From: Felberbaum, Michael [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4819A643CA2945CDB1A2631B83E69673-MICHAEL.FEL]
Sent: 4/25/2022 4:30:33 PM
To: Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]; Jefferson, Erica [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0bc0bd0f8766484b803f584eb491ace6-Erica.Jeffe]
Subject: Re: draft
Attachments: 20220429 AHCJ FDA Priorities MF Edits.docx

Updated attached in tracked changes. Welcome your thoughts!

From: Felberbaum, Michael <Michael.Felberbaum@fda.hhs.gov>
Sent: Sunday, April 24, 2022 9:26:16 PM
To: Califf, Robert <(b) (6)@fda.hhs.gov>; Jefferson, Erica <Erica.Jefferson@fda.hhs.gov>
Subject: Re: draft

I'll have to censor myself a bit. ☺

From: Califf, Robert <(b) (6)@fda.hhs.gov>
Sent: Sunday, April 24, 2022 9:24:50 PM
To: Felberbaum, Michael <Michael.Felberbaum@fda.hhs.gov>; Jefferson, Erica <Erica.Jefferson@fda.hhs.gov>
Subject: Re: draft

Yes; I think it would be fun to let you write that part! What should they do (or not do)?

rmc

From: Michael Felberbaum <Michael.Felberbaum@fda.hhs.gov>
Date: Sunday, April 24, 2022 at 3:06 PM
To: Robert Califf <(b) (6)@fda.hhs.gov>, Erica Jefferson <Erica.Jefferson@fda.hhs.gov>
Subject: Re: draft

Thank you! Will take a closer look. What would you think about leaning in more on what journalists can do to help build public trust (or at least not purposefully try to erode it further for the sake of sensationalism and clicks)?

From: Califf, Robert <(b) (6)@fda.hhs.gov>
Sent: Sunday, April 24, 2022 3:01:05 PM
To: Felberbaum, Michael <Michael.Felberbaum@fda.hhs.gov>; Jefferson, Erica <Erica.Jefferson@fda.hhs.gov>
Subject: draft

FDA Priorities

AHC Journalists

April 29th, 2022


(b)(5) Draft


(b)(5) Draft


(b)(5) Draft

From: Jefferson, Erica [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0BC0BD0F8766484B803F584EB491ACE6-ERICA.JEFFE]
Sent: 4/27/2022 11:21:03 PM
To: Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]
CC: Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]
Subject: Re: JAM with Peter on vax process for under 5

No we're dealing with 27 parents who want to take their 2 and 3 year olds to Turks and Caicos and Europe this summer. I know (b) (6)

From: Califf, Robert <(b) (6)@fda.hhs.gov>
Sent: Wednesday, April 27, 2022 9:17 PM
To: Jefferson, Erica
Cc: Tierney, Julia; Fristedt, Andi; McBride, Maren; Klimczak, Katherine
Subject: Re: JAM with Peter on vax process for under 5

Ha

For better or worse, we're not dealing with those people here…

rmc

From: Erica Jefferson <Erica.Jefferson@fda.hhs.gov>
Date: Wednesday, April 27, 2022 at 11:06 PM
To: Robert Califf <(b) (6)@fda.hhs.gov>
Cc: Julie Tierney <Julia.Tierney@fda.hhs.gov>, Andi Fristedt <Andi.Fristedt@fda.hhs.gov>, Maren McBride <Maren.McBride@fda.hhs.gov>, "Klimczak, Katherine" <Katherine.Klimczak@fda.hhs.gov>
Subject: Re: JAM with Peter on vax process for under 5

Ok, fair enough. We'll work with Peter on providing a example or two. But, I'm trying to think through how we'd explain what is involved in a statistical analysis to people who still think ivermectin and a Z-pac are still viable Covid-19 treatment options.

From: Califf, Robert <(b) (6)@fda.hhs.gov>
Sent: Wednesday, April 27, 2022 9:03 PM
To: Jefferson, Erica
Cc: Tierney, Julia; Fristedt, Andi; McBride, Maren; Klimczak, Katherine
Subject: Re: JAM with Peter on vax process for under 5

This is good, but not what I was looking for. I don't think people have a clue as to what's involved in actually reviewing the application once it comes in the door. Or why would it take 6 weeks after we get the full application and data? I've been on all sides of this, and the number of issues that can come up and the work

involved is well known to people at FDA and people in the industry. I need a good description for Friday anyway, as at that point, that will be the question.

rmc

From: Erica Jefferson <Erica.Jefferson@fda.hhs.gov>
Date: Wednesday, April 27, 2022 at 8:15 PM
To: Robert Califf <(b) (6)@fda.hhs.gov>
Cc: Julie Tierney <Julia.Tierney@fda.hhs.gov>, Andi Fristedt <Andi.Fristedt@fda.hhs.gov>, Maren McBride <Maren.McBride@fda.hhs.gov>, "Klimczak, Katherine" <Katherine.Klimczak@fda.hhs.gov>
Subject: JAM with Peter on vax process for under 5

Hi Rob –

As discussed, Peter will be filming a "Just a Minute" video tomorrow afternoon (12:00 p.m.) answering the question you asked: "What is the process for making a COVID-19 vaccine available to children under five years old?" We will move quickly to edit post on Friday, nearly synced with the planned VRBPAC release. I'm attaching the script.

Please let me know if you have any questions or thoughts.

Thanks,
Erica

Erica V. Jefferson (she/her)
Associate Commissioner for External Affairs
U.S. Food and Drug Administration
Tel: 240-702-3994
erica.jefferson@fda.hhs.gov

Executive Assistant: Kristen.Tugwell@fda.hhs.gov (temporary)

From: Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]
Sent: 4/12/2022 9:18:28 PM
To: Walensky, Rochelle P (CDC) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=df848b046e3947be9b8809afe76917e9-HHS-aux7-cd]
Subject: FW: Research letter on Corticosteroid/COVID-19 work published today in JAMA
Attachments: jama_bradley_2022_ld_220020_1649354358.18365.pdf

Here ya go…

I really do believe we could move the needle by more consistent professional detailing. Its painful to see people die or suffer needlessly when a simple vax would prevent most and for the remainder there is effective treatment.

I'm going to send you another one that is in press that tells one of the important stories in our socially determined health outcomes.

rmc

From: Patrizia Cavazzoni <Patrizia.Cavazzoni@fda.hhs.gov>
Date: Sunday, April 10, 2022 at 4:24 PM
To: Robert Califf <(b) (6)@fda.hhs.gov>
Subject: Research letter on Corticosteroid/COVID-19 work published today in JAMA

This was just published by our pharmacoepi group.
Patrizia

Letters

RESEARCH LETTER

Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021

In June 2020, preliminary results for the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial conducted in the UK indicated benefit from dexamethasone in severely ill hospitalized patients with COVID-19 but potential harm in those not requiring oxygen.[1,2] In October 2020, the National Institutes of Health (NIH) issued COVID-19 treatment guidelines advising against systemic corticosteroid use in patients with mild to moderate COVID-19.[1] Using 2 large US health care claims databases, we examined systemic corticosteroid use among nonhospitalized patients with COVID-19.

Supplemental content

Methods | Data from Medicare fee-for-service and the US Food and Drug Administration's (FDA's) Sentinel System were used. Medicare is a federal health insurance program mostly serving those aged 65 years or older.[3] The Sentinel System comprises primarily claims data from commercially insured patients of all ages in a distributed network of data partners.[4] The Sentinel Rapid COVID-19 data source used in this analysis included 2 national insurance claims data partners and 2 integrated delivery care systems.

Nonhospitalized, noninstitutionalized patients with incident COVID-19 between April 2020 and August 2021 (July 2021 for Sentinel) were included. Incident outpatient COVID-19 was defined as a diagnosis code for COVID-19 or positive SARS-CoV-2 laboratory test (Sentinel only) recorded on an outpatient claim, including emergency department claims without subsequent hospitalization. Those with COVID-19 within the prior 183 days and those with use of systemic corticosteroids within the prior 90 days were excluded. Patients were followed up from COVID-19 diagnosis date until the earliest occurrence of a claim for a new oral or injectable corticosteroid in an outpatient setting, hospitalization, death, disenrollment, or 14 days. Demographics, clinical characteristics, and among corticosteroid initiators, corticosteroid type, timing, setting of initiation, prescriber specialty, and concomitant therapies were examined (eTable in the Supplement).

Table. Characteristics and Comorbidities of Patients With COVID-19 and Those Initiating Systemic Corticosteroids Within 14 Days of Diagnosis

	Medicare (April 1, 2020-August 31, 2021)			US FDA's Sentinel System (April 1, 2020-July 31, 2021)		
	COVID-19 diagnosis	Corticosteroid use[a]	Rate, %[b]	COVID-19 diagnosis	Corticosteroid use[c]	Rate, %[b]
Demographic and clinical characteristics						
Total No. of patients	576 885	94 781	16.4	766 105	72 124	9.4
Age, mean (SD), y	74.6 (7.2)	74.4 (6.9)		48.5 (19.9)	57.7 (16.7)	
Age group, No. (%), y						
<44				339 385 (44.3)	18 008 (25.0)	5.3
45-64				204 350 (26.7)	23 552 (32.7)	11.5
65-79	443 664 (76.9)	74 300 (78.4)	16.7	176 533 (23.0)	24 811 (34.4)	14.1
≥80	133 211 (23.1)	20 481 (21.6)	15.4	45 837 (6.0)	5753 (8.0)	12.6
Sex, No. (%)						
Male	249 044 (43.2)	42 516 (44.9)	17.1	357 697 (46.7)	32 988 (45.7)	9.6
Female	327 841 (56.8)	52 265 (55.1)	15.9	408 408 (53.3)	39 136 (54.3)	9.2
Race and ethnicity, No. (%)[d]						
Asian	9391 (1.6)	1080 (1.1)	11.5	19 210 (2.5)	1146 (1.6)	6.0
Black or African American	26 425 (4.6)	3048 (3.2)	11.5	50 417 (6.6)	4530 (6.3)	9.0
Hispanic	14 423 (2.5)	1944 (2.1)	13.5	53 420 (7.0)	4453 (6.2)	8.3
Native American	3226 (0.6)	409 (0.4)	12.7	2965 (0.4)	280 (0.4)	9.4
Native Hawaiian/other Pacific Islander				3738 (0.5)	329 (0.5)	8.8
White	500 563 (86.8)	85 302 (90.0)	17.0	298 976 (39.0)	30 797 (42.7)	10.3
Other[e]	6971 (1.2)	862 (0.9)	12.4			
Unknown	15 886 (2.8)	2136 (2.3)	13.4	390 799 (51.0)	35 042 (48.6)	9.0
US region, No. (%)[f]						
Northeast	104 929 (18.2)	8864 (9.4)	8.4	139 333 (18.2)	7284 (10.1)	5.2
Midwest	135 261 (23.5)	20 394 (21.5)	15.1	152 091 (19.9)	11 792 (16.3)	7.8
South	241 340 (41.8)	53 437 (56.4)	22.1	302 766 (39.5)	43 523 (60.3)	14.4
West	94 553 (16.4)	12 056 (12.7)	12.8	161 097 (21.0)	9167 (12.7)	5.7

(continued)

Table. Characteristics and Comorbidities of Patients With COVID-19 and Those Initiating Systemic Corticosteroids Within 14 Days of Diagnosis (continued)

	Medicare (April 1, 2020-August 31, 2021)			US FDA's Sentinel System (April 1, 2020-July 31, 2021)		
	COVID-19 diagnosis	Corticosteroid use[a]	Rate, %[b]	COVID-19 diagnosis	Corticosteroid use[c]	Rate, %[b]
Comorbidities, No. (%)						
Hematologic cancer	10 798 (1.9)	1784 (1.9)	16.5	4159 (0.5)	581 (0.8)	14.0
Congestive heart failure	40 961 (7.1)	7022 (7.4)	17.1	22 893 (3.0)	3285 (4.6)	14.3
Hospitalized acute myocardial infarction	2173 (0.4)	319 (0.3)	14.7	1147 (0.1)	85 (0.1)	10.9
Hypertension	351 427 (60.9)	59 589 (62.9)	17.0	217 346 (28.4)	30 880 (42.8)	14.2
Stroke or transient ischemic attack	1890 (0.3)	261 (0.3)	13.8	1098 (0.1)	85 (0.1)	7.7
Chronic kidney disease	65 747 (11.4)	10 770 (11.4)	16.4	40 355 (5.3)	5559 (7.7)	13.8
Diabetes	148 235 (25.7)	24 070 (25.4)	16.2	110 730 (14.5)	14 733 (20.4)	13.3
Taking immunosuppressant therapies	33 600 (5.8)	5625 (5.9)	16.7	15 702 (2.0)	2122 (2.9)	13.5
Obesity	90 793 (15.7)	17 250 (18.2)	19.0	104 244 (13.6)	15 416 (21.4)	14.8
Chronic obstructive pulmonary disease	41 908 (7.3)	9892 (10.4)	23.6	26 625 (3.5)	5581 (7.7)	21.0
Asthma	30 596 (5.3)	6706 (7.1)	21.9	32 055 (4.2)	5123 (7.1)	16.0
Rheumatologic and inflammatory conditions	37 238 (6.5)	6669 (7.0)	17.9	28 411 (3.7)	4042 (5.6)	14.2
Smoking	69 016 (12.0)	12 191 (12.9)	17.7	51 602 (6.7)	7215 (10.0)	14.0
Combined Charlson and Elixhauser comorbidity indices[g]						
Mean (SD)	0.8 (1.8)	0.8 (1.8)		0.5 (1.4)	0.7 (1.7)	
Median (IQR)	0 (0-1.0)	0 (0.1-1.0)				

[a] A total of 13 007 eligible patients (2.25%) were censored because they died, were disenrolled, or were hospitalized within 14 days after COVID-19 diagnosis.

[b] Calculated as corticosteroid use/outpatient COVID-19 diagnosis.

[c] A total of 336 eligible patients (<1%) were censored because they died or were disenrolled and 29 960 (3.9%) because they were hospitalized within 14 days after COVID-19 diagnosis.

[d] In Sentinel, race and ethnicity were separate variables, so a patient could have both a race and Hispanic ethnicity; therefore, the percentages do not equal 100%.

[e] Patients reported "other" and did not select another category.

[f] A small percentage of patients were not categorized into a region; therefore, the percentages do not equal 100%.

[g] The assessment period was 183 days prior to COVID-19 diagnosis. Additional details appear in the Supplement.

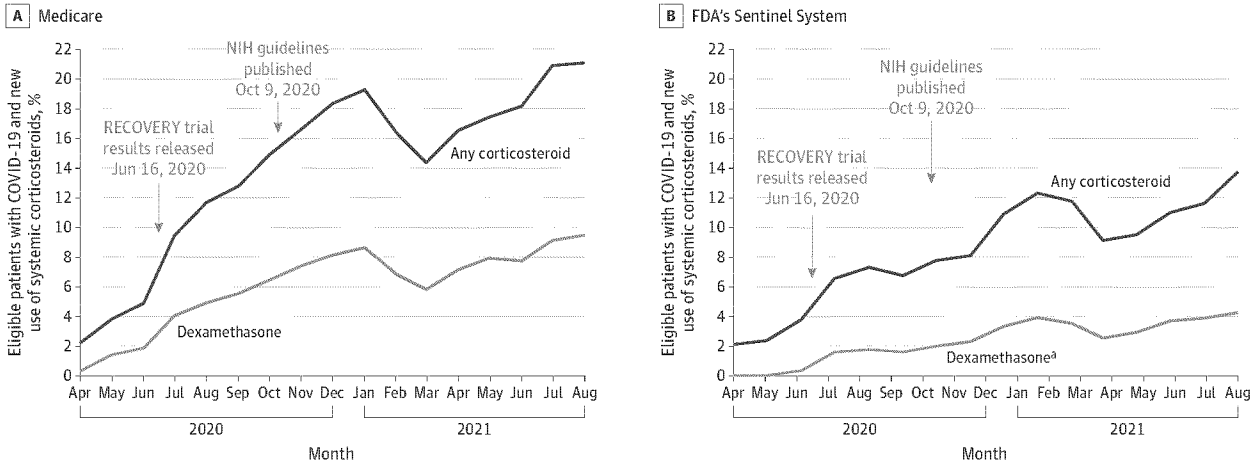
Analyses were descriptive and performed using SAS version 9.4 (SAS Institute Inc). This study was classified as public health surveillance by the FDA and exempted from review by the institutional review board in accordance with the updated Common Rule.

Results | There were 576 885 eligible patients with COVID-19 in Medicare and 766 105 in Sentinel, the mean age was 74.6 years (SD, 7.2 years) and 48.5 years (SD, 19.9 years), respectively, and the proportion of males was 43.2% and 46.7% (**Table**). Of these, 16.4% in Medicare and 9.4% in Sentinel received systemic corticosteroids in an outpatient setting within 14 days of COVID-19 diagnosis (**Figure**). The proportion of patients initiating corticosteroids in the South was higher than in any other region. Use increased with age until approximately 79 years. Corticosteroid use increased over time from 2.2% initiating in April 2020 to 21.1% in August 2021 in Medicare, and from 2.2% in April 2020 to 13.8% in July 2021 in Sentinel.

Among pharmacy dispensings, the most commonly used corticosteroids were dexamethasone in Medicare (43.8%) and prednisone in Sentinel (34.1%). The most common prescriber specialties in Medicare were internal medicine or family/general practice (39.9%) and emergency medicine (18.6%). Treatment often started on the day of COVID-19 diagnosis (58.8% for Medicare vs 51.3% for Sentinel), largely through pharmacy dispensings (70.8%-80.3%) rather than during medical encounters. On the day corticosteroid use was initiated, 24.7% in Medicare had visited the emergency department vs 22.9% in Sentinel. Azithromycin was the most common concomitant therapy (44.8% for Medicare vs 48.8% for Sentinel)—often initiated on the same date as the corticosteroid—followed by monoclonal antibodies (Medicare: 7.1%; Sentinel: 2.0%), inhaled corticosteroids (Medicare: 2.4%; Sentinel: 6.7%), ivermectin (Medicare: 3.9%; Sentinel: 3.5%), and nonoral anticoagulants (Medicare: 3.6%; Sentinel: 3.1%).

Discussion | Despite NIH recommendations, increasing numbers of nonhospitalized patients with COVID-19 were prescribed systemic corticosteroids, often on the day of diagnosis. Use appeared to be more prominent in the South and was not restricted to older patients. Limitations of the study included inability to capture date of symptom onset and indication for use, and potential for misclassifying mild to moderate COVID-19 disease due to overburdened resources and limited ability to accurately capture elements to define disease severity, including oxygen use. Given the increasing use of corticosteroids through August 2021, the potential safety signal,[2,5,6] and the lack of efficacy data in patients with mild to moderate COVID-19,[1] it is critical that prescribers consider the NIH guidelines in the therapeutic management of nonhospitalized patients with COVID-19.

