) is positively charged to drive lipid to interact with the mRNA; cholesterol is included to provide structure and stability to the particles; the zwitterionic lipid, DSPC, is incorporated to increase the fusogenic properties of the particles; the polyethylene glycol-lipid conjugate, PEG2000-DMG, confers steric stabilization of the nanoparticles [26].	
4.5 Other sequence features that may impact safety (e.g. sequences in DNA that might facilitate insertion or recombination)	Nucleoside-modified mRNA containing N1-methylpseudouridine instead of uridine [26,50].	
4.6 Is the sequence likely to induce immunity to all strains/genotypes of the target pathogen?	No, but sera from participants immunized on a prime-boost schedule with the mRNA-1273 COVID-19 vaccine were tested for neutralizing activity against several SARS-CoV-2 variants, including variants of concern (VOCs) and variants of interest (VOIs), compared to neutralization of the wild-type SARS-CoV-2 virus (designated as D614G), the strain used in the vaccine. Results showed minimal effects on neutralization titers against the B.1.1.7 (Alpha) variant (1.2-fold reduction compared with D614G); other VOCs such as B.1.351 (Beta, including B.1.351-v1, B.1.351-v2, and B.1.351-v3), B.1.617.2 (Delta), and P.1 (Gamma) showed decreased neutralization titers ranging from 2.1-fold to 8.4-fold reductions compared with D614G, although all remained susceptible to mRNA-1273–elicited serum neutralization. More recently the neutralizing antibody titers against the B.1.529 (Omicron) variant were shown to be reduced by 35-fold compared with D614G one month after receipt of a priming series of mRNA-1273 and 8.4-fold reduced after 6 months and 2.9-fold reduced after receipt of a 50 μg dose [51,52,85].	

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Table 1 (*continued*)

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines		
4.7 What is known about the immune response to the vaccine in animals and/or humans (binding, functional, and neutralizing antibody, B-cell, T-cell memory, etc.)?	mRNA-1273 is immunogenic in all species (mice, hamsters, NHPs) assessed, showing a dose-dependent response in IgG binding antibody titers and a significant correlation between binding and neutralizing antibody activity. Additionally, antigen-specific T-cell responses are detected in mice and in NHPs [55-57].	
5. Delivery and Administration	**Information**	**Comments/ Concerns**
5.1 Describe how components of the vaccine formulation that facilitate stability* and delivery into cells (Section 2.4) impact the safety profile of the vaccine?		The lipid nanoparticle is comprised of four lipids in addition to the mRNA drug substance to form an mRNA-lipid complex (lipid nanoparticle [LNP]) [31]. The four lipids are cholesterol; IONIZABLE AMINO LIPID HEPTADECAN-9-YL 8 ((2 HYDROXYETHYL)(6 OXO 6-(UNDECYLOXY)HEXYL)AMINO)OCTANOATE LIPID; DSPC; and PEG2000 DMG. The LNP protects the mRNA from endogenous nuclease and other chemical degradation and also serves as the delivery vehicle to the target cells. The excipient components of the formulation buffer, Sucrose, Tromethamine Hydrochloride (Tris) and Acetate are generally regarded as safe (GRAS) and not expected to impact safety. Moderna's mRNA vaccines containing these LNP components are designed to produce an immune response intended to prevent disease. Nonclinical toxicology studies demonstrate this expected immunologic response and have exhibited a similar safety profile regardless of the antigen. In most cases, findings appear to be driven by injection site reactions that result in transient systemic inflammatory responses, which are likely attributed to one or more of the vaccine components. This response is consistent in nature with other vaccine products, lacking any major target organs and resolves rapidly [56].
* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed important for safety purposes. For example, among the risks that WHO, FDA, and EMA list for the use of DNA vaccines is the hazard of integration into recipient's chromosomal DNA with the resulting risk of insertional mutagenesis or spreading of antibiotics resistance genes. The probability of chromosomal integration increases if the introduced pDNA has been linearized, and this is the reason that regulatory authorities require the plasmid preparation intended for vaccination or gene therapy to contain a high percentage of supercoiled material (usually > 80%). The percentage of supercoiled material is also used as a criterion of DNA vaccine stability at different storage temperatures.		
5.2 Describe how the mode of vaccine delivery may impact safety *(e.g., electroporation (please specify name of device), intradermal needle injection)		Standard IM injection
* Also consider the safety impact of multi-dose delivery methods, the use of multi dose vaccine vials, and any special considerations for disposal.		
5.3 How might any co-administered components (e.g. adjuvants, cytokines, immunomodulatory molecules) impact the safety profile?	Not applicable	
5.4 If applicable, describe the heterologous prime-boost regimen that this vaccine is a part of and the possible impact on safety	Homologous and heterologous booster vaccines had an acceptable safety profile and were immunogenic in adults who had completed a primary Covid-19 vaccine regimen at least 12 weeks earlier [86].	
6. Toxicology and Nonclinical	**Information**	**Comments/ Concerns**
6.1 What is known about biodistribution of the platform nucleic acid in its final formulation and mode of administration in animal models?	Biodistribution was assessed in Sprague Dawley rats using a similar mRNA-based vaccine formulated in IONIZABLE AMINO LIPID HEPTADECAN-9-YL 8 ((2 HYDROXYETHYL)(6 OXO 6-(UNDECYLOXY)HEXYL) AMINO)OCTANOATE LIPID –containing LNPs. The time after dosing at which the maximum concentration of mRNA was observed (Tmax) in plasma was 2 h and was followed by a rapid elimination phase with a t1/2 estimated to range from 2.7 to 3.8 h. The highest mRNA concentrations were observed at the injection site followed by the proximal (popliteal) and distal (axillary) lymph nodes, consistent with distribution via the lymphatic system. Overall, only a relatively small fraction of the administered mRNA dose distributed to distant tissues, and the mRNA did not persist past 1 to 3 days in tissues other than the injection site, lymph nodes, and spleen [26].	
6.2 How long does the RNA or DNA persist in vivo (may specify in tissue/serum, proximal/distal to site of administration)?	The plasma T1/2 is estimated to be in a range from 2.7 to 3.8 h. T1/2 was 14.9 h for muscle of site of injection, 34.8 h for proximal lymph nodes, 31.1 h for distal lymph nodes, and 63.0 h for spleen [53].	

