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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: COVID vaccine trials

There have been three FDA phase 2/3 efficacy trials of COVID vaccines: Pfizer BNT162b2, Moderna mRNA-1273, and J&J Ad26.COV2.S. One vaccine has been approved for routine use (Pfizer) and the other two have been approved for emergency use. The three trials together involved 113,000+ participants (43,548, 30,420, and 39,321 = 113,289), evenly divided between vaccine and placebo.

According to Wikipedia the Food and Drug Administration granted emergency use authorization to the Pfizer–BioNTech vaccine on December 10, 2020; mass vaccinations began on December 14, 2020. The Moderna vaccine was granted emergency use authorization on December 17, 2020, and the Janssen (Johnson & Johnson) vaccine was granted emergency use authorization on February 27, 2021. By April 19, 2021, all U.S. states had opened vaccine eligibility to residents aged 16 and over. On May 10, 2021, the FDA approved the Pfizer-BioNTech vaccine for adolescents aged 12 to 15. On August 23, 2021, the FDA granted full approval to the Pfizer–BioNTech vaccine for individuals aged 16 and over. (https://en.wikipedia.org/wiki/COVID-19_vaccination_in_the_United_States)

Conclusions, as stated in the abstracts of the publications, are reproduced below.

Pfizer publication

A two-dose regimen of BNT162b2 conferred 95% protection against COVID-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

Moderna publication

The mRNA-1273 vaccine showed 94.1% efficacy at preventing COVID-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified. (Funded by the Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases; COVE Study Group; ClinicalTrials.gov number, NCT04470427.)

J&J publication

A single dose of Ad26.COV2.S protected against symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection and was effective against severe–critical disease, including hospitalization and death. Safety appeared to be similar to that in other phase 3 trials of COVID-19 vaccines. (Funded by Janssen Research and Development and others; ENSEMBLE Study Group; ClinicalTrials.gov number, NCT04505722.)

The primary analyses in all three trials were “per protocol”, that is, limited to those treated as specified in the study protocol.

The preferred primary analysis is “intention to treat” or “per assignment”, that is, analysis in which all persons randomized are counted regardless of whether they received the assigned treatment

and regardless of whether treatments were “per protocol”. The trouble with “per protocol” analyses is the potential for bias since only those treated in accordance with the protocol are counted.

In the Pfizer trial there were 8 cases of COVID-19 with onset at least 7 days after the second dose among persons assigned to receive the vaccine, compared to 162 cases among those receiving placebo, producing a relative effectiveness rate of

$$(162 - 8)/162 = 0.95$$

The CONSORT chart in the publication lists 304 in the vaccine assigned group and 316 in the placebo assigned groups not included in the effectiveness analysis for reasons listed below.

Reason for exclusion	Vaccine assigned	Placebo assigned
Withdrawn	100	96
Not eligible	0	86
Lost to followup	62	61
Ongoing or pending status	56	46
No longer eligible	51	0
Adverse event	28	18
Pregnant	4	5
Withdrawn	2	2
Medication error	0	1
Died	1	1
	304	316

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The purpose herein is to summarize the three trials as gleaned from information in ClinicalTrials.gov and the three publications.

Table 1: ClicalTrials.gov

	Pfizer	Moderna	J&J
Registration no.	NCT04368728	NCT04470427	NCT04505722
Date registered	27 July 2020	11 July 2020	31 July 2020
1 st person enrolled	29 July 2020	27 July 2020	7 Sep 2020
Results posted	No	No	No
Anticipated completion date	15 May 2023	27 October 2022	Jan 2023
Sponsors & collaborators	BioNTech SE & Pfizer	ModernaTX, Inc., Biomedical Advanced Research & Development Authority, & NIAID	Janssen Vaccines & Prevention B.V.

Table 2: Primary publication

	Pfizer	Moderna	J&J
Journal	NEJM	NEJM	NEJM
Title	Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine	Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine	Safety and efficacy of single-dose Ad26.COV2.S vaccine against COVID-19
Masthead format	Authors & corporate name	Authors & corporate name	Authors & corporate name
Authors	29	36	30
Corporate name	Clinical Trials Group	COVE Study Group	ENSEMBLE Study Group
Date published	16 Dec 2020	30 Dec 2020	21 Apr 2021
Study sites	152	99	219
US study sites	130	99	117

Table 3: Design features

	Pfizer	Moderna	J&J
Study treatments	2	2	2
Test treatment	BNT162b2 mRNA COVID-19 vaccine	mRNA-1273 SARS-CoV-2 vaccine	Ad26.COV2.S COVID-19 vaccine
Control treatment	Matching placebo	Matching placebo	Matching placebo
Doses	Two, 21 days apart	Two, 28 days apart	Single dose
Treatment assignment	1:1 random	1:1 random	1:1 random
Stratification variables	Not specified	Age & COVID status	Not specified
Study sites	152	99	219
US based	130	99	117
Masked	Double	Double	Double
Data monitoring committee	Yes	Yes	Yes
Primary analysis	Per protocol	Per protocol	Per protocol
Effectiveness estimate	95%	94.1%	66.9%

Table 4: Study groups: Randomized and per protocol counts

		Total	Vaccine	Placebo	% vac	% plbo
Randomized						
	Pfizer	43,448	21,720	21,728	49.99%	50.01%
	Moderna	30,420	15,210	15,210	50.00%	50.00%
	J&J	44,325	?	?		
	Total	118,193	36,930	36,938		
Per protocol						
	Pfizer	37,086	18,556	18,530	50.04%	49.96%
	Moderna	28,207	14,134	14,073	50.11%	49.89%
	J&J	39,321	19,630	19,691	49.92%	50.08%
	Total	104,614	52,320	52,294	50.01%	49.99%

Table 5: Composition per protocol

			Vaccine	Placebo	%	%
Age						
	Pfizer	Mdn	52	52		
	Moderna	Mean	51.4	51.3		
	J&J	Mdn	52	52		
Gender; male						
	Pfizer	19,075	9,639	9,436	50.53%	49.47%
	Moderna	15,985	8,062	7,923	50.43%	49.57%
	J&J	24,053	12,071	11,982	50.19%	49.82%
	Total	59,113	29,927	29,496	50.63%	49.90%
Ethnicity; white						
	Pfizer	31,266	15,636	15,630	50.01%	49.99%
	Moderna	23,984	12,029	11,955	50.15%	49.85%
	J&J	25,696	12,858	12,838	50.04%	49.96%
	Total	80,946	40,523	40,423	50.06%	49.94%