Figure. Proportion of Patients With COVID-19 Initiating Systemic Corticosteroids Within 14 Days of Diagnosis



FDA indicates Food and Drug Administration; NIH, National Institutes of Health; RECOVERY, Randomised Evaluation of COVID-19 Therapy.

[a] The name of the corticosteroid was only available for pharmacy dispensings.

Marie C. Bradley, PhD, MPharm, MScPH
Silvia Perez-Vilar, PhD, PharmD
Yoganand Chillarige, MPA
Diane Dong, RN, MPH
Ashley I. Martinez, PharmD, PhD
Andrew R. Weckstein, BA
Gerald J. Dal Pan, MD, MHS

Author Affiliations: Office of Surveillance and Epidemiology, US Food and Drug Administration, Silver Spring, Maryland (Bradley, Perez-Vilar, Dal Pan); Acumen LLC, Burlingame, California (Chillarige); Department of Veterans Affairs Center for Medication Safety, Hines, Illinois (Dong); Department of Population Medicine, Harvard Medical School, Boston, Massachusetts (Martinez); Aetion Inc, New York, New York (Weckstein).

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Corresponding Author: Marie C. Bradley, PhD, MPharm, MScPH, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20903 (marie.bradley@fda.hhs.gov).

Author Contributions: Mr Chillarige and Dr Martinez had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bradley, Perez-Vilar, Chillarige, Martinez, Weckstein, Dal Pan.
Acquisition, analysis, or interpretation of data: Bradley, Perez-Vilar, Chillarige, Dong, Martinez, Weckstein.
Drafting of the manuscript: Bradley, Perez-Vilar.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Chillarige, Dong, Martinez, Weckstein.
Obtained funding: Dal Pan.
Administrative, technical, or material support: Bradley, Martinez, Weckstein, Dal Pan.
Supervision: Bradley, Perez-Vilar, Chillarige, Dal Pan.

Conflict of Interest Disclosures: Mr Chillarige reported receiving personal fees from Acumen LLC. Mr Weckstein reported being employed by and having an ownership interest (stock options or existing equity) in Aetion, a technology company that provides analytic software and services to the health care industry. No other disclosures were reported.

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Role of the Funder/Sponsor: The authors who were employees or contractors of the FDA, the CMS, or the Veterans Health Administration (VHA) played a role in the design; however, other officials at the FDA, the CMS, and the VHA had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The manuscript was subjected to administrative review before submission, but this review did not alter its content.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect those of the FDA, the CMS, the VHA, or the DHHS.

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1. National Institutes of Health. Therapeutic management of nonhospitalized adults with COVID-19. Updated February 1, 2022. Accessed March 30, 2022. https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/

2. RECOVERY: Randomised Evaluation of COVID-19 Therapy. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. Accessed February 18, 2022. https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19

3. Centers for Medicare & Medicaid Services. Medicare program: general information. Accessed March 3, 2021. https://www.cms.gov/Medicare/Medicare-General-Information/MedicareGenInfo/index

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5. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704.

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From: Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]
Sent: 3/30/2022 9:41:46 PM
To: Kimberly, Brad [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=08bc909ed76d49868a5ff92c3c70fb72-Bradley.Kim]
CC: Colonius, Tristan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2b3590c046734a2e928858bd579ed852-Tristan.Col]; Felberbaum, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4819a643ca2945cdb1a2631b83e69673-Michael.Fel]; Garcia, Megan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6d1dd5d1aa014d28ae3712ade1f8e9bf-Megan.Garci]; Jefferson, Erica [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0bc0bd0f8766484b803f584eb491ace6-Erica.Jeffe]; Mulieri, Chris [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=298e49cef842458dad2312551ffdf184-Charles.Mul]; Rebello, Heidi [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2834ce193ca949799ef063e34a2cfa0b-Heidi.Rebel]; Taiwo, Wumi [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6c493907c6d04b9e9d166c3bfb814646-Olawumi.Tai]; Thorpe, Valarie [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4263524681134dc4a9c7f8ff9752864b-Valarie.Tho]; Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]
Subject: Re: RMC TWEETS: Ivermectin Study...

This is good. Do it!

Thx

rmc

From: Kimberly, Brad <Brad.Kimberly@fda.hhs.gov>
Date: Wednesday, March 30, 2022 at 6:44 PM
To: Califf, Robert <(b) (6)@fda.hhs.gov>
Cc: Colonius, Tristan <Tristan.Colonius@fda.hhs.gov>, Felberbaum, Michael <Michael.Felberbaum@fda.hhs.gov>, Garcia, Megan <Megan.Garcia@fda.hhs.gov>, Jefferson, Erica <Erica.Jefferson@fda.hhs.gov>, Mulieri, Chris <Charles.Mulieri@fda.hhs.gov>, Rebello, Heidi <Heidi.Rebello@fda.hhs.gov>, Taiwo, Wumi <wumi.taiwo@fda.hhs.gov>, Thorpe, Valarie <Valarie.Thorpe@fda.hhs.gov>, Tierney, Julia <Julia.Tierney@fda.hhs.gov>
Subject: RMC TWEETS: Ivermectin Study...

Good evening… looking to get your concurrence on this tweet regarding the NEJM study. We'll attach Topol's tweet to yours. His words were very strong.

CLEARED TWEETS - ROB.docx

Thanks!
Brad

Brad Kimberly
Director, Social Media

Web & Digital Services
Office of External Affairs

U.S. Food and Drug Administration
Tel: 240-402-1002 | Cell: (b) (6)
brad.kimberly@fda.hhs.gov

From: Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]
Sent: 4/27/2022 11:18:32 PM
To: Jefferson, Erica [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0bc0bd0f8766484b803f584eb491ace6-Erica.Jeffe]
CC: Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]; Fristedt, Andi [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8ebcdc6531394636a5afcb391a6c0cc3-Andi.Friste]; McBride, Maren [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b65d2b38307f4b489e266d2178c46793-Maren.Kahn]; Klimczak, Katherine [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=01a6c20534774be590c50f0d455c81de-Katherine.K]
Subject: Re: JAM with Peter on vax process for under 5

We need to send an autographed copy to Dr. Tufecki.

rmc

From: Erica Jefferson <Erica.Jefferson@fda.hhs.gov>
Date: Wednesday, April 27, 2022 at 11:06 PM
To: Robert Califf (b) (6)@fda.hhs.gov>
Cc: Julie Tierney <Julia.Tierney@fda.hhs.gov>, Andi Fristedt <Andi.Fristedt@fda.hhs.gov>, Maren McBride <Maren.McBride@fda.hhs.gov>, "Klimczak, Katherine" <Katherine.Klimczak@fda.hhs.gov>
Subject: Re: JAM with Peter on vax process for under 5

Ok, fair enough. We'll work with Peter on providing a example or two. But, I'm trying to think through how we'd explain what is involved in a statistical analysis to people who still think ivermectin and a Z-pac are still viable Covid-19 treatment options.

From: Califf, Robert < (b) (6)@fda.hhs.gov>
Sent: Wednesday, April 27, 2022 9:03 PM
To: Jefferson, Erica
Cc: Tierney, Julia; Fristedt, Andi; McBride, Maren; Klimczak, Katherine
Subject: Re: JAM with Peter on vax process for under 5

This is good, but not what I was looking for. I don't think people have a clue as to what's involved in actually reviewing the application once it comes in the door. Or why would it take 6 weeks after we get the full application and data? I've been on all sides of this, and the number of issues that can come up and the work involved is well known to people at FDA and people in the industry. I need a good description for Friday anyway, as at that point, that will be the question.

rmc

From: Erica Jefferson <Erica.Jefferson@fda.hhs.gov>
Date: Wednesday, April 27, 2022 at 8:15 PM
To: Robert Califf < (b) (6)@fda.hhs.gov>
Cc: Julie Tierney <Julia.Tierney@fda.hhs.gov>, Andi Fristedt <Andi.Fristedt@fda.hhs.gov>, Maren McBride

<Maren.McBride@fda.hhs.gov>, "Klimczak, Katherine" <Katherine.Klimczak@fda.hhs.gov>
Subject: JAM with Peter on vax process for under 5

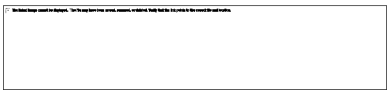
Hi Rob –

As discussed, Peter will be filming a "Just a Minute" video tomorrow afternoon (12:00 p.m.) answering the question you asked: "What is the process for making a COVID-19 vaccine available to children under five years old?" We will move quickly to edit post on Friday, nearly synced with the planned VRBPAC release. I'm attaching the script.

Please let me know if you have any questions or thoughts.

Thanks,
Erica

Erica V. Jefferson (she/her)
Associate Commissioner for External Affairs
U.S. Food and Drug Administration
Tel: 240-702-3994
erica.jefferson@fda.hhs.gov



Executive Assistant: Kristen.Tugwell@fda.hhs.gov (temporary)

From: Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]
Sent: 4/29/2022 7:55:56 AM
To: Felberbaum, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4819a643ca2945cdb1a2631b83e69673-Michael.Fel]
Subject: How about this?
Attachments: 20220429 AHCJ FDA Priorities-- penultimate.docx

FDA Priorities

AHC Journalists

April 29th, 2022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From: Califf, Robert [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=AD88732BE1ED4912A058EE9DD9906F66-ROBERT.CALI]
Sent: 3/27/2022 9:02:33 AM
To: Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]
Subject: FW: FRIDAY HOMEWORK 03.25.2022 - INTERNAL CONFIDENTIAL
Attachments: 3.25.2022_FDA budget all hands.docx; 0930-FINAL_Misinformation_Combat_Plan_March2022.pptx; Draft CTP All Hands for RMC Review.docx

---

From: Olivarria, Frank <Frank.Olivarria@fda.hhs.gov>
Date: Friday, March 25, 2022 at 8:12 PM
To: Califf, Robert <(b) (6)@fda.hhs.gov>
Cc: Tierney, Julia <Julia.Tierney@fda.hhs.gov>, Jefferson, Erica <Erica.Jefferson@fda.hhs.gov>, Rebello, Heidi <Heidi.Rebello@fda.hhs.gov>, Sheehy, Janice <Janice.Sheehy@fda.hhs.gov>, Copeland, Jakea <Jakea.Copeland@fda.hhs.gov>, Helms Williams, Emily <Emily.HelmsWilliams@fda.hhs.gov>
Subject: FRIDAY HOMEWORK 03.25.2022 - INTERNAL CONFIDENTIAL

Good evening Dr. Califf,

For your action (three items):

ITEM(S) FOR YOUR REVIEW (INTERNAL/CONFIDENTIAL/NOT FOR PUBLIC DISTRIBUTION)

Action: Commissioner review, feedback, edits, or Commissioner clearance requested by Monday, 3/28, 9 AM:

3.25.2022_FDA budget all hands.docx

ITEM #1: Draft All Hands Message from Commissioner Califf: *The President's FY 2023 Budget*

- **Anticipated Release Date:** not provided, inquired
- **HW POC**: Bessy Guevara (OEA)

Action: Commissioner review, feedback, edits, or Commissioner clearance requested by Monday, 3/28, 9 AM:

Draft CTP All Hands for RMC Review.docx

ITEM #2: Draft All Hands Message from Commissioner Califf: *Personnel News – Center for Tobacco Products Acting Director*

- **Anticipated Release Date:** Week of 3/28, TBD
- **Note:** Close hold
- **HW POC**: Heidi Rebello (OEA)

Action: Commissioner review, feedback/further thoughts requested by Monday, 3/28, 9 AM:

0930-FINAL_Misinformation_Combat_Plan_March2022.pptx

ITEM #3: OEA Slide Deck: *Curbing Misinformation / Disinformation (background/action plan)*

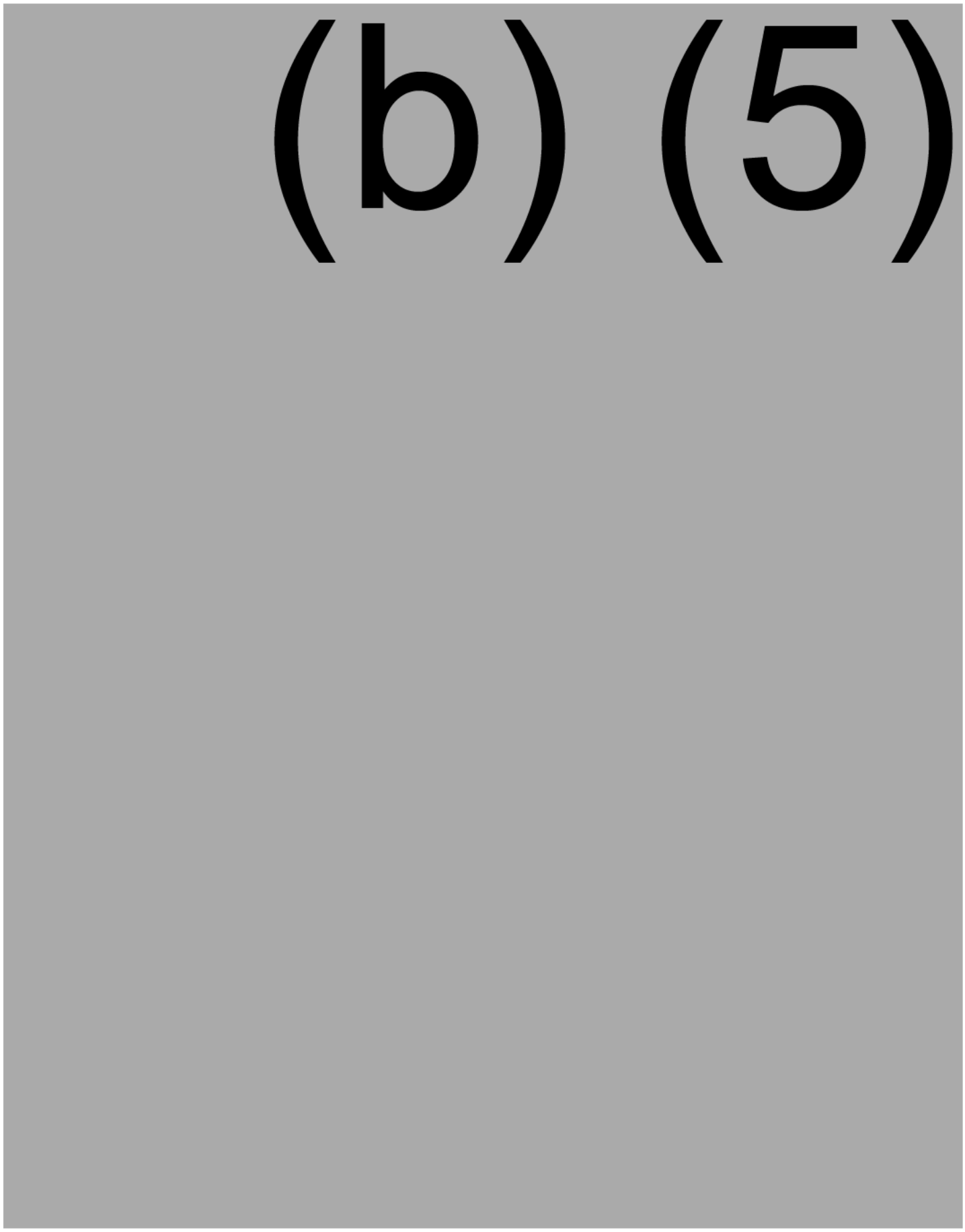
- **Anticipated Presentation Date:** Week of April 4th
- **Note:** OEA aims to discuss this slide deck with OCC the week of 4/4, your feedback and

thoughts on this are kindly requested for consideration at the OEA/OCC meeting

- **HW POC**: Erica Jefferson (OEA)