Table 1 (*continued*)

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines		
6.3 What is the risk of integration of sequences from the platform nucleic acid into the host genome?	Considered highly unlikely since the mechanism of action of the vaccine requires translation by ribosomes outside of the nucleus. The physical separation of mRNA from the host DNA and absence of reverse transcriptase, makes this scenario very unlikely.	
6.4 What is the possible risk of autoimmunity or a harmful immune response?		*NOTE: These references are from external sources and reflect the opinions of outside investigators and organizations and do not necessarily reflect Moderna's perspective on these issues* People with autoimmune conditions were included in COVID-19 vaccine clinical trials. No imbalances were observed in the occurrence of symptoms consistent with autoimmune conditions or inflammatory disorders in clinical trial participants who received COVID-19 vaccine compared to placebo. People with autoimmune conditions may receive any FDA-authorized COVID-19 vaccine [54].
6.5 Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products	Repeat dose toxicity studies were conducted, 6 GLP studies with other IONIZABLE AMINO LIPID HEPTADECAN-9-YL 8 ((2 HYDROXYETHYL)(6 OXO 6-(UNDECYLOXY)HEXYL)AMINO)OCTANOATE LIPID LNP-encapsulated mRNA vaccines and one non-GLP study with mRNA-1273. Nonclinical toxicity studies demonstrate the expected immunologic response with mRNA vaccines and have exhibited a similar safety profile regardless of the translated antigen. In most cases, findings appear to be driven by injection site reactions that result in a transient systemic inflammatory or activation of the immune system. This response is consistent in nature with other vaccine products, lacking any major target organs and resolves rapidly. In vitro and in vivo genotoxicity studies were conducted in accordance with regulatory guidelines with IONIZABLE AMINO LIPID HEPTADECAN-9-YL 8 ((2 HYDROXYETHYL)(6 OXO 6-(UNDECYLOXY) HEXYL)AMINO)OCTANOATE LIPID and IONIZABLE AMINO LIPID HEPTADECAN-9-YL 8 ((2 HYDROXYETHYL)(6 OXO 6-(UNDECYLOXY)HEXYL) AMINO)OCTANOATE LIPID -containing LNPs, respectively. In vitro studies demonstrated no evidence of genotoxic potential. In two in vivo studies, SM-102-containing LNPs were shown to be negative or have slightly positive findings; the latter of which could have been caused by other toxicological findings (e.g., hyperthermia, disturbance of erythropoiesis, cytokine changes, etc.) at high systemic doses. Collectively, the genotoxic potential is considered to be low. A GLP-compliant developmental and reproductive toxicity (DART) study in pregnant female Sprague Dawley rats was conducted at the human clinical (100 μg/dose) dose. There were no effects on female fertility, embryo-foetal or post-natal survival, growth or development in the F1 offspring [53,77].	
6.6 Summarize the preclinical immunogenicity and efficacy data that supports the use of this product in humans including any related information from similar products	Nonclinical studies in mice, hamsters, and NHPs evaluated mRNA-1273-induced immune responses, protection from high-dose virus SARS-CoV-2 challenge. The studies demonstrated that mRNA-1273 was immunogenic in all species assessed, showing a dose-dependent response in IgG binding antibody titers and a significant correlation between binding and neutralizing antibody activity. In addition, antigen-specific T-cell responses were observed in studies in mice and in the NHP study. Th1-directed CD4 and CD8 T-cell responses were measured post-boost in animals that were vaccinated with mRNA-1273. mRNA-1273 vaccination of nonhuman primates induced strong SARS-CoV-2 neutralizing activity with no detectable viral replication and limited inflammation. Th1 response levels were higher than in the control group in both the 100-μg dose and in the 10-μg dose,	

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Table 1 (*continued*)

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines		
	with the former eliciting the highest Th1 response levels. Viral replication prevention in the upper and lower airways was observed in the vaccinated NHPs, and not in the control group, after a challenge with SARS-CoV-2. The results of Corbett et al. complement the immunogenicity and safety data established by a phase 1 clinical study with humans [26,55].	
6.7 What is the evidence of disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD).) or absence thereof *in vitro* or in animal models? [14]	The following studies address the theoretical concern of enhanced respiratory disease mediated by vaccine-induced antibody responses and/or Th2-directed T-cell responses observed with other vaccines against viral respiratory diseases. Direct measurement of Th1-directed responses in mice and NHPs, indirect measurement of IgG2a/c/IgG1 antibody subclasses in mice, and the high levels of neutralizing antibody in all species lessened concerns regarding disease enhancement associated with administration of mRNA-1273. In addition, mice, NHPs, and hamsters were challenged with high-dose SARS-CoV-2 virus. In these studies, dose levels were included that were predicted to be optimal (fully protective) and suboptimal (sub protective). At higher doses, mice and NHPs were fully protected from viral replication in both lungs and nasal passages. At sub protective dose levels, animals either remained fully protected in the lungs or had reduced viral burden post-challenge versus control animals. There were no observations of increased viral load in vaccinated animals at protective or sub protective dose levels, further supports that mRNA-1273 does not drive enhanced disease. No evidence of Th2 biased antibodies with lower IgG2a/IgG1 subclass response ratios nor pathological changes, consistent with VAERD were observed in the lungs of either mRNA-1273 vaccine dose groups 1 week after challenge [56,57].	
6.8 Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit- risk?	Double stranded mRNA can activate pattern recognition receptors (PRRs) such as TLR3 and TLR7/8 in endosomes, cytosolic sensors like MDA5 and RIG-I, and NOD-like receptors (NLRs). This signaling process results in innate immune activation which triggers the adaptive immune system. The manufacture process including purification, codon optimization, and bases replacement are used to modulate innate immune activation to balance immune response and reactogenicity. The benefit-risk of this activity is heavily weighted toward benefit [58].	
7. Human Efficacy and Other Important Information	**Information**	**Comments/ Concerns**
7.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g. natural history, passive immunization, animal challenge studies)?	In the pivotal phase 3 placebo-controlled randomized trial (NCT04470427), there were 185 participants with symptomatic Covid-19 illness in the placebo group, (56.5 per 1000 person years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P < 0.001 Thirty participants in the trial had severe Covid-19; all 30 were in the placebo group consistent with vaccine efficacy of 100% [95% CI, could not be estimated to 1.0]), and one death among these participants was attributed to Covid-19. The vaccine efficacy to prevent Covid-19 was consistent across subgroups stratified by demographic and baseline characteristics: age groups (18 to <65 years of age an.65 years), presence of risk for severe Covid-19, sex, and race and ethnic group (non-Hispanic White and communities of color) [59]. At the time of the final analysis of the blinded phase of the phase 3 study, vaccine efficacy to prevent COVID-19 was 93.2% [95% CI 91.0 to 94.8] and to prevent severe disease was 98.2% [95% CI 92.8 to 99.6%]. Vaccine efficacy remained consistent across	

Table 1 (*continued*)

Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines
ethnic and racial groups, age groups and amongst participants with coexisting medical conditions [25]. During the open-label period of the phase 3 study, when participants originally randomized to placebo received mRNA-1273, relative vaccine effectiveness of the more recent administration of mRNA-1273 compared with vaccination at the time of randomization. The analysis, conducted during the period of the emergence of the delta variant showed a 36.4% [95% CI 17.1 to 51.5%] lower risk of COVID-19 infection in more recently vaccinated study participants [59]. The phase 1, dose-escalation, open-label trial (NCT04283461) was designed to identify the optimal dose for further clinical development. The trial enrolled 85 healthy adults, 18 years of age and older, who received two vaccinations, 28 days apart, with mRNA-1273 in a dose of 25 μg, 100 μg, or 250 μg. There were 10–15 participants in each dose group. Across all age groups, adverse reactions were more common after second dose and the rates of reactions tended to increase with magnitude of the dose. After the second vaccination, more than half of the participants in the 250-μg group reported fever; one of the events (maximum temperature, 39.6 °C) was graded severe. Systemic adverse events were more common after the second vaccination, particularly with the highest dose, and three participants (21%) in the 250-μg dose group reported one or more severe adverse events. Older adults received only the 25 and 100 μg dose of vaccine. At the time of the interim analysis, through Day 57, no serious adverse events had been reported. Across all age cohorts, with each dose of vaccine, antibody responses, assessed by both binding and neutralizing assays, increased with higher dose. Regardless of dose and age, the immune response in adults after two doses of vaccine was comparable to the median titer of convalescent serum. Considering the greater immune response of the 100 and 250 μg cohorts after 2 doses and balanced by the increased reactogenicity seen in younger adults who received the 250-μg dose, the 100-μg dosage was considered the optimal balance of safety and benefit in terms of immune response [43,44]. Nearly all study participants in the phase 1 study had detectable neutralizing antibody responses 180 days after any of the second dosed of vaccine [93]. The phase 2, randomized, observer-blind, placebo-controlled trial (NCT04405076) was designed to confirm the dose of mRNA-1273 selected for use in the pivotal phase 3 trial. Six-hundred participants were stratified into two age cohorts (18-<55 and > 55) and were randomly assigned (1:1:1) to either 50 or 100 μg of mRNA-1273, or placebo administered as two intramuscular injections 28 days apart. The primary outcomes were safety, reactogenicity, and immunogenicity assessed by anti-SARS-CoV-2-spike binding antibody level (bAb). Secondary outcome was immunogenicity assessed by SARS-CoV-2 neutralizing antibody (nAb) response. mRNA-1273 induced bAb and nAb by 28 days post-vaccination one that were higher at the 100-μg dose relative to the 50-μg dose; this difference was less apparent postvaccination two. Binding antibodies and nAb increased substantially by 14 days following the second vaccination (day 43) to levels exceeding those of convalescent sera and remained elevated through day 57. Fourteen days following the second vaccination (Day 43), nAbs were significantly enhanced to maximum GMTs (95% CI) of 1733 (1611–1865) μg/ml at 50 μg mRNA-1273 and 1909 (1849–1971) μg/ml at 100 ug mRNA-1273 in younger adults, and 1827 (1722–1938) μg/ml at 50 ug mRNA-1273 and 1686 [1521–1869]) μg/ml at 100 μg mRNA-1273 in older adults. These GMTs were 5–6-fold higher those of the