Thank you,
Frank

Frank A. Olivarria
Management and Program Analyst
Immediate Office, Office of the Commissioner
U.S. Food and Drug Administration
Tel: 240-402-9882
Frank.Olivarria@fda.hhs.gov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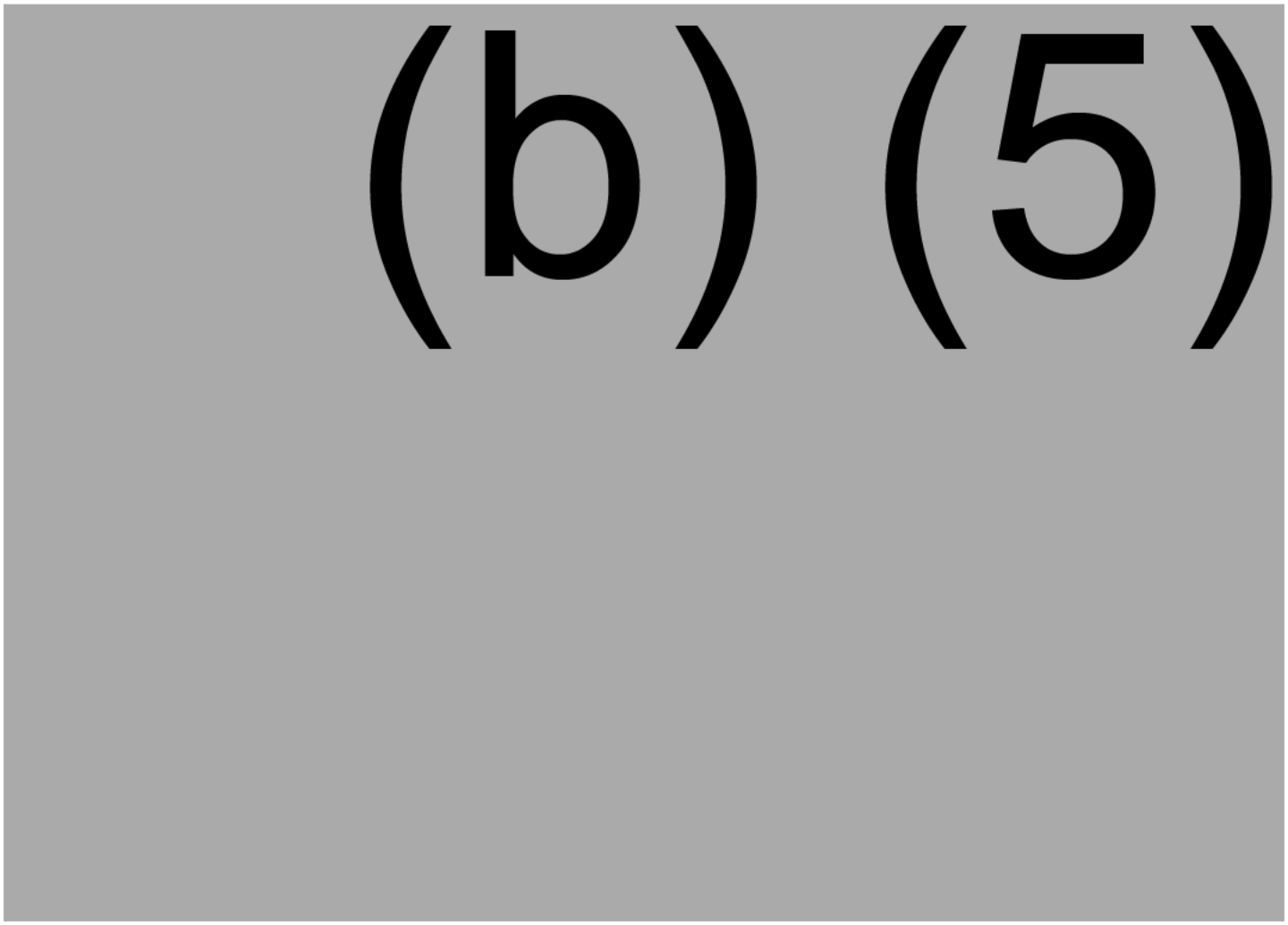
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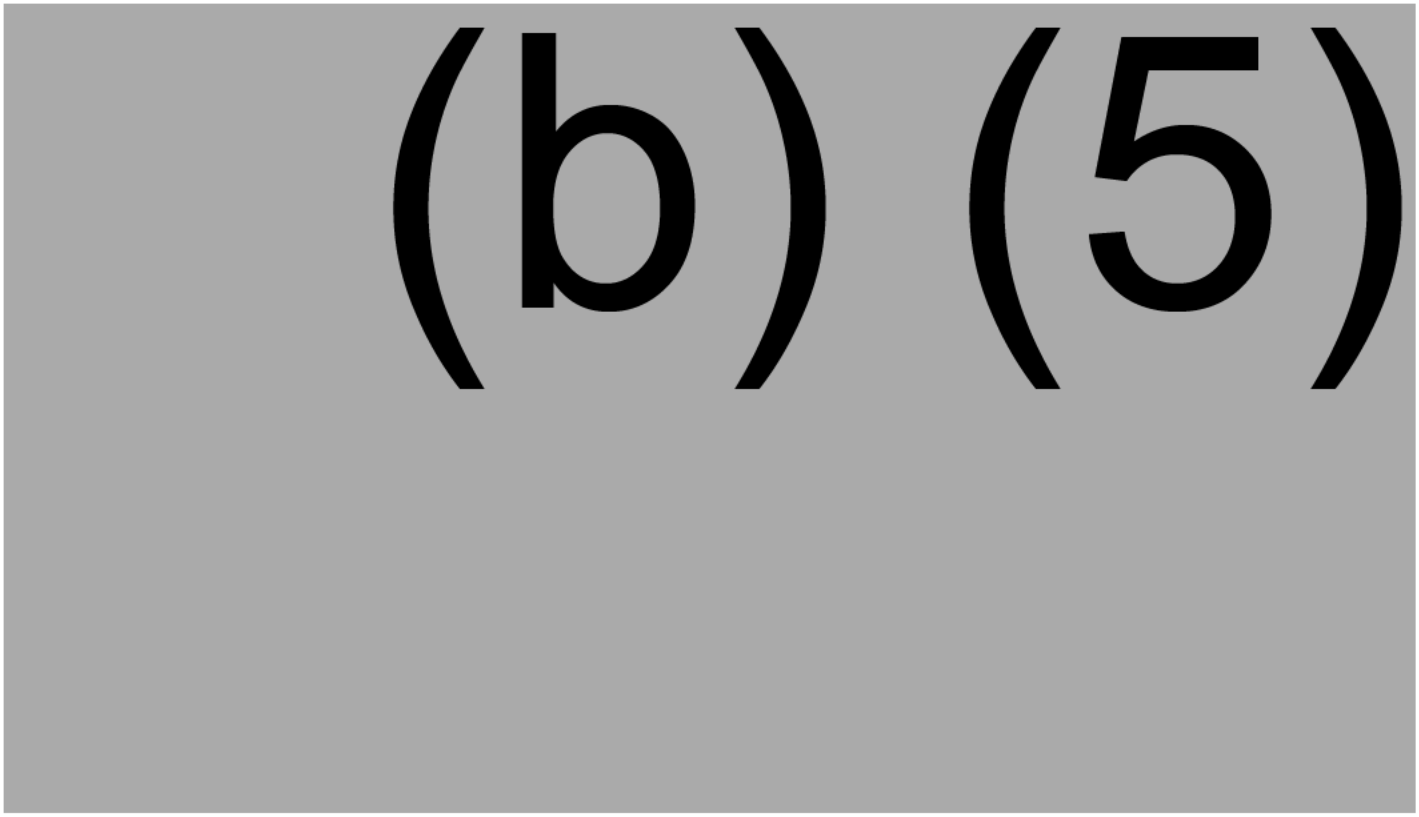
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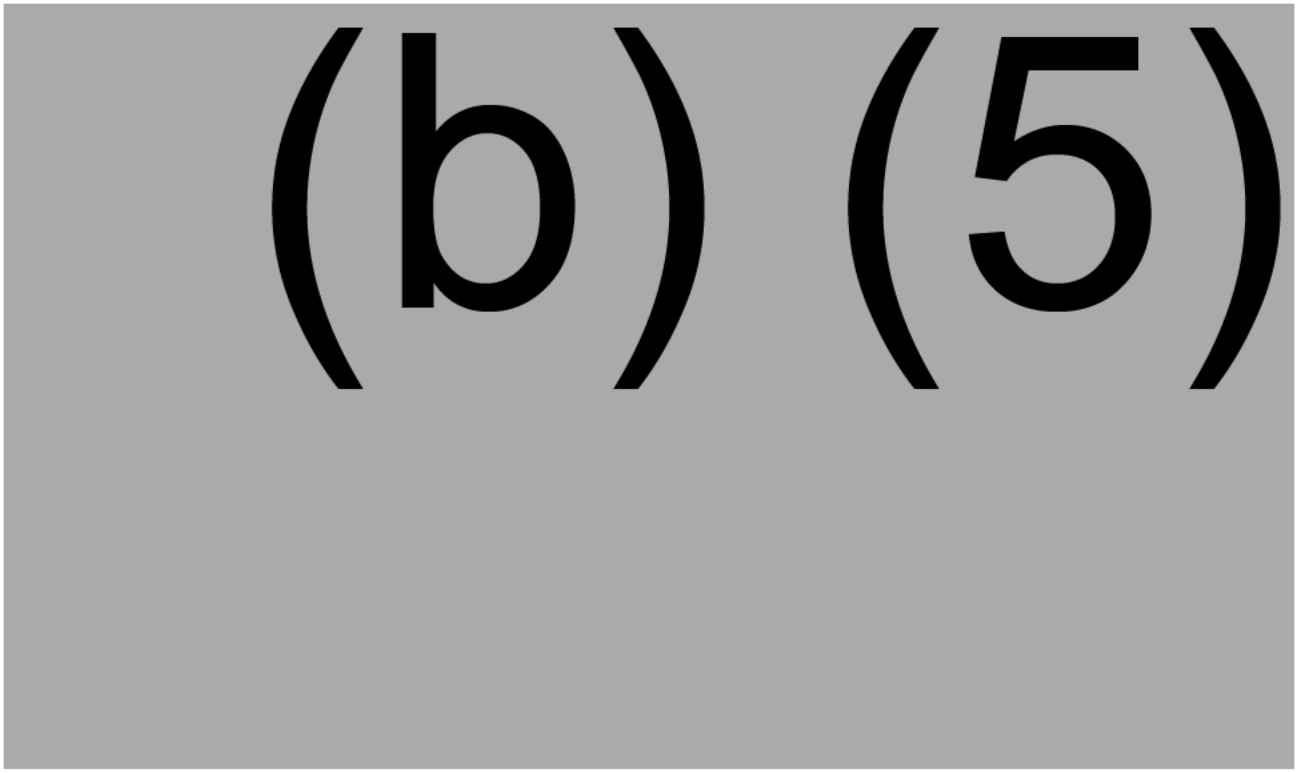

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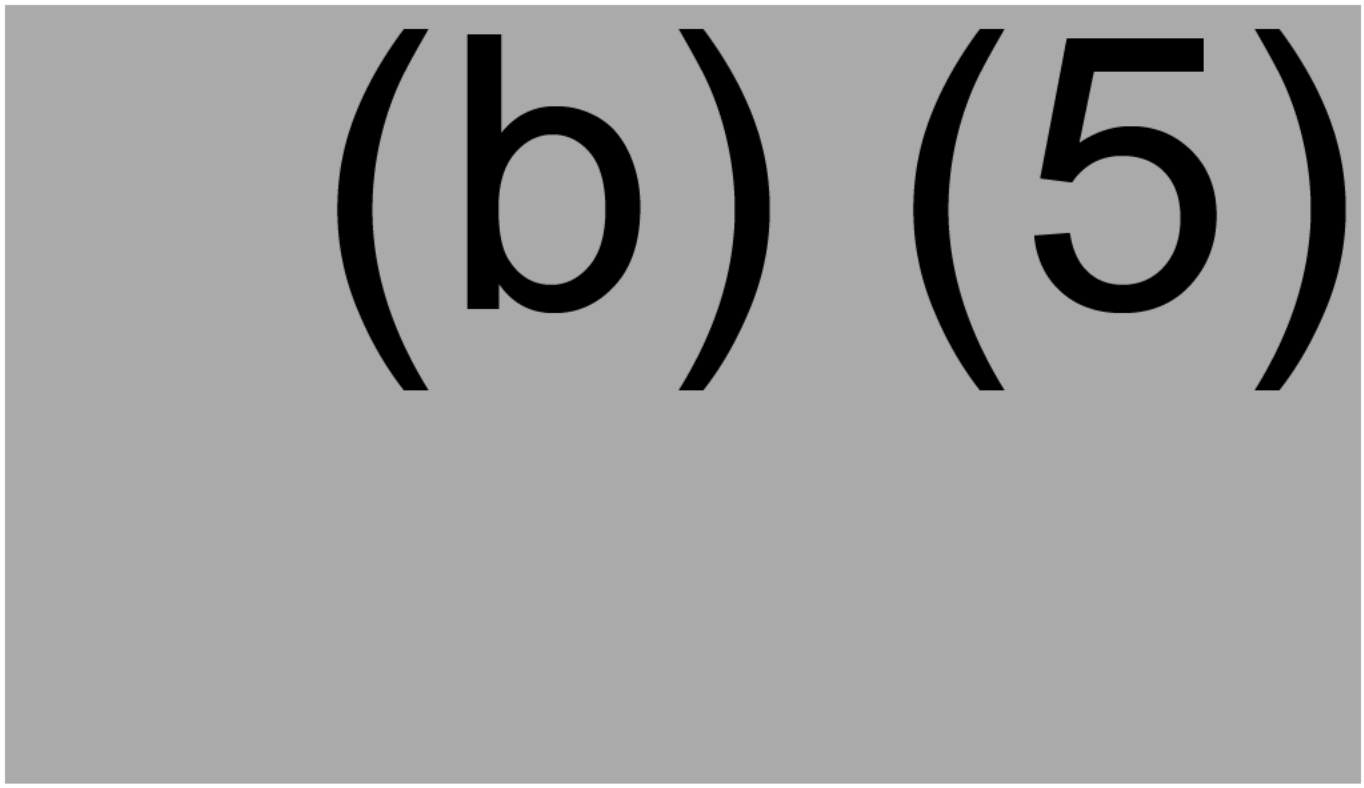

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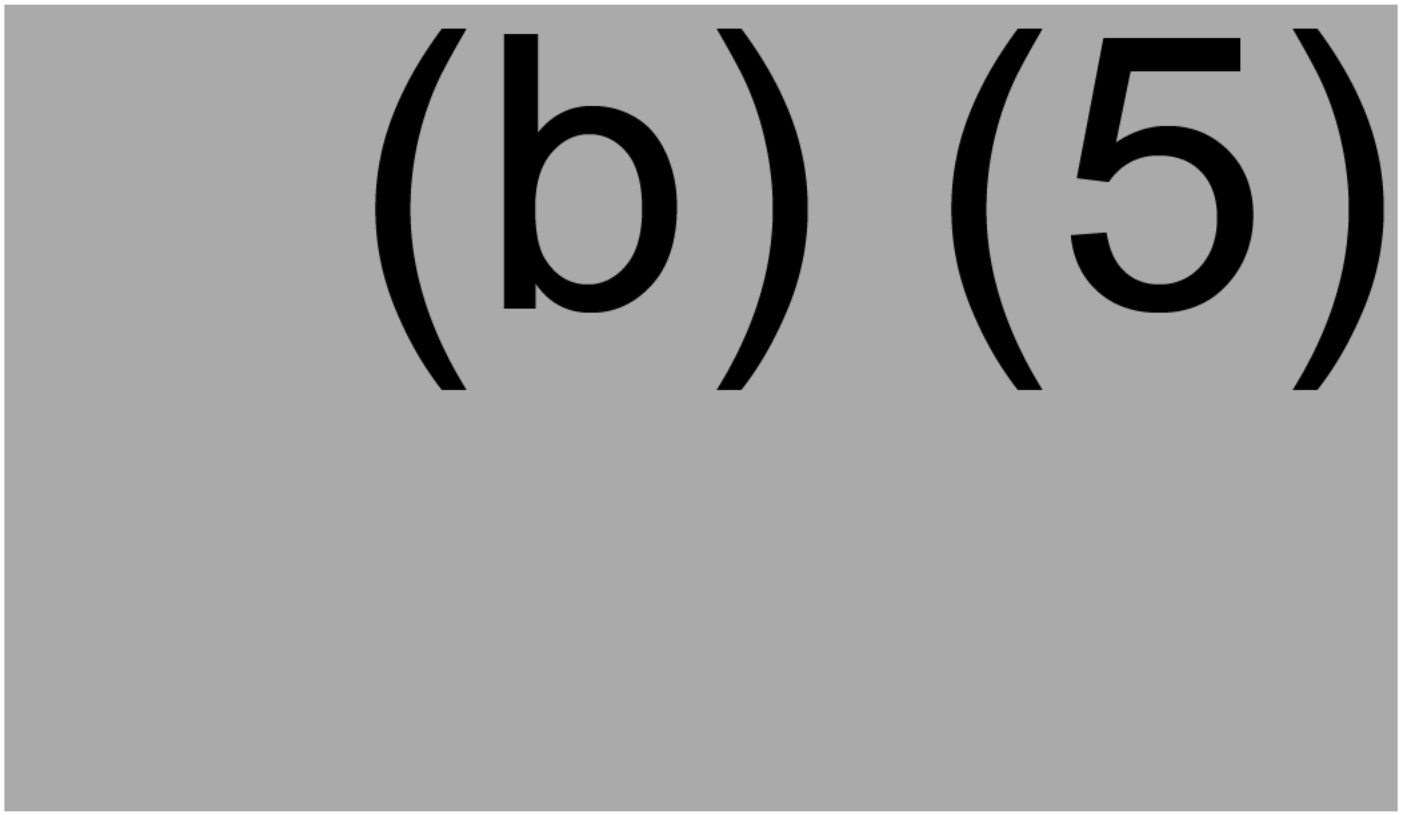
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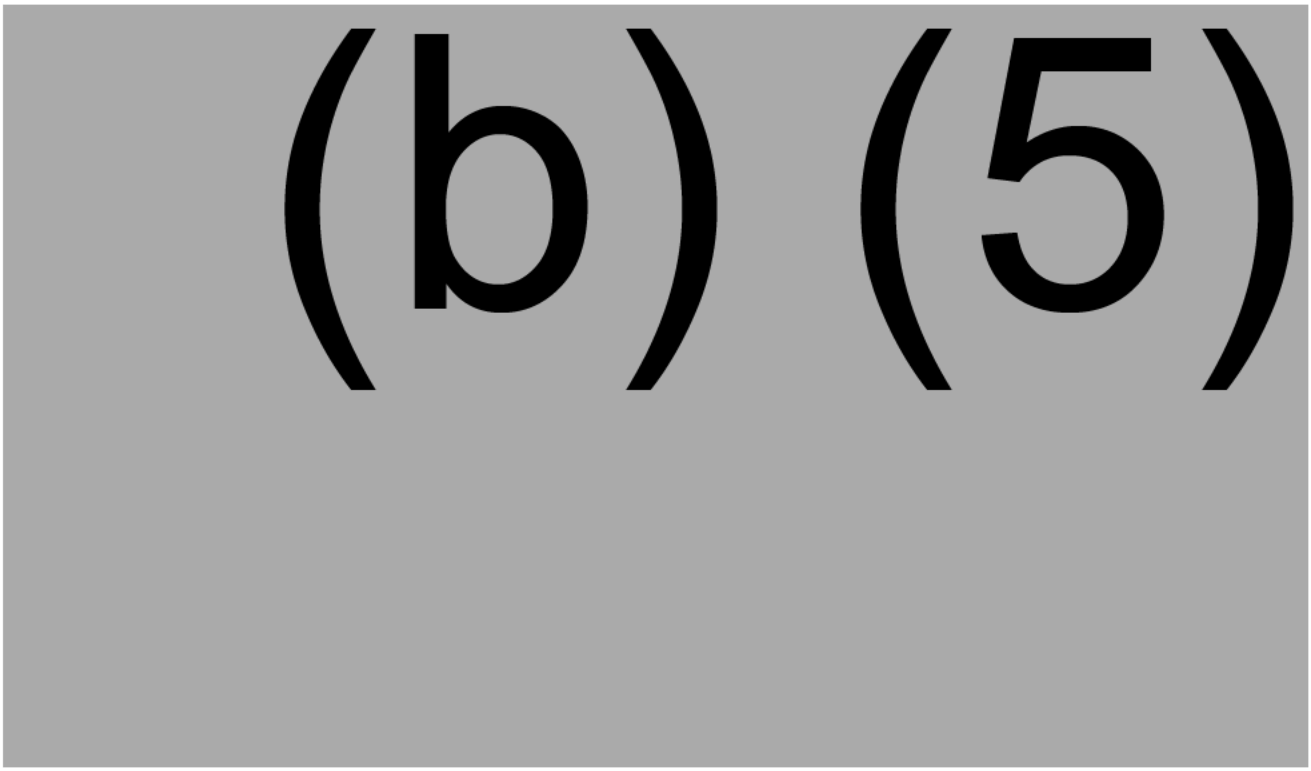
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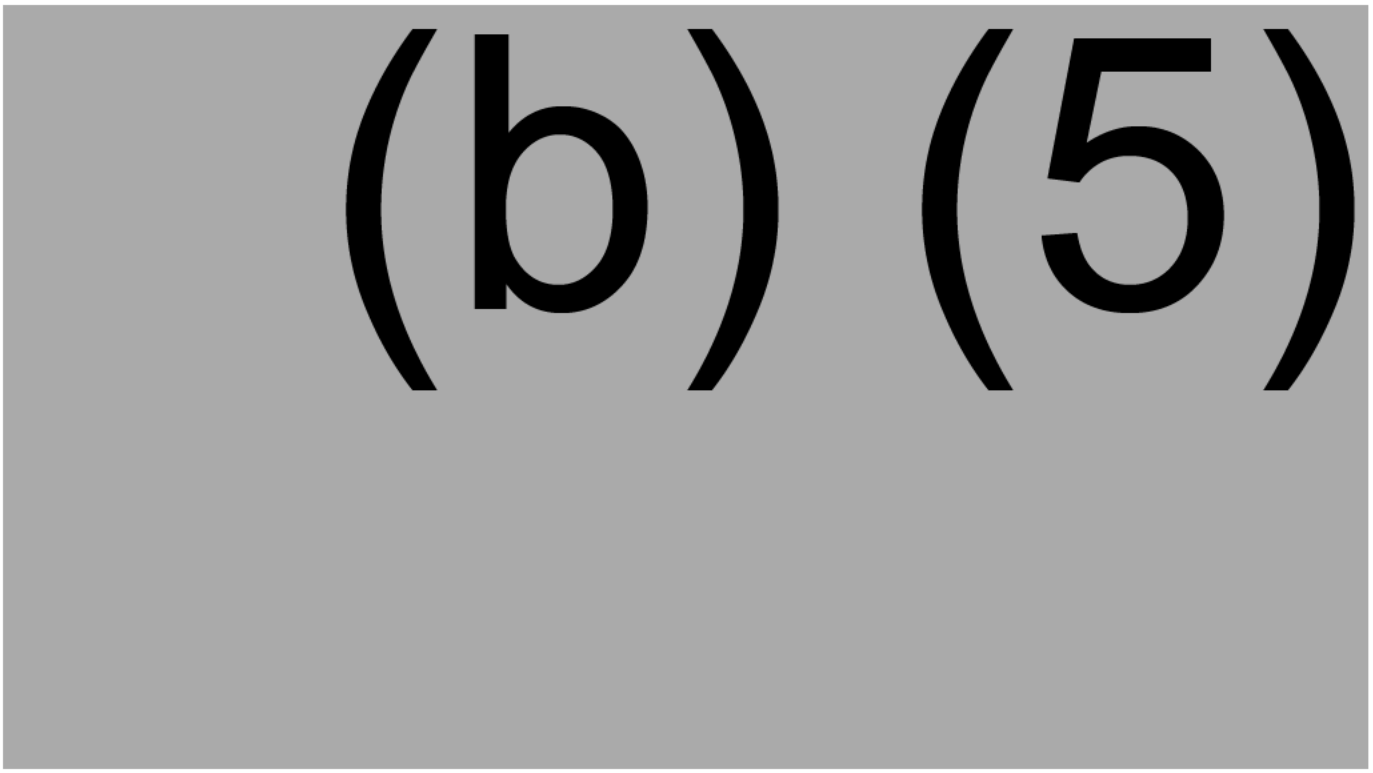
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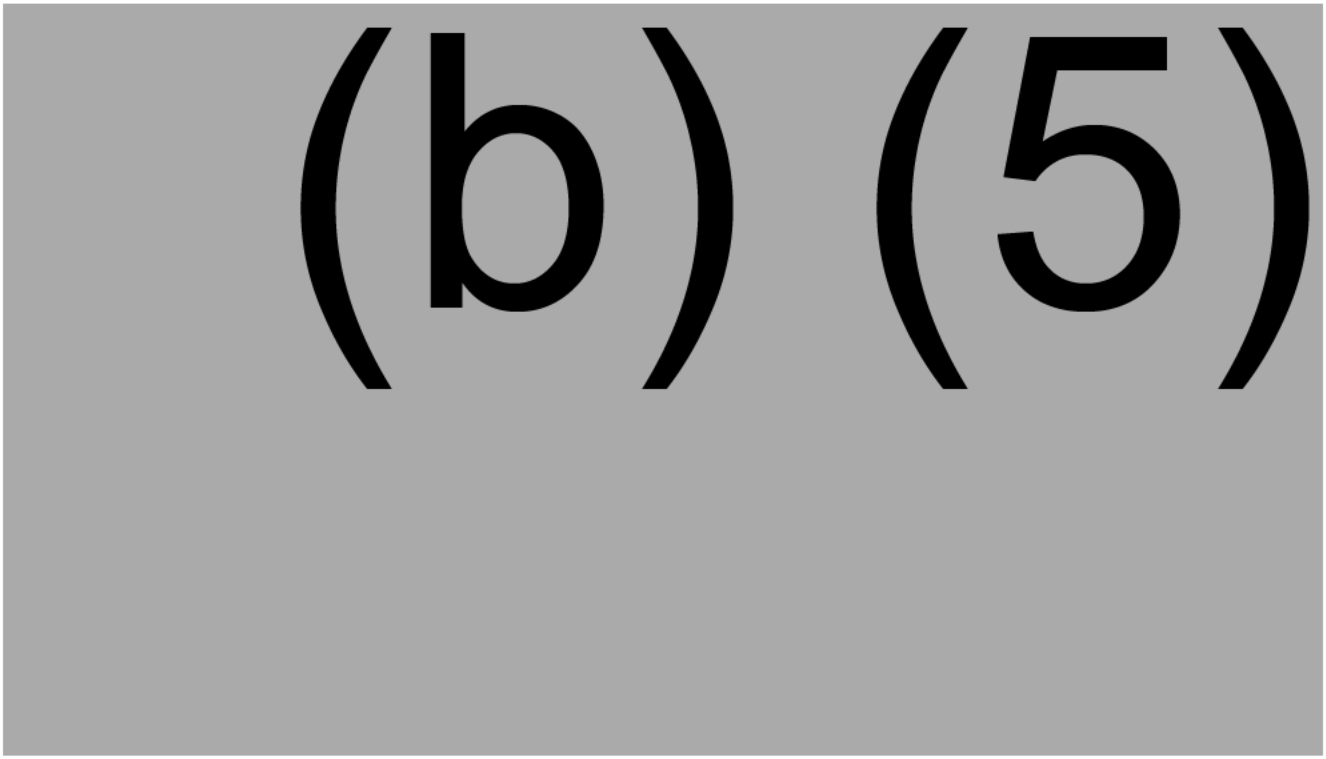

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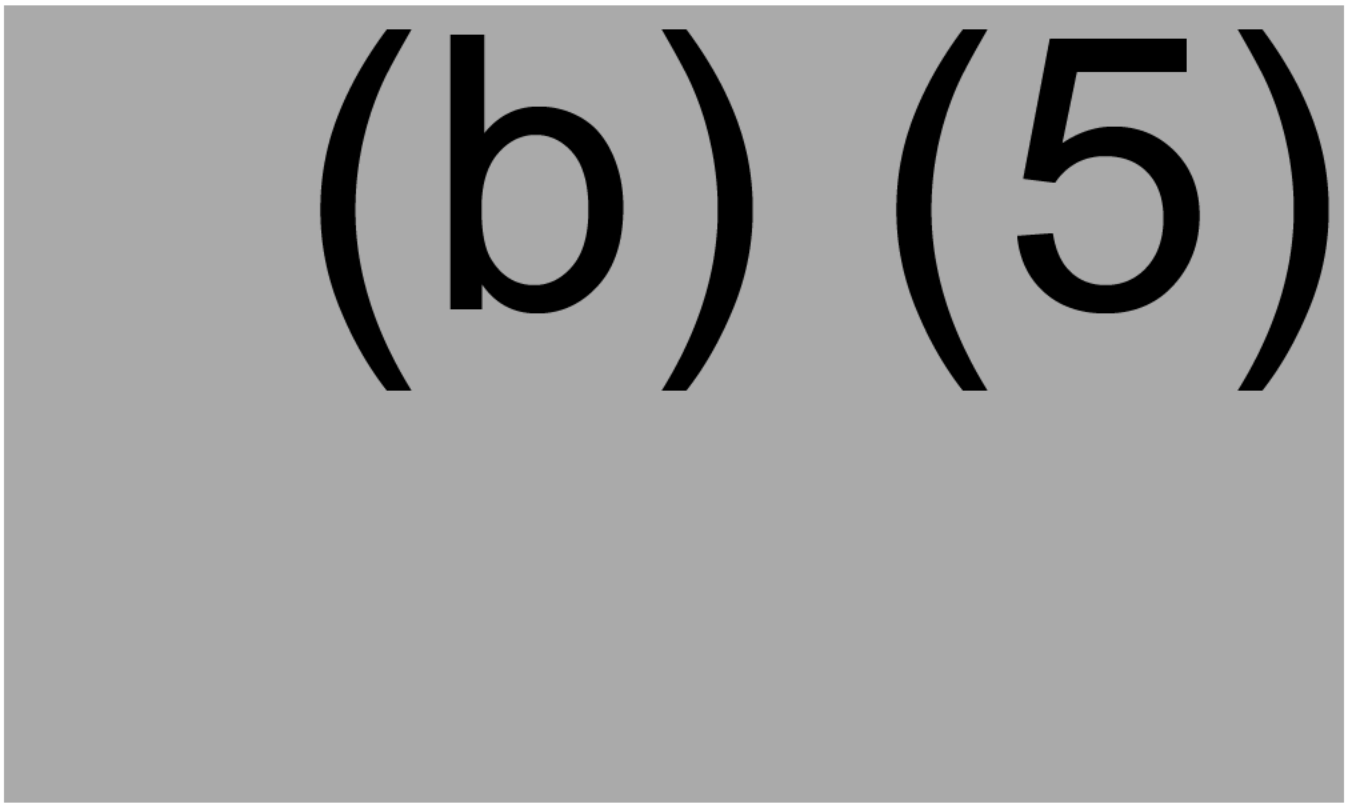

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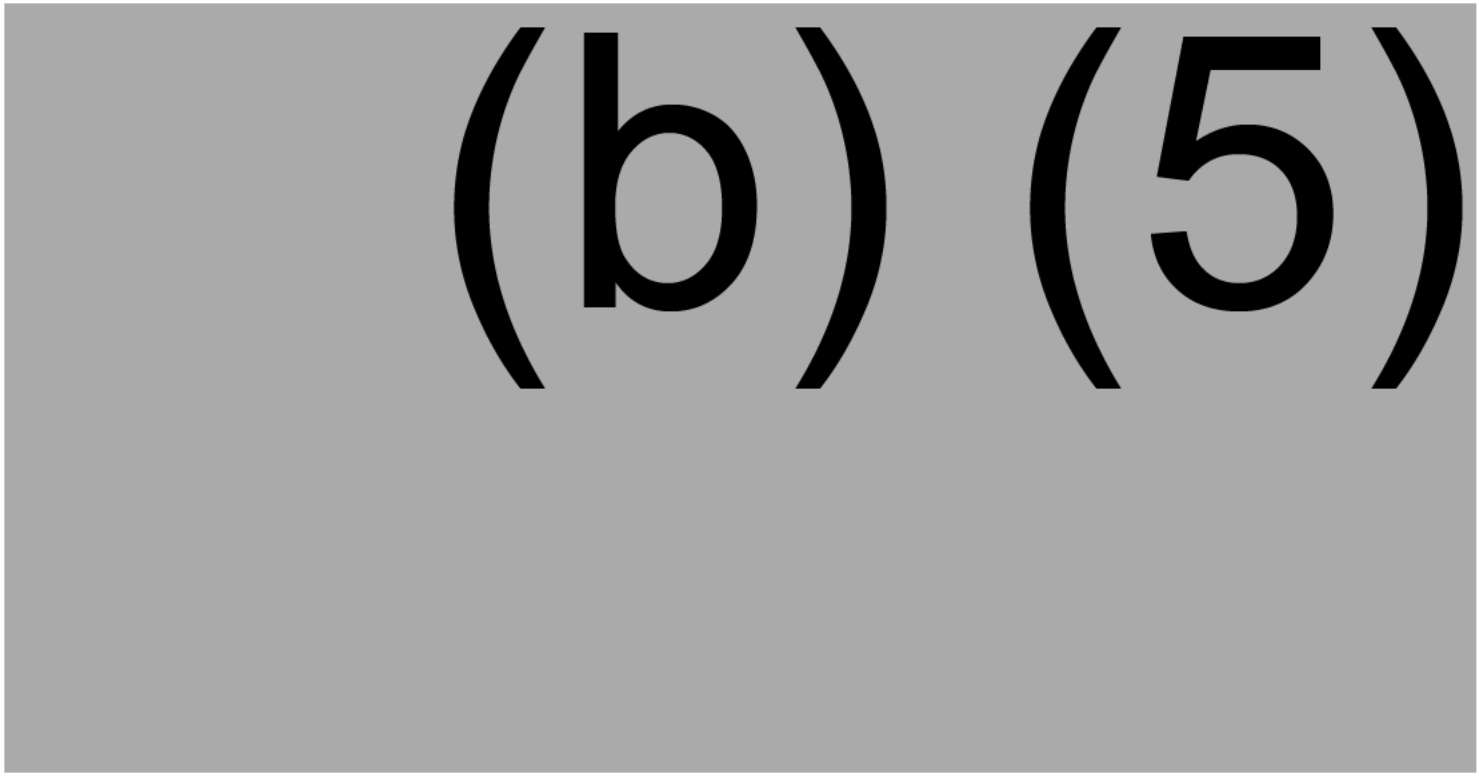