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	convalescent COVID-19 control sera (321 [235–438] μg/ml). Little numeric change in nAb GMTs was observed at 28 days postvaccination two (Day 57) with titers remaining high for both mRNA-1273 dose levels and in both age groups. Vaccination with mRNA-1273 resulted in significant immune responses to SARS-CoV-2 in participants 18 years and older, with an acceptable safety profile, confirming the safety and immunogenicity of 50 and 100 ug mRNA-1273 given as a 2-dose regimen [45]. Clinical trial participants who received a two-dose primary series of the COVID-19 vaccine mRNA-1273 in the phase 2a study (NCT04405076,) were invited to participate in an open-label study approximately 6 months after receipt of the priming series to evaluate the safety and immunogenicity of a single 50 μg booster dose of mRNA-1273. Comparisons were made to a randomly selected subset of adults 18 years of age in the pivotal phase 3 study who received two doses of mRNA-1273. The GMT ratio of the boosted participants compared with those who received the primary series in the phase 3 study was 1.7 [95% CI 1.5 to 2.1]. The difference in the seroresponse rates of the boosted participants minus with those who received the primary series in the phase 3 study was −8.2 [95% CI −12.2 to −5.2%] [87]. The phase 2/3 randomized, placebo-controlled study (NCT04649151) was designed to demonstrate the safety and effectiveness of mRNA-1273 in adolescents 12 to < 18 years of age. The mRNA-1273 vaccine had an acceptable safety profile in adolescents. The immune response was similar to that in young adults, and the vaccine was efficacious in preventing COVID-19. The geometric mean titer ratio of pseudo virus neutralizing antibody titers in adolescents relative to young adults was 1.08 (95% confidence interval [CI], 0.94 to 1.24), and the absolute difference in serologic response was 0.2 percentage points (95% CI, −1.8 to 2.4), which met the noninferiority criterion. No cases of Covid-19 with an onset of 14 days after the second injection were reported in the mRNA-1273 group, and four cases occurred in the placebo group [59-62,82].	
7.2 Describe other key information that may impact benefit-risk	Ongoing studies are being conducted by Moderna in children 6 months to < 12 years of age (NCT04796896). A clinical study is also ongoing in patients who have undergone solid organ transplantation (NCT04860297) and a pregnancy registry is also ongoing (NCT04958304) [63,64].	
8. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):	**Information**	**Comments/Concerns**
8.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine platform, please list separately _____	More than 48,000 study participants have been exposed to either mRNA-1273, mRNA-1273.351 (modified variant vaccine), mRNA-1283 (next generation COVID-19 candidate) or placebo in the mRNA clinical development program. United States: 206,773,482 million doses administered; 75,029,472 fully immunized and 39,997,543 with a booster dose (CDC US COVID data tracker, as of February 15, 2022). EU/EEA doses administered: 186,062,144 (as of February 15, 2022) (https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab) Canada: 3,952,213 at least one dose 3,748,364 fully vaccinated and 1,734,594 fully vaccinated with an additional dose (https://health-infobase.canada.ca/covid-19/vaccination-coverage/) as of February 15, 2022.	