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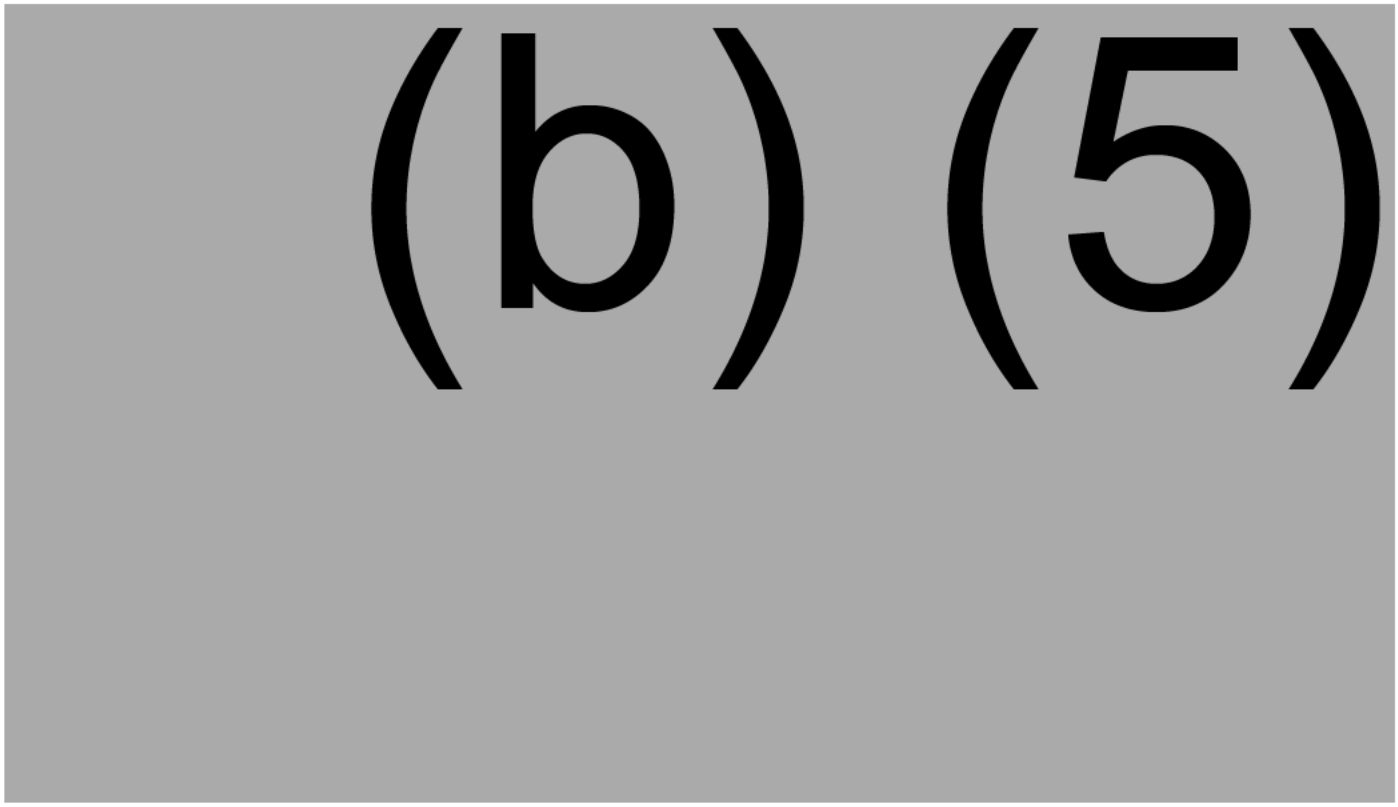
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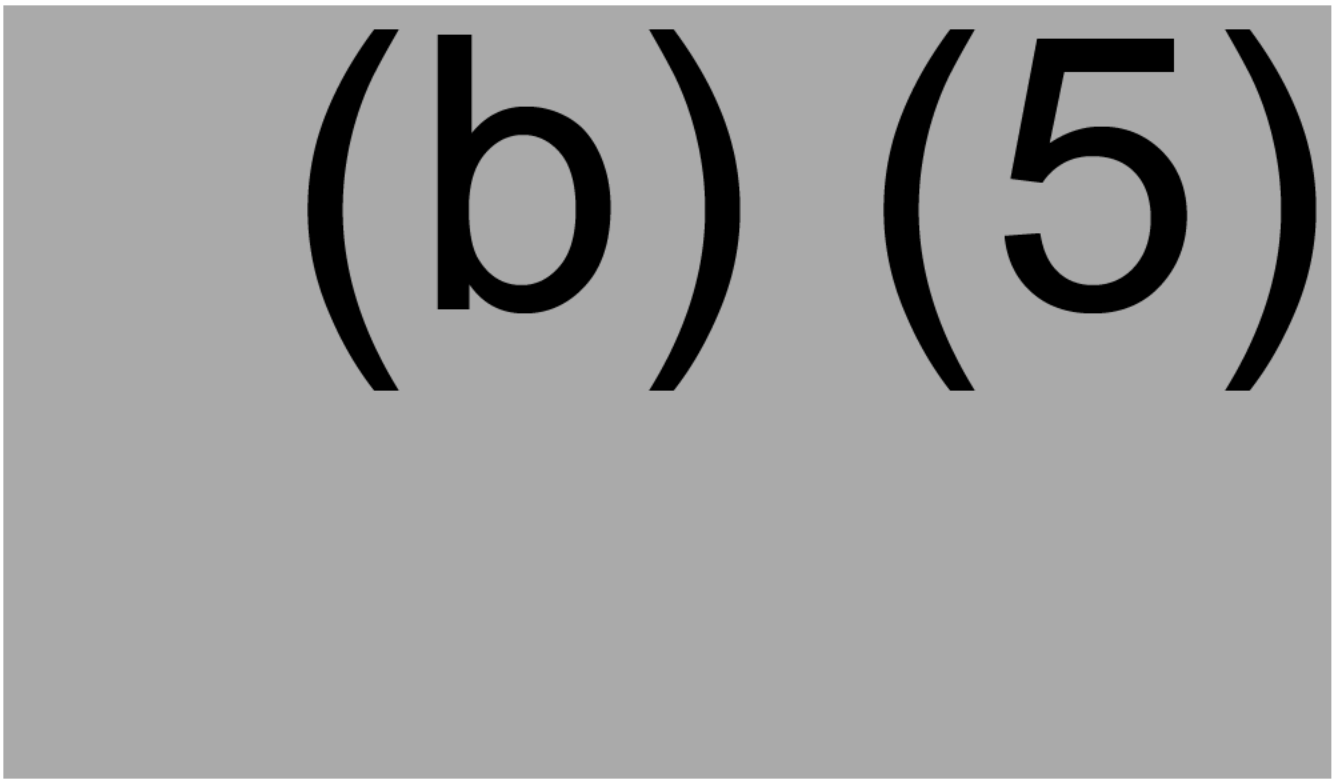
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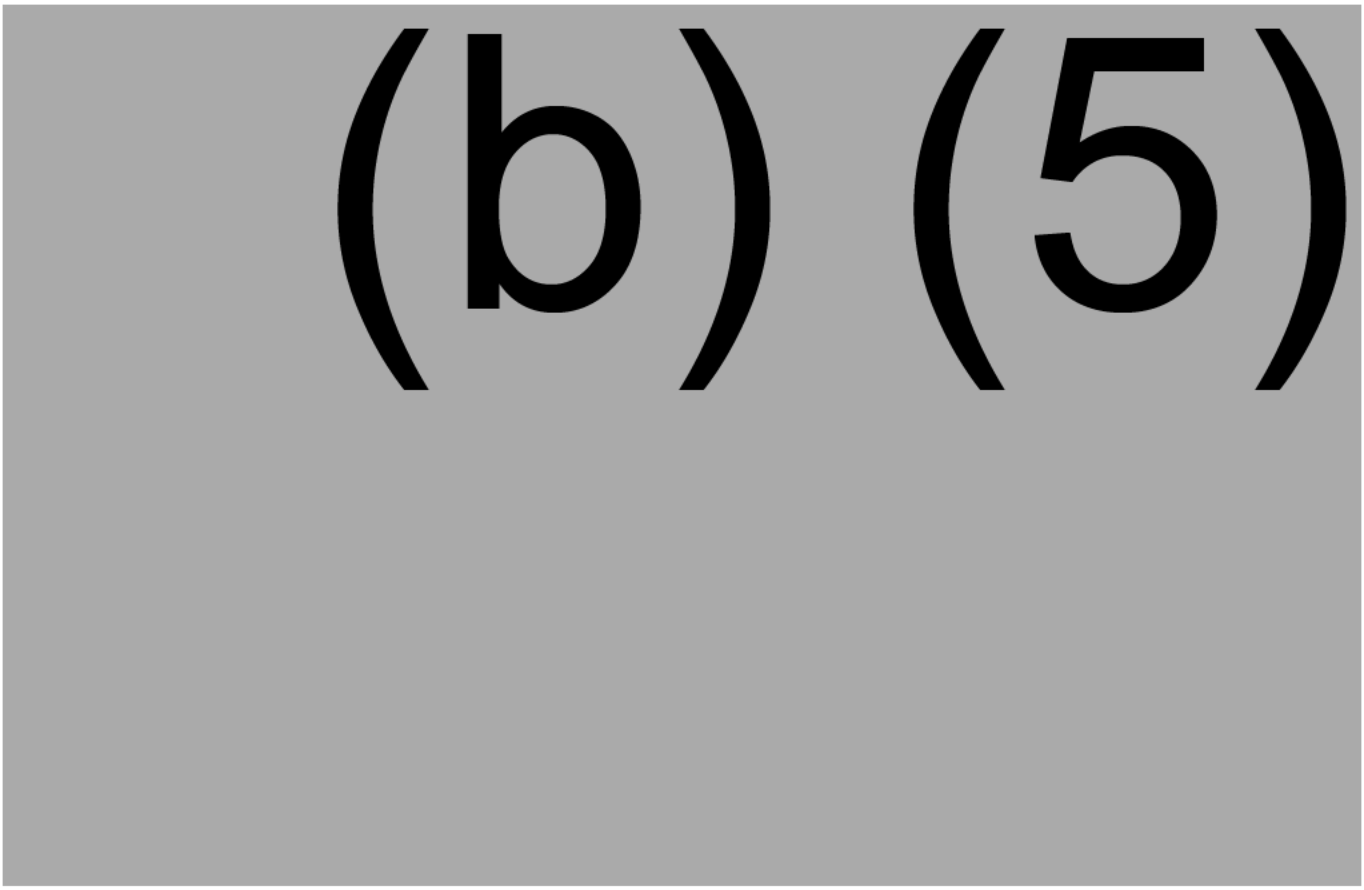

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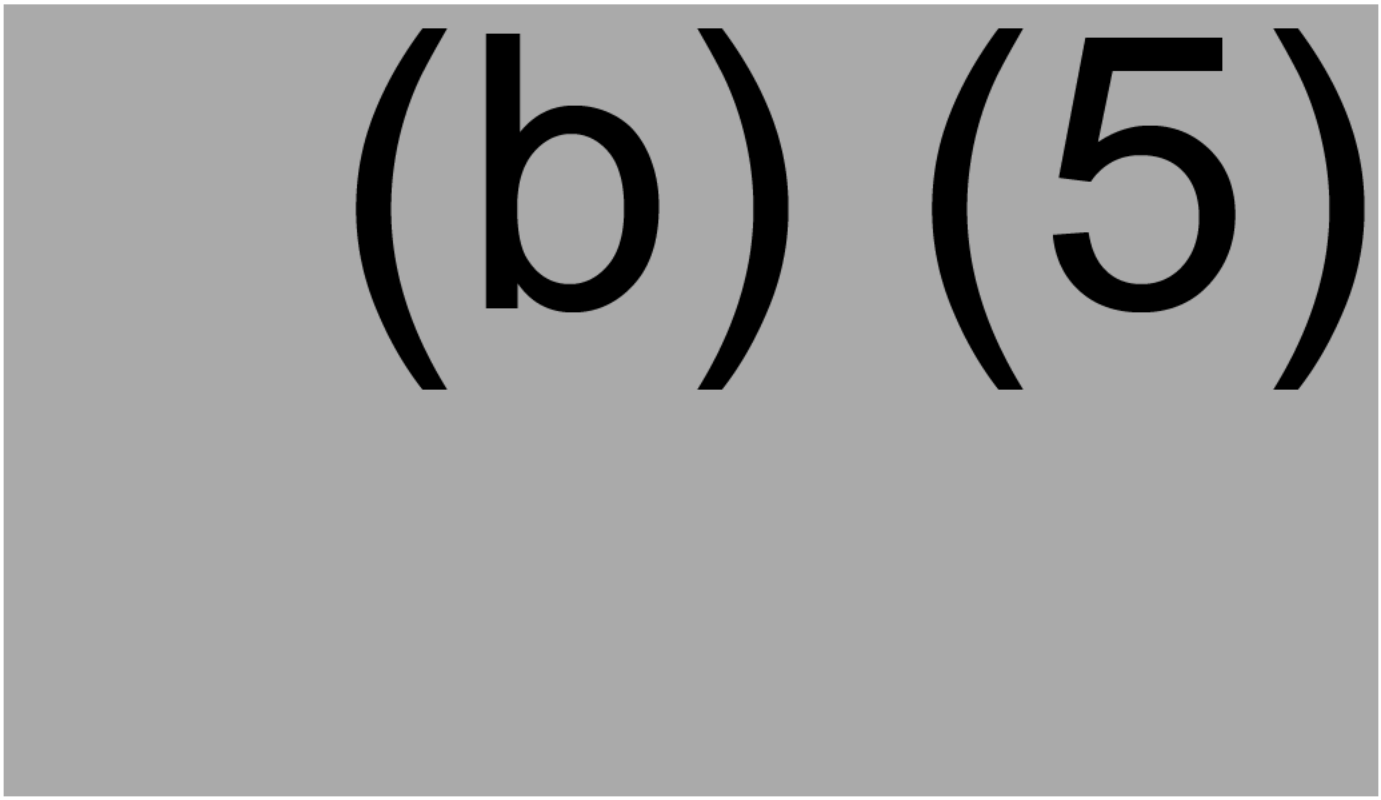

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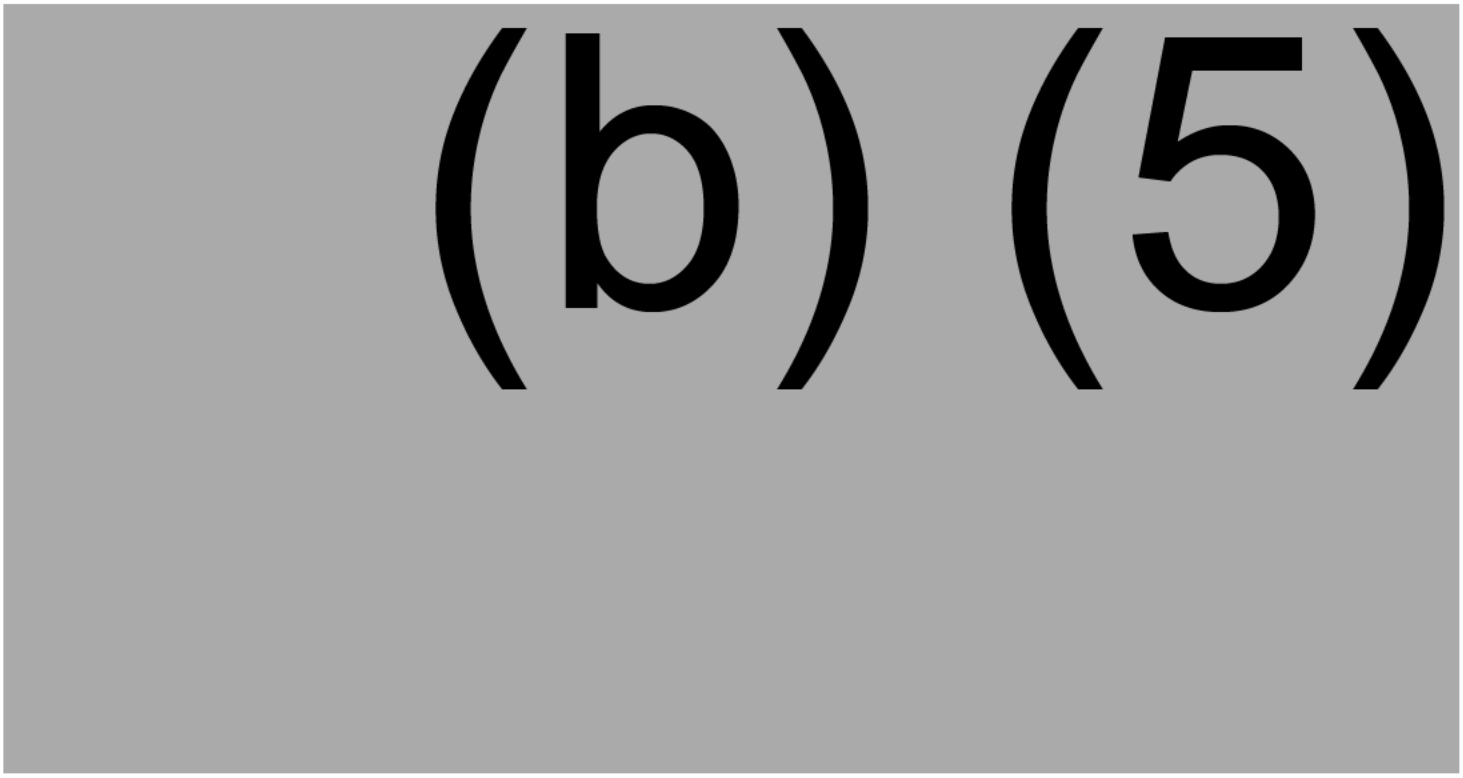

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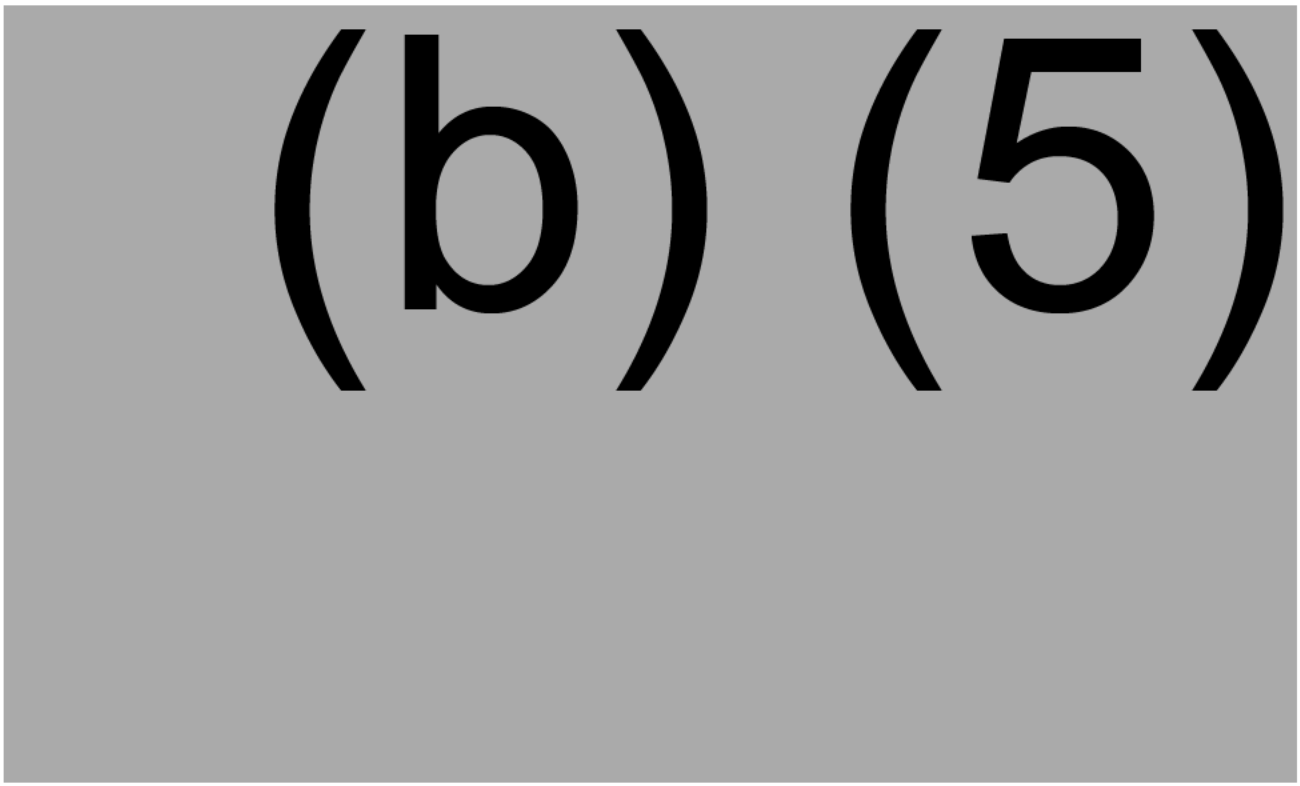

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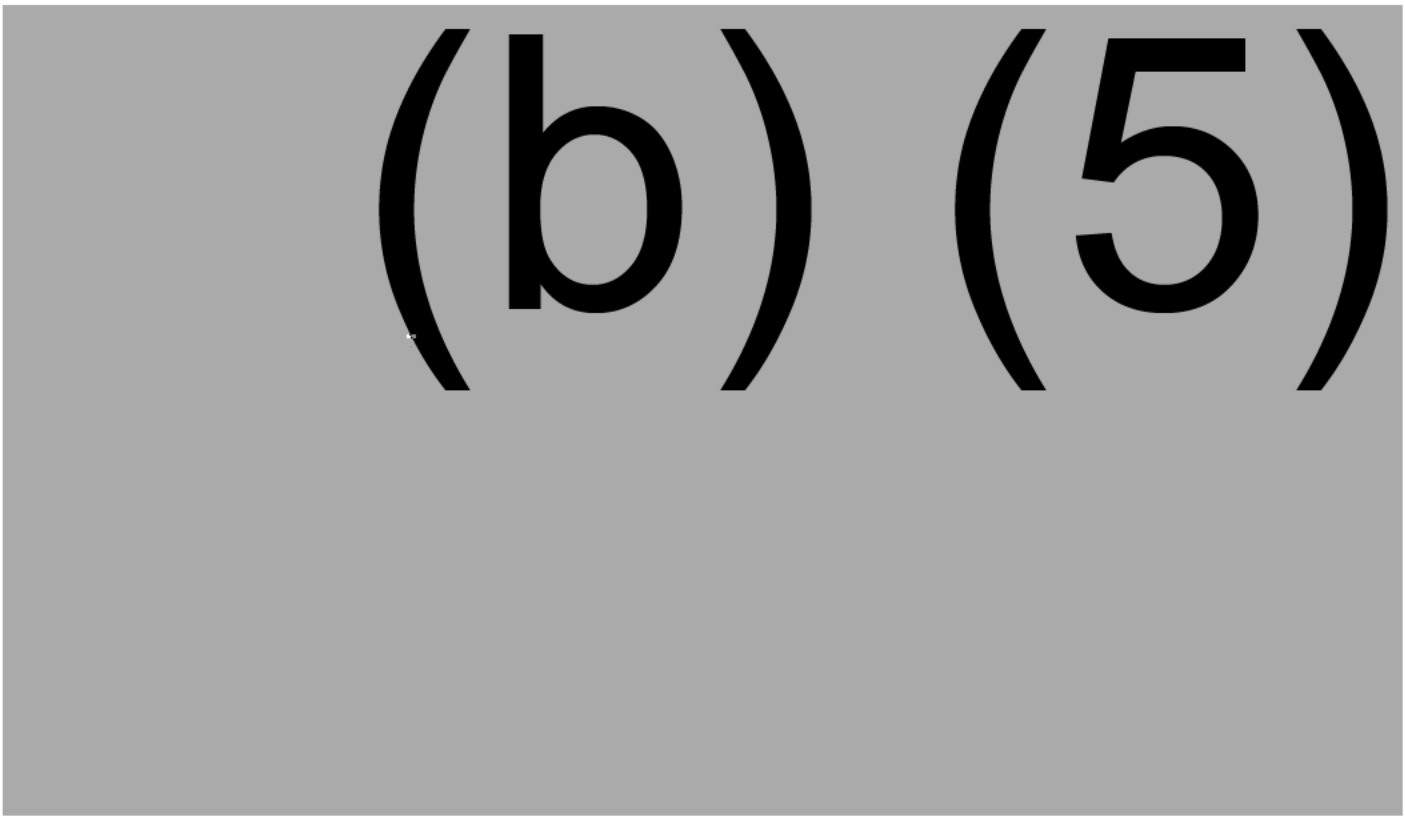

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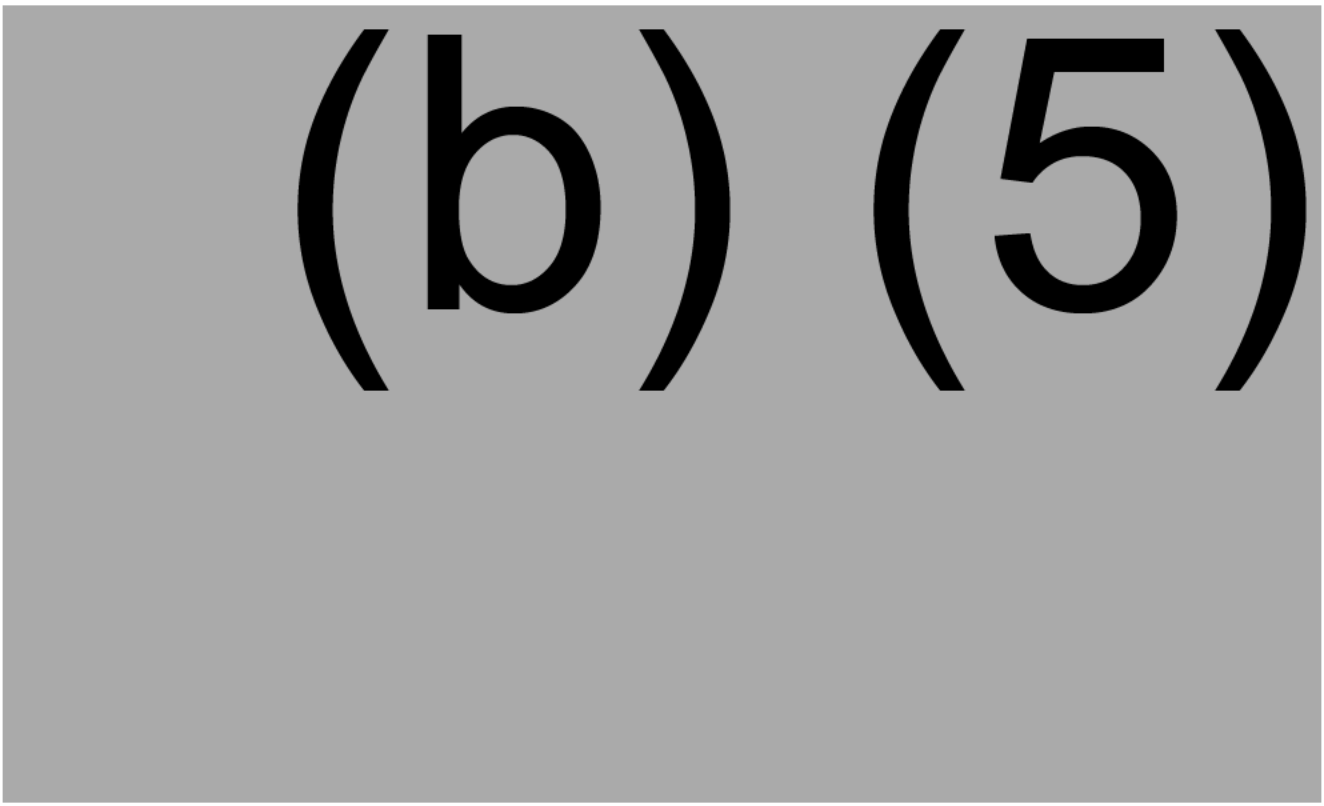

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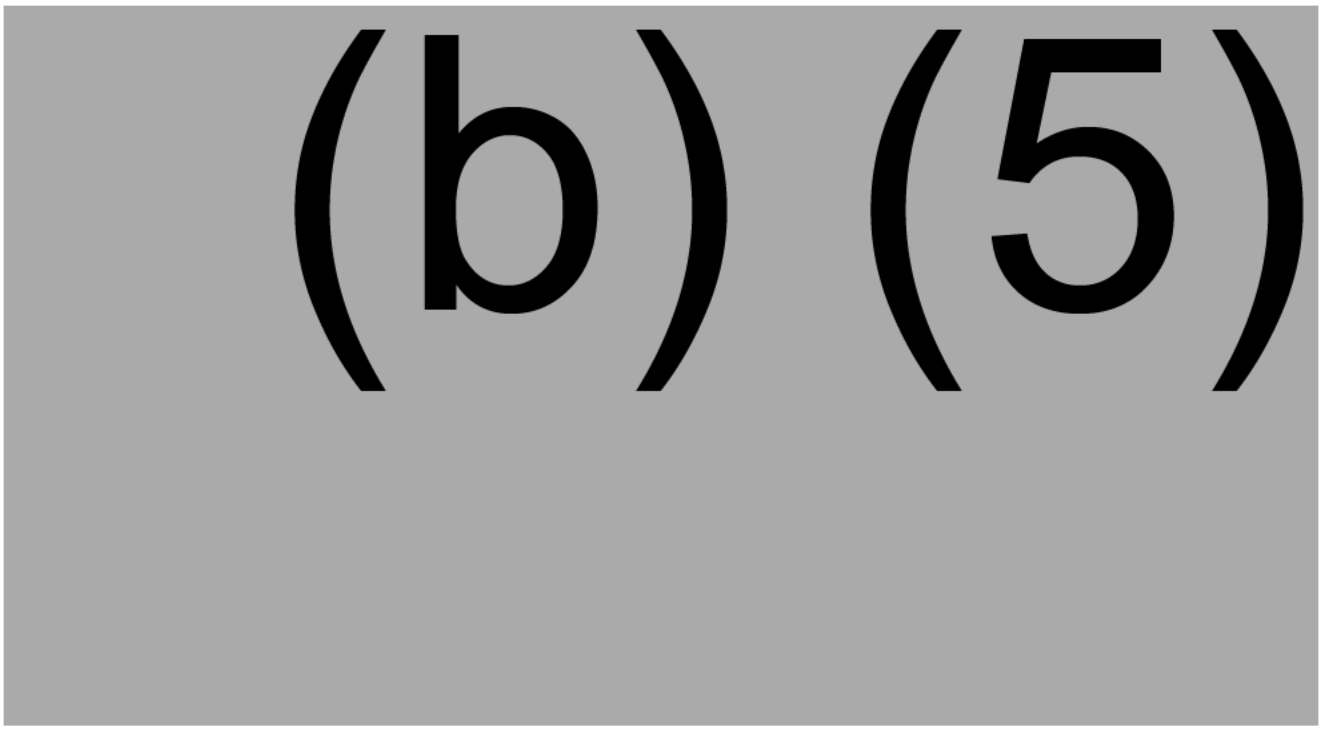

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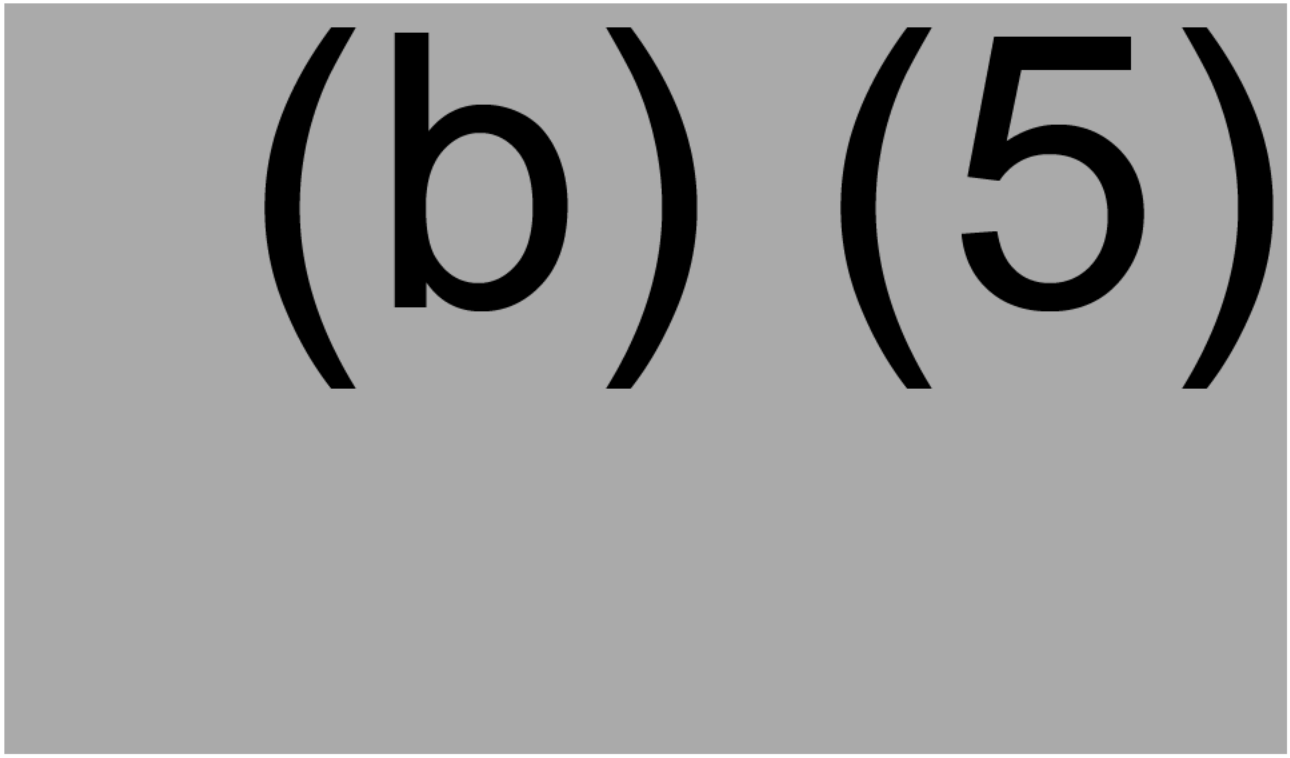

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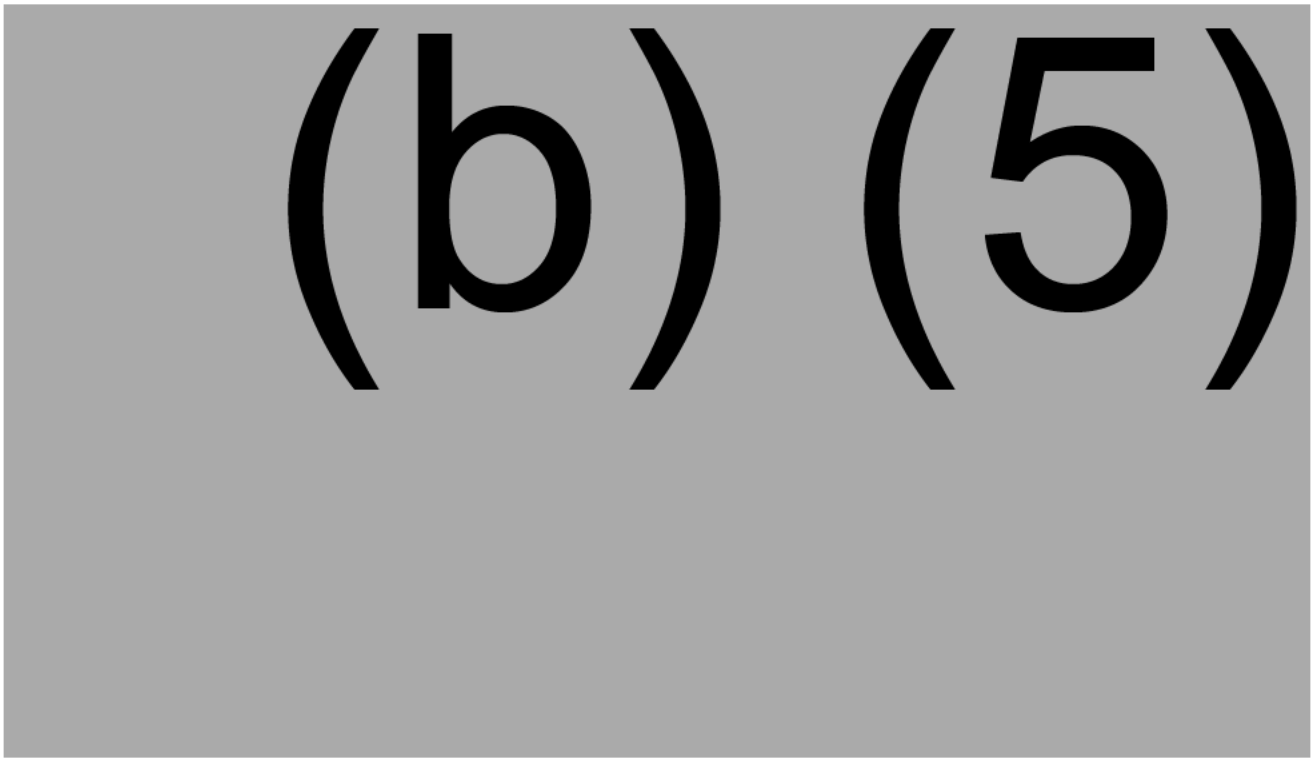

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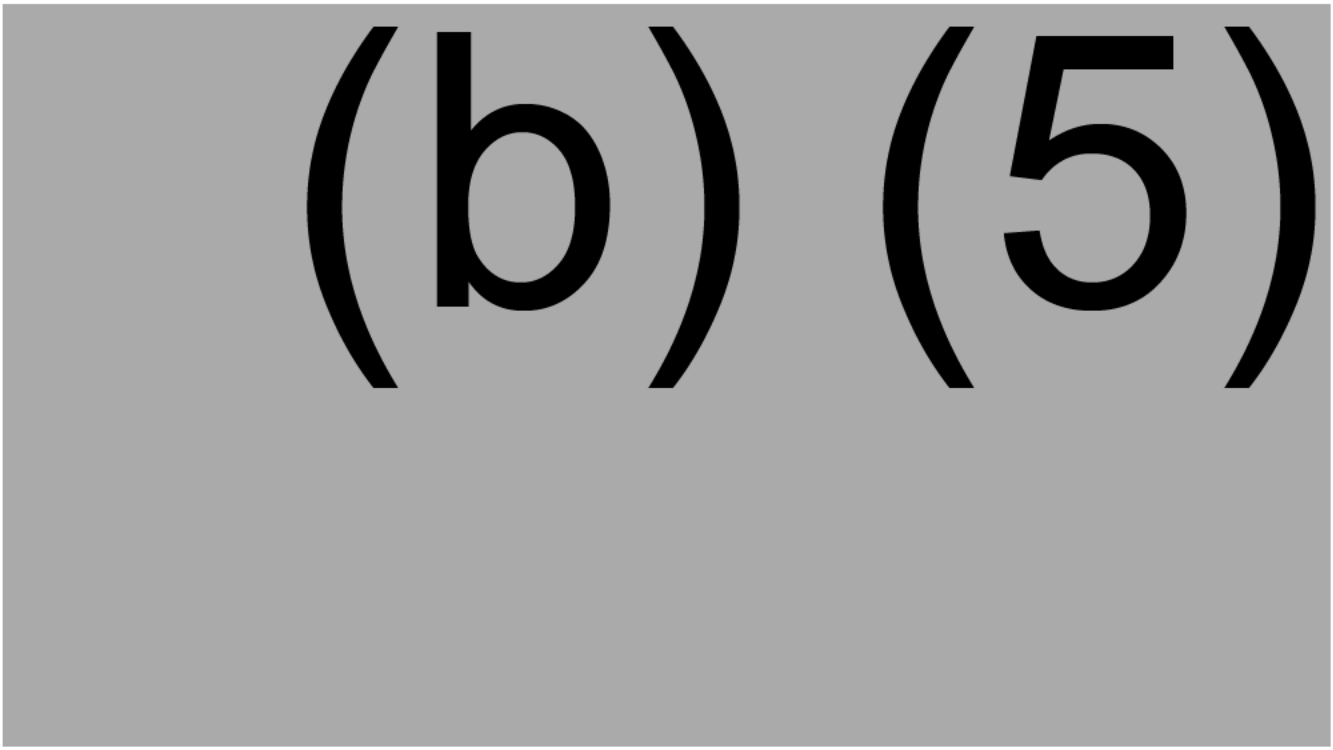