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Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines		
8.2 Method(s) used for safety monitoring:		
• Spontaneous reports/passive surveillance	Yes	If yes, describe method: After a vaccine is approved, using the Vaccine Adverse Event Reporting System (VAERS), the CDC and FDA conduct post-licensure vaccine safety monitoring. VAERS allows these agencies to collect and analyze spontaneously received reports of adverse events following vaccinations to ensure vaccine safety even as it is distributed to the public. All VAERS data is available to the public online. Although VAERS is a useful tool in disseminating vaccine adverse events information to the public, it generally cannot be used to determine causality between a vaccine and an adverse event. Other countries in which the product has been authorized for use maintain their own passive reporting systems. In addition, the MAH collects adverse event data reported to it directly [65].
• Diary	Yes (E-diary)	**Clinical trial experience.** Following each injection, participants recorded any ARs for 7 days in E-diary
• Other active surveillance	Yes	**Clinical trial experience.** Surveillance for COVID-19 symptoms by weekly phone calls or E-diary entries starting from enrollment and throughout the duration of the study. The presence of COVID-19 symptoms resulted in a NP swab for COVID-19. Monthly safety calls; clinic visits Days 57, 119 Serious ARs: Monitored and recorded any serious AEs observed or reported from day 1 to day 759 or to date of withdrawal from study Solicited AEs: Local and systemic, recorded 7 days post-injection in E-Diary Unsolicited AEs: Monitored and recorded any unsolicited AEs observed or reported 28 days after each injection (day of injection and 27 days subsequent) Other: MAAEs and AE's leading to discontinuation from dosing/study participation were monitored and recorded from day 1 to day 759 or to date of withdrawal from study [59]. **Post-authorization experience.** V-safe is a smartphone-based tool that uses text messaging and online surveys to provide health check ins after COVID-19 vaccinations. For v-safe reports including possible medically attended events, the CDC's v-safe call center contacts the vaccine recipient for the completion of a VAERS report.
8.3 What criteria were used for grading the AEs?		
• 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	Yes	
• If no criteria were used for grading, or if other metrics were employed, please describe:		
8.4 List and provide frequency of any related or possibly related serious* AEs and well as any severe expected or unexpected AEs observed: (*see Instructions):	**Clinical trial experience.** During the ongoing pivotal phase 3 efficacy trial, the frequency of grade 3 solicited local adverse reactions were 3.5 % after dose 1 and 7.0% after dose 2 of mRNA-1273, compared with 0.5% in placebo recipients after either dose. The frequency of grade 3 solicited systemic adverse reactions were 2.9% after dose 1 and 15.7% after dose 2 of mRNA-1273 compared with 2.0% in placebo recipients after either dose. The most common grade 3 solicited local adverse reaction was pain, 3.2% after dose 1 and 4.6% after dose 2. The most common grade 3 solicited systemic adverse reactions were fatigue, 1.1% after dose 1 and 10.6% after dose 2, and myalgia, 0.6% after dose 1 and 10.0% after dose 2. Grade 3 axillary lymphadenopathy was reported in 0.3% vs 0.2% vaccine/placebo recipients after dose 1 and in 0.5% vs 0.1% of vaccine/placebo recipients after dose 2. Grade 3 swelling was reported in 6.7% vs 0.3% vaccine/placebo recipients after dose 1 and in 12.6% vs. 0.3% vaccine/placebo after dose 2. Grade 3 erythema was reported in 3.0% vs 0.4%	

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	vaccine/placebo after dose 1 and in 9.0% vs. 0.4% vaccine/placebo after dose 2. The most frequently reported systemic reactions that persisted beyond 7 days in vaccine recipients/placebo recipients 18 to 64 years were fatigue (5.7%/5.0%), headache (4.8%/4.0%), myalgia (2.7%/2.7%), and arthralgia (2.6%/2.8%); in the older cohort were fatigue (5.8%/4.5%), arthralgia (3.7%/3.8%), myalgia (2.9%/2.7%), and headache (2.8%/2.7%). As of 25 November 2020, there were 12 SAE assessed as related to study product, 7 reported by mRNA-1273 recipients and 5 reported by placebo recipients. The 7 related SAE in mRNA-1273 recipients were: intractable nausea and vomiting, facial swelling reported by two vaccine recipients with a history of injection of dermatological fillers, rheumatoid arthritis, dyspnea with exertion and peripheral edema, autonomic dysfunction and B-cell lymphocytic lymphoma. The proportion of participants who reported severe unsolicited AEs was 1.4% following any vaccine dose (275 participants) and 1.3% following any placebo dose (225 participants). The most frequently reported severe AEs that occurred in greater numbers of vaccine than placebo recipients were headache, myalgia, arthralgia, injection site erythema, and injection site pain. Medically attended adverse events (MAAE) from dose 1 through 28 day following any dose were reported for 8.0% of participants in the vaccine group and 8.4% of those in the placebo group. The majority of these events were considered not related to study vaccinations and were primarily attributed to local and systemic reactogenicity following vaccinations. Hypersensitivity adverse events were reported in 1.5% of vaccine recipients and 1.1% of placebo recipients. Hypersensitivity events in the vaccine group included injection site rash and injection site urticaria, which are likely related to vaccination. It is not known what component(s) of the vaccine are related to hypersensitivity reactions. Delayed injection site reactions that began > 7 days after vaccination were reported in 1.2% of vaccine recipients and 0.4% of placebo recipients. Delayed injection site reactions included pain, erythema, and swelling and are likely related to vaccination. As of December 3, 2020, 13 deaths were reported (6 vaccine, 7 placebo). Seven deaths occurred in the placebo group (three from myocardial infarction, one from intraabdominal perforation, one from systemic inflammatory response in a participant with chronic lymphocytic leukemia and diffuse bullous rash, one from COVID-19, one from unknown cause. Six deaths occurred in the vaccine group (two from participants older than 75 years of age with preexisting cardiac disease, one from, two from uncertain cause [70 year old participant with cardiac, 56 year old participant with hypertension and chronic back pain being treated with opioid medication (official cause of death was head trauma)], one from 72 year old participant with Crohn's disease and short bowel syndrome who was hospitalized for thrombocytopenia and acute kidney failure due to obstructive nephrolithiasis and developed complications resulting in multiorgan failure and death, and one by suicide [53,59,66,67,71,89]. At the conclusion of the blinded period of the phase 3 study on March 26, 2021 with a median of 212 days of safety follow up from randomization and 183 days from the second dose, the frequencies of solicited local and systemic adverse events were consistent with those reported previously, with such events occurring less frequently in the placebo group (in 48% and 43% of participants after the first and second injections, respectively) than in the mRNA-1273

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	group (88% and 92%). The frequencies of unsolicited, severe, and serious adverse events reported during the 28 days after either injection were generally similar in the two groups in the overall safety population, regardless of age or risk factors for severe Covid-19. Hypersensitivity reactions were reported in 1.8% of placebo recipients and in 2.2% of vaccine recipients, with anaphylaxis occurring in 2 participants (<0.1%) in each group.Dermal filler reactions were reported in 14 placebo recipients (<0.1%) and in 20 mRNA-1273 recipients (0.1%) with a history of dermal filler injections. Three cases of Bell's palsy (<0.1%) were reported in the placebo group and 8 in the mRNA-1273 group (<0.1%); no case was considered to be related to the placebo or the vaccine. Thromboembolic events were observed in 43 placebo recipients (0.3%) and in 47 mRNA-1273 recipients (0.3%). No cases of myocarditis were reported. Pericarditis events occurred in 2 participants each (<0.1%) in the placebo and mRNA-1273 groups (both events > 28 days after the second dose) and were considered serious. A total of 32 deaths had occurred by completion of the blinded phase, with 16 deaths each (0.1%) in the placebo and mRNA-1273 groups; no deaths were considered to be related to injections of placebo or vaccine, and 4 were attributed to Covid-19 (3 in the placebo group and 1 in the mRNA-1273 group) [25]. A group of participants in the Phase 2a study (NCT04405076) consented to receive a 50 μg booster dose of mRNA-1273 at least 6 months (range of 5.8 to 8.5 months) after the priming series. A similar percentage of participants in this study compared with participants who received priming doses of mRNA-1273 in the pivotal phase 3 study re reported solicited adverse reactions. No serious adverse events were reported through 28 days after receiving the booster dose [87]. **Post Marketing Experience.** In April 2021, reports from Israel and the US Department of Defense indicated that cases of myocarditis and pericarditis were being observed in recipients of the COVID mRNA vaccines. Initial findings from Israeli and US military studies prompted researchers, vaccine manufacturers, and public health agencies, including the CDC, to further investigate a potential association between myocarditis and mRNA COVID-19 vaccination [96,97]. These reports were followed by analyses conducted using VAERS, the Vaccine Safety Datalink, and by VAST, which characterized this finding through the identification of reporting rates by age, gender, dose, and time to onset. For the Moderna COVID-19 vaccine, VAERS reported that the rate per million first doses among 17–39-year-olds within 21-day risk window was 7.5 (95% CI 2.4–17.6)); for second doses 19.8 (95% CI 9.9–35.5) [68,98,99]. These findings concluded that the events occurred mostly in adolescents and young adults (median age for mRNA COVID-19 vaccines 24 years (range 12–87):, in males more than females (66% and 79% males, following first and second doses, respectively), and were typically observed within 4 days following vaccination – more commonly after the second dose of vaccine. Although reports of myocarditis and pericarditis have been reported following the receipt of adenovirus vectored COVID vaccines, the association is much stronger following receipt of an mRNA vaccine. It is considered a class effect. Public health interest has subsequently focused upon myocarditis, which is more commonly observed than pericarditis. Myocarditis was reported at a rate of 14.6 per million in 12- to 39-year-olds for all mRNA vaccines through the VSD and VAERS as of February 2022 [88].

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	The mechanistic basis for the finding is not yet understood, although the differential risk by gender and age suggests a hormonal contribution (effect of testosterone). The CDC introduced a case definition for use in identifying suspected cases of myocarditis and pericarditis [100]. The Brighton Collaboration has also introduced case definitions for this purpose [101]. The clinical course of myocarditis observed following receipt of a COVID-19 vaccine is distinct from that associated with other causes of myocarditis, including SARS-CoV-2 infection. Preliminary results of a CDC led survey of 360 individuals (and their providers) aged 18–29 years, reporting myocarditis following COVID mRNA vaccination, 81% had probably/fully recovered (1% had residual cardiac findings). Vaccine associated cases tend to be mild, self-limited, and resolve with conservative management within 1–2 weeks [102]. Thesefindingscontracts with classicviralmyocarditis and MIS-C-myocarditis [103]. Anaphylaxis was reported at an initial estimated rate of 2.5 anaphylaxis cases per million first mRNA-1273 vaccine doses administered.	
8.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccine vs. control groups:	There were no statistically significant differences in serious AEs or lab abnormalities [25,59].	
Describe the control group: _____.	The control group received a placebo (0.9% sodium chloride (normal saline) injection) [59].	
8.6 List and provide frequency of Adverse Events of Special Interest	AESIs prospectively monitored during clinical trials: Multisystem Inflammatory syndrome in children (MIS-C) (NCT04649151): No cases reported [82].	
8.7 What is the evidence of disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) (if any) in humans?	After the second dose of vaccine, the majority of COVID-19 cases occurred in the placebo group rather than the group that received mRNA-1273, confirming no clinical evidence for vaccine enhanced disease associated with mRNA-1273 vaccination during the short-term observation period of this initial report [59].	
8.8 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?	Yes	
Did it identify any safety issue of concern? • If so describe	No	
9. Overall Risk Assessment	**Information**	**Comments/ Concerns**
9.1 Please summarize key safety issues of concern identified to date, if any:	**Post marketing Experience.** Myocarditis and Pericarditis: The risk of myocarditis and pericarditis was estimated to be 25.5 excess cases per million mRNA COVID-19 vaccine doses administered following dose 2 in 18 to 39-year-olds. The rate of myocarditis was higher after dose 2 compared to dose 1, 4.6 cases per million doses administered [60,88]. Updates were made to the Moderna Fact Sheet to include information regarding the occurrence of myocarditis and pericarditis following vaccination. Post marketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 18 through 24 years of age. Although some cases required intensive care support, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management. Information is not yet available about potential long-term sequelae [89]. Anaphylaxis: Anaphylaxis, a potentially life-threatening allergic reaction, has been reported rarely following mRNA-1273 vaccination. Information about anaphylaxis and signs of a severe allergic reaction is included in the Moderna Fact Sheet [68].	
How should they be addressed going forward	Anaphylaxis: [104] The CDC currently recommends an observational period of 30 min for those who have a history of immediate allergic reaction or 15 min for all other people. The CDC also notes that emergency medical	