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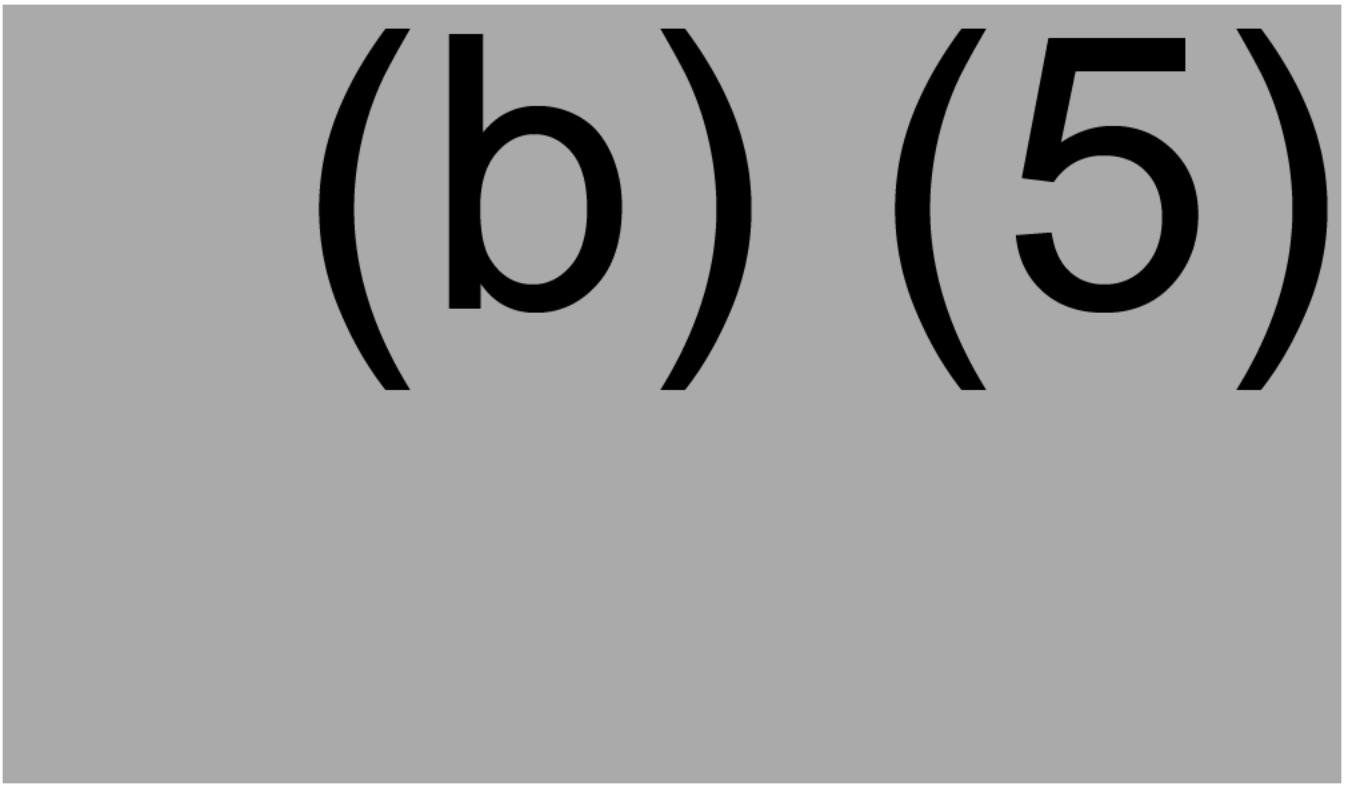

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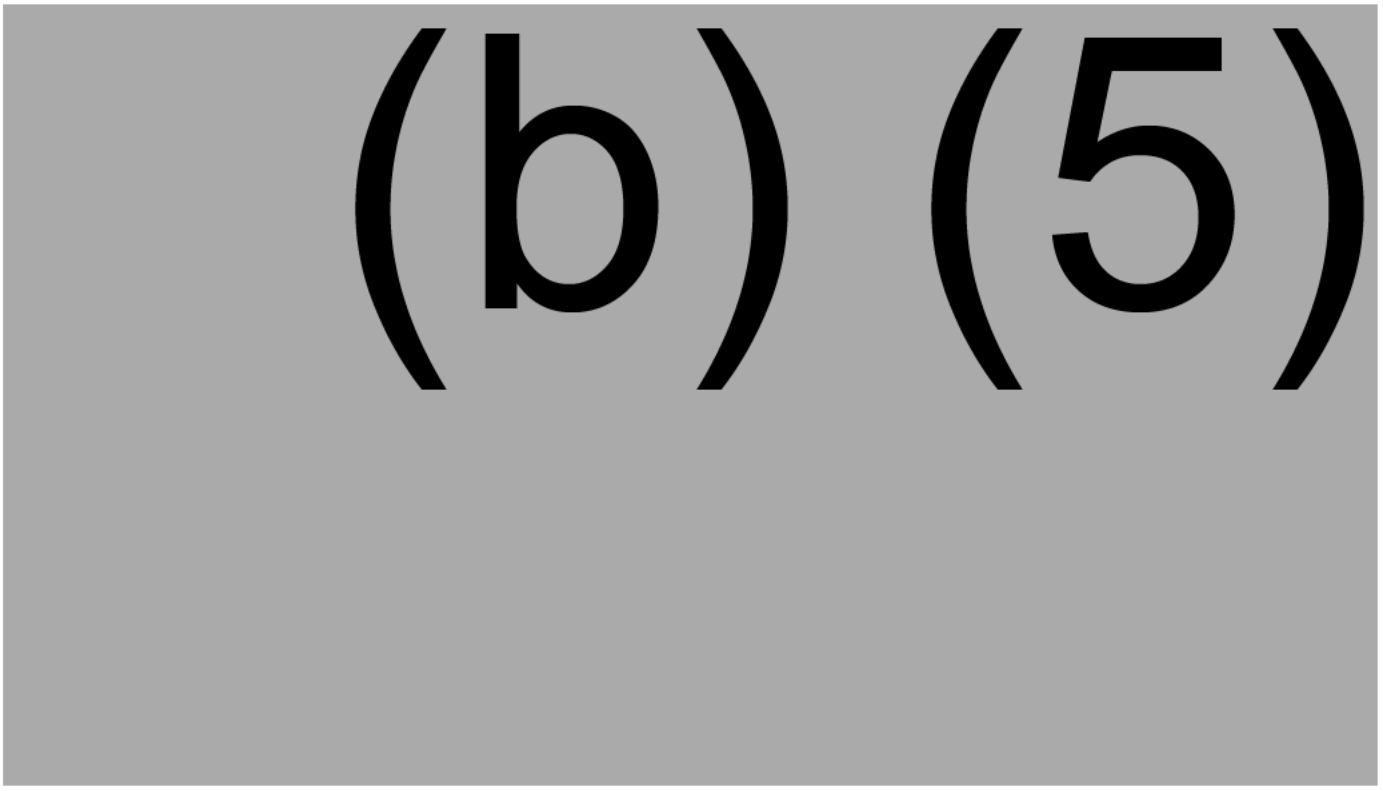

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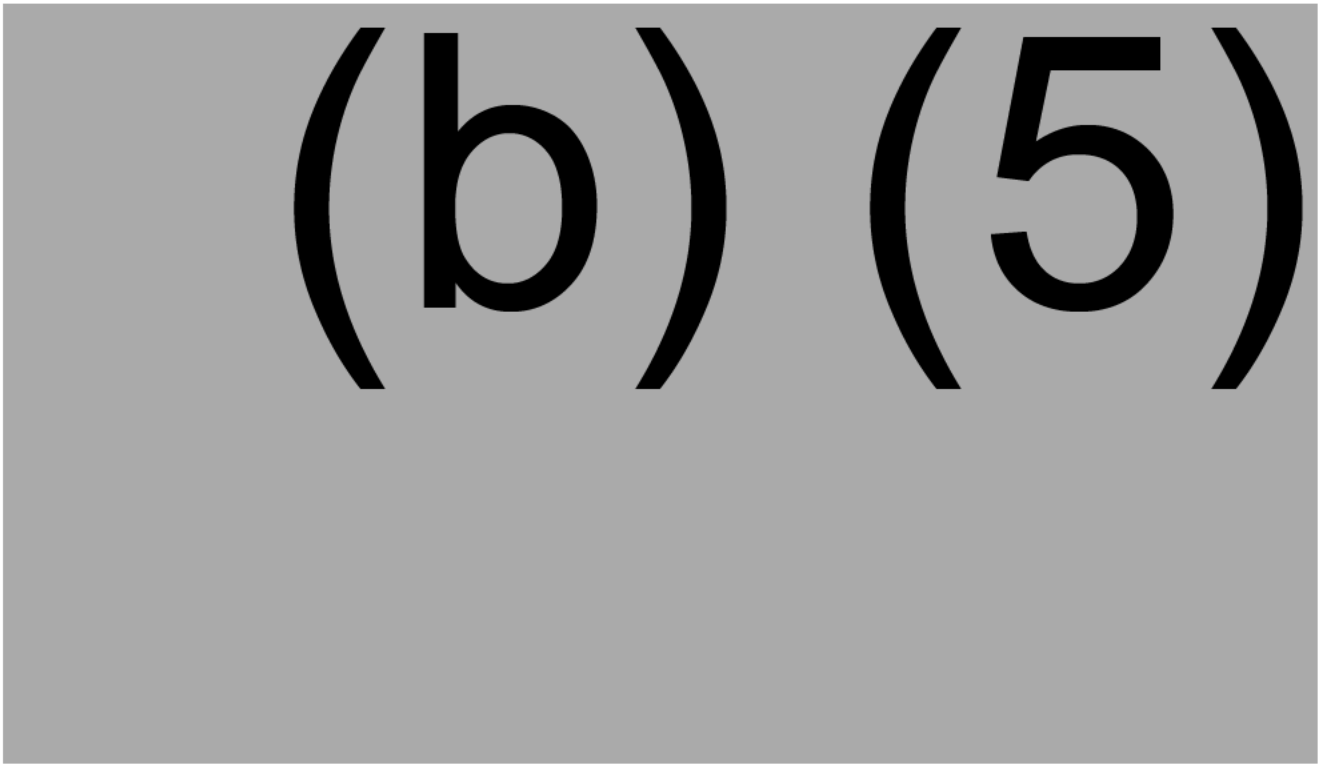

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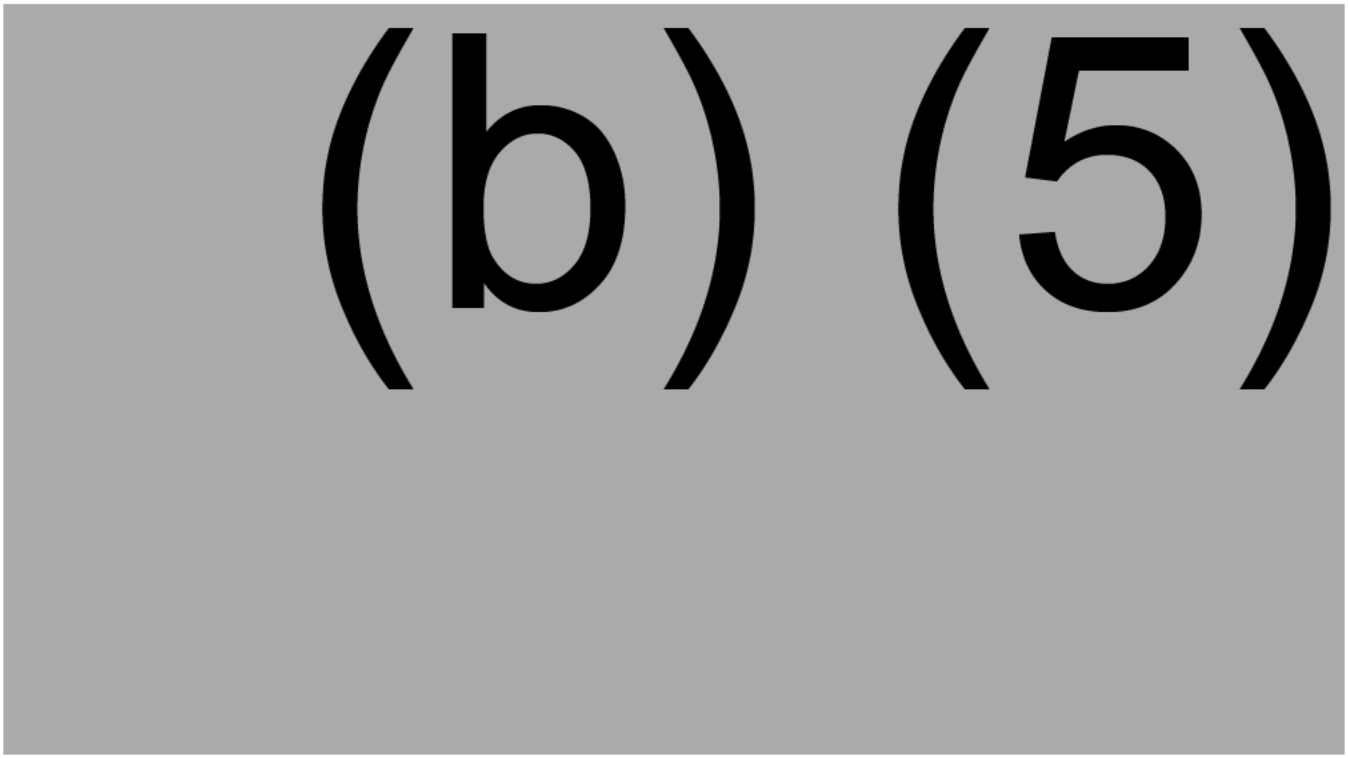

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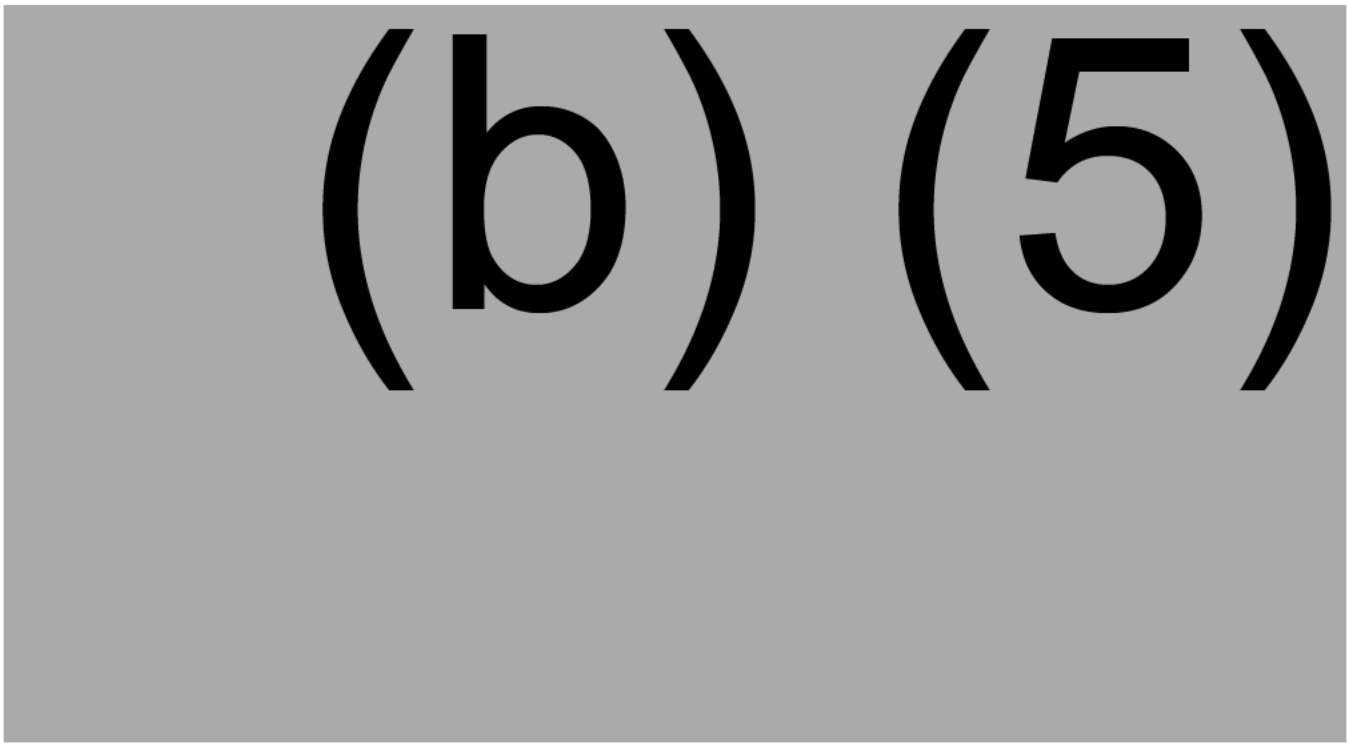
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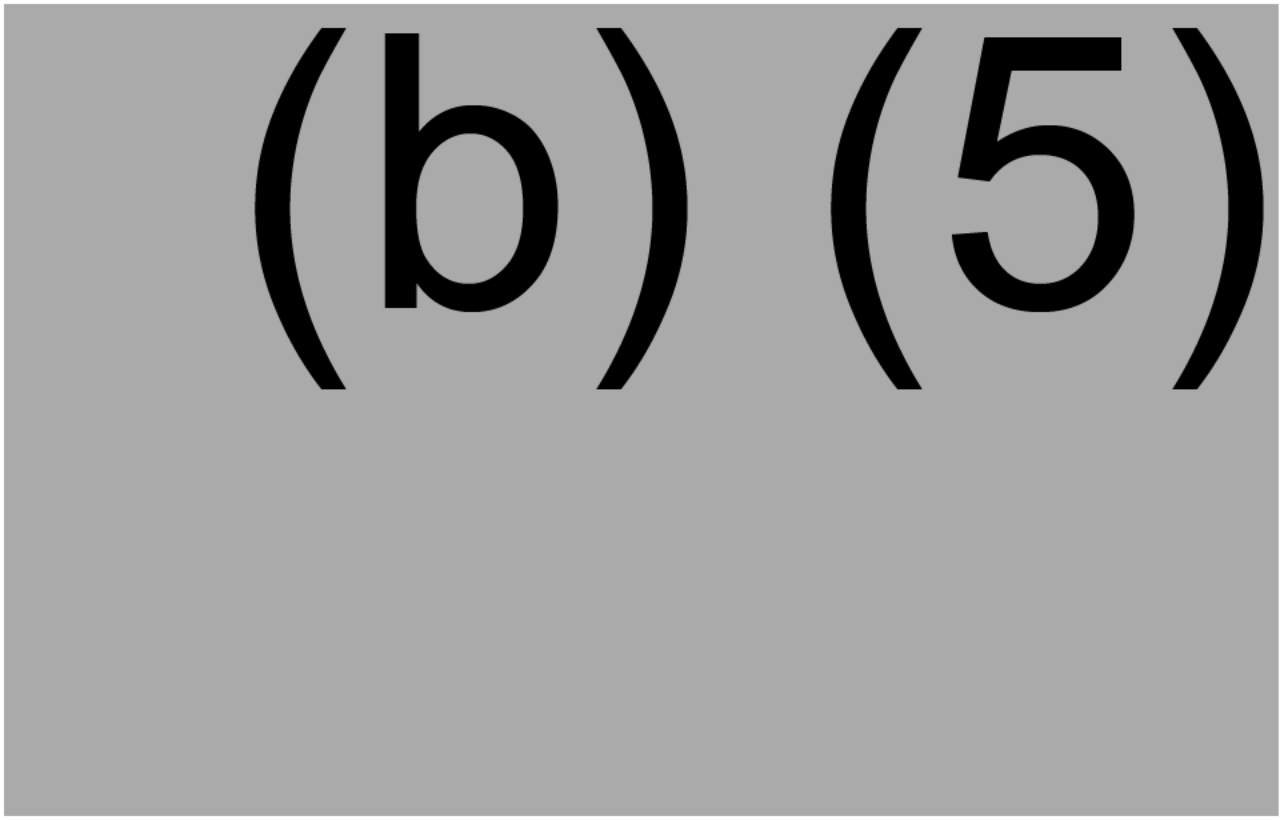
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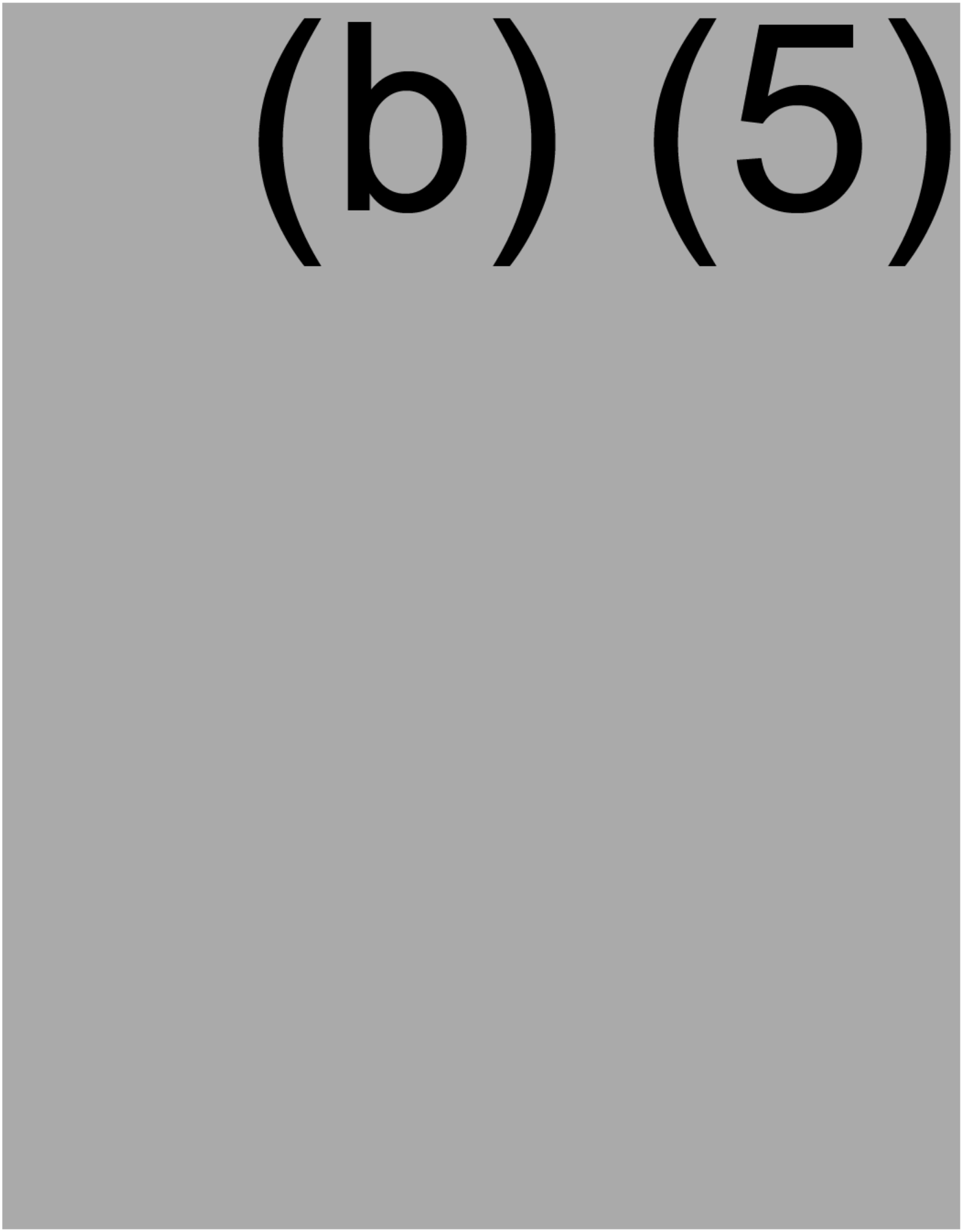
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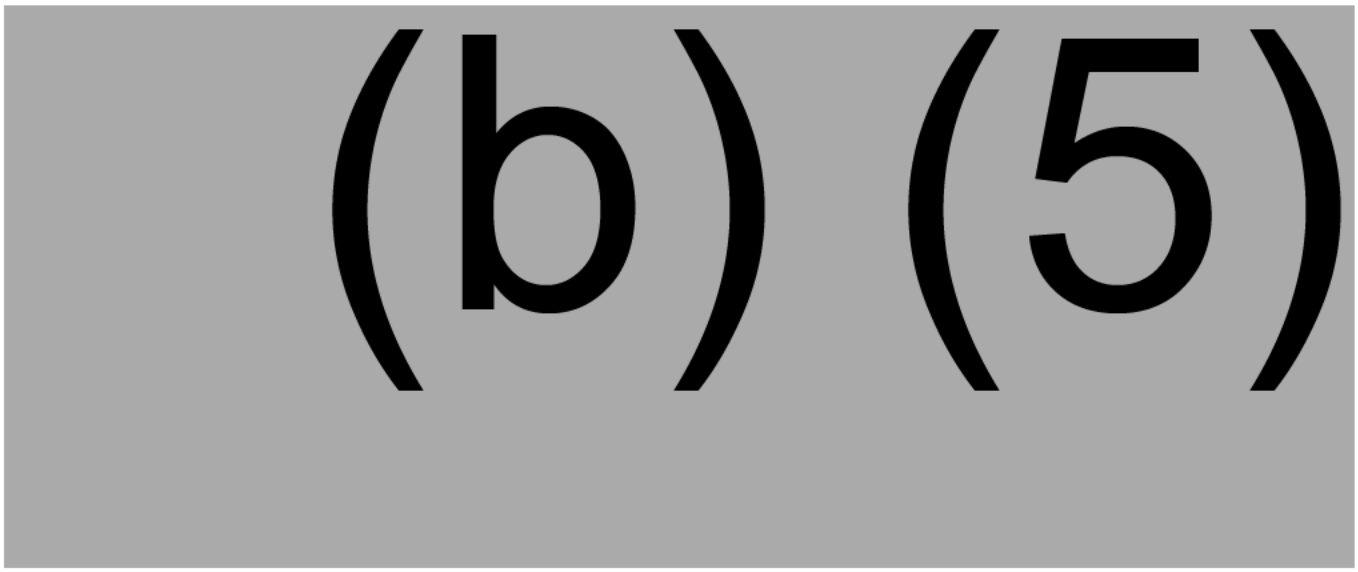
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From: Olivarria, Frank [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=C180721DB774423F99990DD86E67057C-FRANK.OLIVA]
Sent: 3/28/2022 1:09:54 PM
To: Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]
CC: Sheehy, Janice [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f45a6c96f5274724a1be5970eb648ff7-JSheehy]
Subject: Follow Up (OEA Slide Deck-Misinformation): FRIDAY HOMEWORK 03.25.2022 - INTERNAL CONFIDENTIAL
Attachments: 0930-FINAL_Misinformation_Combat_Plan_March2022.pptx