Table 1 (*continued*)

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	equipment to treat anaphylaxis should be readily available at vaccination locations and that the second dose of mRNA-1273 should not be given to those who experienced anaphylaxis following the first dose. Myocarditis and Pericarditis: Healthcare professionals should be aware of possible symptoms of myocarditis and pericarditis including chest pain (acute or persisting), shortness of breath, or palpitations after vaccination. Subjects should be instructed to seek immediate medical attention if they develop these symptoms following vaccination [54,69,71,89].	
9.2 What is the potential for causing serious unwanted effects and toxicities in:	**Describe the toxicities**	**Please rate risk as:** **none, minimal, low, moderate, high, or unknown**
• healthy humans?	Myocarditis, pericarditis, and anaphylaxis (see section 9.1)	
• immunocompromised humans?	Long-term data is not yet available, and data for the use of mRNA-1273 in immunocompromised populations and use in subjects with autoimmune/ inflammatory disorders and comorbidities are still limited. Therefore, diligent follow-up and surveillance practices are essential for continued vaccine safety monitoring and determining the ongoing risk–benefit analysis of mRNA-1273. **Immunocompromised Population:** Immune response to the mRNA-1273 vaccine may have a diminished immune response in immunocompromised persons, including individuals receiving immunosuppressant therapy. The safety and efficacy of SPIKEVAX® in immunocompromised people continues to be monitored and studied in observational and clinical studies. The safety, efficacy, and benefit of additional doses of COVID-19 vaccines in immunocompromised persons will continue to be evaluated in clinical trials. There are currently insufficient data to make conclusions about the safety of the vaccine in the subpopulation of immunocompromised individuals [53,80]. A third priming dose of mRNA-1273 has been authorized under emergency use (EUA) for use in immunocompromised adults. **SOT Population:** Unknown	Insufficient Data
• human neonates, infants, children?	There are currently insufficient data to make conclusions about the safety of the vaccine in the subpopulation of children less than 12 years of age [53].	Insufficient Data
• pregnancy and in the fetus in humans?	In the P301 trial, pregnant or breastfeeding women were excluded from participation. However, during the clinical trial thirteen pregnancies were reported through December 2, 2020 (6 vaccine, 7 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (2 vaccine, 3 placebo), within 30 days after LMP in 5 participants (2 vaccine, 3 placebo), >30 days after LMP in 2 participants (1 vaccine, 1 placebo), and date of LMP not known in 1 participant (1 vaccine, 0 placebo). Unsolicited AEs related to pregnancy include a case of spontaneous abortion and a case of elective abortion, both in the placebo group. One participant in the placebo group is lost to follow-up. Pregnancy outcomes are otherwise unknown at this time There are currently insufficient data to make conclusions about the safety of the vaccine in the subpopulation of pregnant and lactating individuals [53,59,70].	Insufficient Data
• elderly?	No significant toxicities identified to date In subgroup analyses of adults $\geq$ 65 years of age, rates of solicited reactions (any, Grade 3 or higher) and all other unsolicited adverse events (AEs) (all and related) were comparable to those observed in all participants [53,59].	Minimal
• in any other special populations (e.g., institutionalized people, individuals with associated chronic comorbidity)?	Unknown	

on the cell surface, within an intracellular compartment or secreted as a virus-like particle. The precision and standardization of the mRNA platform enable rapid development and efficient manufacturing scale-up of vaccines without reliance on a process that requires growth of the pathogen. The delivered mRNA does not enter the cell nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The half-life for mRNA after injection is dependent on normal cellular processes for degradation but this can be modulated by modifications of the sequence and the formulation of the drug product [5].

The mRNA is chemically similar to naturally occurring mammalian mRNA with the exception that the uridine nucleoside normally present is fully replaced with N1-methyl-pseudouridine, a naturally occurring pyrimidine base present in mammalian transfer RNAs [6,7]. This nucleoside is included in the mRNA in place of the normal uridine base to minimize inflammatory response to the mRNA by pathogen-associated molecular pattern receptors [8]. The cap structure used in the mRNA is identical to the natural mammalian Cap 1 structure [9,10]. The effective delivery of mRNA-based vaccines and therapies is enabled by the use of lipid nanoparticles (LNPs), which protect nucleic acid degradation by exo- and endonucleases [11,12] and facilitate cellular uptake and expression [13,14,78], Used in both the Pfizer/BioNTech and Moderna COVID-19 mRNA vaccines, this delivery system is particularly effective as it leverages LNP surface properties [15-18], the ability of LNPs to facilitate endosomal escape through ionization of the amino lipid [19,20] and tissue-specific mRNA delivery based on particle size [21]. Together, these features improve vaccine immunogenicity. The components of the LNP system are well characterized and understood and in the most part rapidly metabolized. The ionizable amino lipid component appears to be the primary driver of LNP potency and tolerability, and therefore a key differentiator in tolerability appears to be the design of the ionizable amino lipid to increase biodegradability [22] as has been achieved in the Moderna proprietary lipid SM-102.

Moderna currently has nineteen (19) vaccines and therapeutics in clinical trials based on this platform [23]. Moderna COVID-19 vaccine is delivered via intramuscular injection, and the immune response depends on mRNA uptake by antigen presenting cells at the injection site and draining lymph nodes. After delivery, the mRNA utilizes the cell's translational machinery to produce the spike protein, which after proper assembly and processing is trafficked to the cell membrane for display to the immune system. Upon translation into a target protein antigen, the endogenous RNAses of the cell degrade the mRNA, provide a natural limit to the duration of drug product [26].

2.2. The Moderna COVID-19 vaccine (mRNA-1273)

The Moderna COVID-19 vaccine stimulates innate immune responses, resulting in the production of proinflammatory cytokines and type 1 interferon. This process activates B-cell and T-cell responses from the adaptive immune system. The mRNA-1273 vaccine directly activates B-cells, including memory B-cells, resulting in the secretion of antibodies that bind and neutralize SARS-CoV-2 viruses. The mRNA-1273 vaccine also directly activates T-cells, which eliminate infected cells and support B-cell responses and induces a Th1-biased CD4 T-cell responses in humans [24].

To characterize the nonclinical immunogenicity and efficacy of mRNA-1273, Moderna and the Vaccine Research Center of the NIAID performed nonclinical studies in mice, hamsters, and NHPs to evaluate mRNA-1273-induced immune responses, protection from high-dose virus SARS-CoV-2 challenge, and to address the theoretical concern of enhanced disease mediated by vaccine-induced antibody responses and/or Th2-directed T-cell responses observed with other vaccines against viral respiratory diseases. Overall, nonclinical animal studies demonstrated that the mRNA-1273 vaccine is immunogenic, fully protects animals from challenge at optimal dose levels, and does not drive enhanced disease at protective or sub protective dose levels. The initial clinical development of Moderna COVID-19 vaccine was also conducted in collaboration with NIAID through the phase 1 dose-ranging first in human trial of the vaccine (NCT04283461).

The primary efficacy objective of the Phase 3 pivotal study was met, with the efficacy of the Moderna COVID-19 vaccine to prevent symptomatic COVID-19 disease observed to be 94.1% after more than 151 cases accrued at the time of the interim analysis [59]. The vaccine was highly efficacious in preventing severe COVID-19 and in preventing COVID-19 regardless of prior SARS-CoV-2 infection. The population included adults with risk factors for complications of COVID-19, including older age and underlying medical comorbidities, in addition to racial and ethnic minority groups that have been disproportionately affected by COVID-19. In an exploratory subgroup analysis, the estimates of efficacy of the mRNA-1273 vaccine against symptomatic COVID-19 disease was comparable across the demographic groups analyzed, including older adults and younger adults with pre-existing medical risk factors. The estimates of efficacy remained high against COVID-19 and severe COVID-19 at the time of the final analysis of the blinded phase of the study and was also consistent across subgroups [25].

The mRNA-1273 vaccine safety profile during clinical development is largely based on data from the pivotal Phase 3 study. Solicited local and systemic adverse reactions were more common in participants who received the mRNA-1273 vaccine compared with placebo, and systemic adverse reactions were more common after the second injection. The majority of these reactions occurred within the first 1 to 2 days after administration of mRNA-1273 and persisted for a median of 2 to 3 days or less. The overall incidences of unsolicited adverse events (AEs) reported up to 28 days after vaccination and serious adverse events (SAEs) reported throughout the entire study were similar in participants who received the Moderna COVID-19 vaccine or placebo. There were fewer cases of severe COVID-19 or COVID-19 in participants who received the mRNA-1273 vaccine compared with placebo, and no evidence of vaccine-associated enhanced respiratory disease has been observed. The safety profile of mRNA-1273 remained consistent at the time of the final blinded analysis, with a median of over 6 months of safety follow up [25,93]. Additional safety data beyond this time frame were not available at the time of publication and are a potential limitation of this review.

Post marketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The observed risk is higher among males under 30 years of age with an estimate of 40.6 cases per million second doses of mRNA COVID-19 vaccine [94]. The observed risk is highest in males 18 through 24 years of age. Although some cases [88] required hospitalization, available data from short-term follow-up suggest that most individuals have had resolution of symptoms with conservative management [89]. Information is not yet available about potential long-term sequelae [71,89]. The mRNA-1273 vaccine SPIKEVAX® received full FDA approval on January 31, 2022. It should be noted that the data lock point for this review is February 15, 2022, and an attempt was made to include all publicly available information and data from peer-reviewed publications prior to that time in this manuscript.

3. Disclaimer

The findings, opinions, conclusions, and assertions contained in this consensus document are those of the individual members of the Working Group. They do not necessarily represent the official

positions of any participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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