Hi Dr. Califf, you completed two of three items here, but one remains outstanding, below, I also have one item outstanding from Thursday, sending that now as well.

Action: Commissioner review, feedback/further thoughts requested by Monday, 3/28, 9 AM: 0930-FINAL_Misi...	**ITEM #3: OEA Slide Deck:** *Curbing Misinformation / Disinformation (background/action plan)* • **Anticipated Presentation Date:** Week of April 4th • **Note:** OEA aims to discuss this slide deck with OCC the week of 4/4, your feedback and thoughts on this are kindly requested for consideration at the OEA/OCC meeting • **HW POC**: Erica Jefferson (OEA)

Thank you,
Frank

From: Olivarria, Frank
Sent: Friday, March 25, 2022 8:12 PM
To: 'Dr. Califf' (b) (6)@fda.hhs.gov>
Cc: Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Jefferson, Erica <Erica.Jefferson@fda.hhs.gov>; Rebello, Heidi <Heidi.Rebello@fda.hhs.gov>; Sheehy, Janice <Janice.Sheehy@fda.hhs.gov>; Copeland, Jakea <Jakea.Copeland@fda.hhs.gov>; 'Emily Helms Williams' <Emily.HelmsWilliams@fda.hhs.gov>
Subject: FRIDAY HOMEWORK 03.25.2022 - INTERNAL CONFIDENTIAL

Good evening Dr. Califf,

For your action (three items):

ITEM(S) FOR YOUR REVIEW (INTERNAL/CONFIDENTIAL/NOT FOR PUBLIC DISTRIBUTION)

Action: Commissioner review, feedback, edits, or Commissioner clearance requested by Monday, 3/28, 9 AM: << File: 3.25.2022_FDA budget all hands.docx >>	**ITEM #1: Draft All Hands Message from Commissioner Califf:** *The President's FY 2023 Budget* • **Anticipated Release Date:** not provided, inquired • **HW POC**: Bessy Guevara (OEA)
Action: Commissioner review, feedback, edits, or Commissioner clearance requested by Monday, 3/28, 9 AM: << File: Draft CTP All Hands for RMC Review.docx >>	**ITEM #2: Draft All Hands Message from Commissioner Califf:** *Personnel News – Center for Tobacco Products Acting Director* • **Anticipated Release Date:** Week of 3/28, TBD • **Note:** Close hold • **HW POC**: Heidi Rebello (OEA)
Action: Commissioner review, feedback/further thoughts requested by Monday, 3/28, 9 AM: << File: 0930-FINAL_Misinformation_Combat_Plan_March2022.pptx >>	**ITEM #3: OEA Slide Deck:** *Curbing Misinformation / Disinformation (background/action plan)* • **Anticipated Presentation Date:** Week of April 4th • **Note:** OEA aims to discuss this slide deck with OCC the week of 4/4, your feedback and thoughts on this are kindly requested for consideration at the OEA/OCC meeting • **HW POC**: Erica Jefferson (OEA)

Thank you,

Frank

Frank A. Olivarria
Management and Program Analyst
Immediate Office, Office of the Commissioner
U.S. Food and Drug Administration
Tel: 240-402-9882
Frank.Olivarria@fda.hhs.gov

From: Greg Pilcher (b) (6)
Sent: 4/7/2022 10:03:27 AM
To: FDA Commissioner [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1e34b2c290a94c4a8d7af884727cd0f8-Commissione]
Subject: [EXTERNAL] Children don't need Covid injections

Dear FDA Commissioner Robert Califf,

It's well known by anybody paying attention that Covid poses no significant risk to young children, including babies. On the other hand, it also is well known, and federal regulators have acknowledged, that the Covid-19 shots do pose very real risks of harm, including specifically by creating an increased risk for heart ailments like myocarditis, as well as a myriad of other complications.

Under such circumstances (i.e., no real risk from Covid-19 but very real risks from the Covid-19 injections), no child ever should be injected with a Covid-19 shot.

Please do not allow Covid-19 shots for children.

While you're at it, please rescind the approvals previously issued for any and all Covid-19 injections for every other cohort. Thinking people know that the shots are far more dangerous that the respiratory virus that is easily treated with common, safe, and highly effective medicines like hydroxychloroquine and ivermectin, and nutraceuticals like vitamins C & D and zinc.

Regards,
Greg Pilcher
(b) (6)

From: Paul Schlimgen (b) (6)
Sent: 4/7/2022 9:25:33 AM
To: FDA Commissioner [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1e34b2c290a94c4a8d7af884727cd0f8-Commissione]
Subject: [EXTERNAL] Babies and Toddlers don't need COVID shots!

Dear FDA Commissioner Robert Califf,

There is no reason to vaccinate young children. The chance of harm for children getting so-called Covid is virtually non existent, approaching 0. It has been demonstrated over time that the Covid vaccine does not stop transmission of the disease. It has been demonstrated that the vaccine creates pathogens in the human body that lingers for at least 12 months, which breaks down internal organs. It has been demonstrated that there are commonly available, inexpensive medicines that "cure" Covid- Ivermectin and Hydochlorine are two, as well as nasal treatments, since Covid starts in the nasal passages. The current vaccine is only approved for emergency use- the only approved vaccine-Commitity or whatever is not available in the US. This is no longer an emergency. People all over the world are being educated- the time of your lies being effective has ended. Please stop your illegal and immoral activities. There is a God, and there is a judgement.

Regards,
Paul Schlimgen
(b) (6)

From: Curtis Wolford (b) (6)
Sent: 4/7/2022 8:38:40 AM
To: FDA Commissioner [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1e34b2c290a94c4a8d7af884727cd0f8-Commissione]
Subject: [EXTERNAL] Children are not science experiments

Dear FDA Commissioner Robert Califf,

Children are not science experiments, and they should never be used as guinea pigs. The covid shots have proven to have enough harmful effects in adults that it is unthinkable to inflict children with these things. Given that there are now enough treatment methods for covid, its variants, and similar illnesses such as Ivermectin, monoclonal antibodies, paxlovid, and remdesivir, the covid shots (aka, vaccines) are no longer necessary, especially for the one group of our society's population that we should always seek to protect from harm (as in the covid shot's multiple and severe side effects) and to keep out of all politically driven decisions.

Regards,
Curtis Wolford
(b) (6)

From: Helen Seiler (b) (6)
Sent: 4/7/2022 12:45:01 PM
To: FDA Commissioner [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1e34b2c290a94c4a8d7af884727cd0f8-Commissione]
Subject: [EXTERNAL] Babies and Toddlers don't need COVID shots!

Dear FDA Commissioner Robert Califf,

Do NOT approve any COVID vaccines for children. Accurate data from around the world shows that the COVID vaccines do NOT prevent people from getting COVID, spreading COVID or dying from COVID. The data also shows that hundreds of thousands of people have either been severely disabled or died as a result of receiving COVID vaccines. If you truly want to do what is best for American citizens, you would promote Ivermectin and other already available treatments such as https://covid19criticalcare.com/covid-19-protocols/

Regards,
Helen Seiler
(b) (6)

From: Robin Watson (b) (6)
Sent: 4/7/2022 12:46:42 PM
To: FDA Commissioner [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1e34b2c290a94c4a8d7af884727cd0f8-Commissione]
Subject: [EXTERNAL] Babies and Toddlers don't need COVID shots!

Dear FDA Commissioner Robert Califf,

If you are trying to eliminate a lot of people, then you are doing a good job.
If not, then read the Pfizer documents that have been forced to be published and look at the outcomes worldwide of inoculations being administered. Children do not need them, nobody does. What we do need is being effectively suppressed by Fauci etc. continuing the decades of damage he has done.
(Hydroxychloroquine, Ivermectin etc)

Regards,
Robin Watson
(b) (6)

From: Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]
Sent: 4/14/2022 11:22:12 AM
To: Randy Pittman (b) (6)
Subject: Re: [EXTERNAL] Please read as I need help in understanding

Sure. We can hope so. Janet W

From: Randy Pittman <(b) (6)>
Sent: Thursday, April 14, 2022 11:13:12 AM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: Re: [EXTERNAL] Please read as I need help in understanding

Thanks for your reply. I appreciate your indepth and long explanation. Im not sure LERONLIMAB will ever be a covid 19 drug. I do believe it will benefit cancers, HIV and NASH. Thanks again Janet!

On Thu, Apr 14, 2022, 7:42 AM Woodcock, Janet <Janet.Woodcock@fda.hhs.gov> wrote:

> Thank you for writing, Mr. Pittman. I know you have written before on this subject. Please be assured that FDA scientists will leave no stone unturned in the search for effective treatments for severe COVID-19.
>
> I have heard from many citizens who are puzzled and frustrated that a wide range of therapies that they support (everything from ivermectin to highly investigational drugs) have not received EUAs. They also speculate that "big Pharma" is somehow to blame. Let me first point out the most widely used drug in the severe phase of disease, a known lifesaver, is dexamethasone, a very inexpensive generic drug in the US. Second, "big Pharma" has tried many novel drugs in this setting that have failed—for example, the monoclonal antibodies that don't help in severe disease and may make things worse. Some repurposed drugs that have received EUAs required multiple trials before the treatment effect was understood and an EUA was granted. Other than remdesivir, that has known antiviral effects against SARS-CoV-2, no purely investigational drug has been approved or EUA'd for the severe disease setting, and remdesivir should be used early.
>
> I think the source of the frustration is the fact that clinical trial reasoning—the way we make a connection between a drug and a positive effect in people—is not well understood, and is different from how you would, say, decide how strong a structural girder needs to be in a bridge or building. We have much less understanding of human biology and disease than we do of many other facets of our life. Time and again we have seen that we can't use mechanistic reasoning to definitively predict what will happen with a treatment. This is why about 9 out of every 10 drugs reaching the clinic still fail to succeed. We just don't know enough and we have to work empirically.
>
> I hope this helps. I do not know the particulars of the leronlimab program, as I have recused myself from decision-making in matters I was involved in at "Operation Warp Speed".
>
> Janet Woodcock

From: Randy Pittman (b) (6)
Sent: Wednesday, April 13, 2022 9:18 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: [EXTERNAL] Please read as I need help in understanding

As a retired Air Force two war veteran I've been a large supporter of what ever it takes to save lives and protect lives. Im trying to figure something out. I just can't understand why Leronlimab has had to fight so hard to see the light of day. From strong peer reviews, numerous virologists in the US, Italy and overseas and now DSMB last week in Brazil stating how safe and effective Leronlimab is. Why is this medicine that has shown it helps with mTNB, HIV, covid as Brazil trial is 4 injections versus 2 done in US CD 12 trial and still closely missed stat sig. I totally understand the CEO was not a medical doctor. I'm very excited that now the CYDY executive board and scientific board has regrouped and loaded it self with top notch doctors with years of experience coming from Big Pharma. I know they are righting the ship so to speak. They all believe Leronlimab works. It is a new age in viral load suppression as it prevents viruses from spreading through the body via CCR5 receptor. It reduces inflammation and transfers through the blood brain barrier. I may be way off from months and years of research on this monoclonal antibody. I just for the life of me can't understand if its that Big Pharma sees this as a threat and their major outdated drugs will become obsolete and Leronlimab would treat so many indications that Big Pharma would lose billions and billions? I mean if 40% of the FDA funding comes from big pharma now wouldn't you want to support the next new advance in medicine and reap the funding they would provide? I look at current Big pharma drugs (not all) as the old gas powered motors polluting the air and Leronlimab as an elite hydrogen machine that just provides an updated cure to numerous indications once thought untreatable. It took penicillin over 7 years to get approved. Thank how many lives would have been saved if it was approved just one or two years earlier. I know the old fashion way of trials, testing and P values worked great for the old drug trials. Maybe a medicine so advanced can't truly be evaluated by the same standards if one thinks outside the box? You can't even relate the testing of a old gas motor (current drugs) to an electric or hydrogen vehicle (new advanced monoclonal antibody Leronlimab). I pray each day that the drug gets an opportunity to help people live. It's been documented it's saved stage 4 pancreatic and mTNB cancer Patience's. It has agreements with MD Anderson oncology, numerous educational institutions are now doing studies with it on Alzheimer's, one on brain cancer etc. If it's a joke medicine or water as some say then how does it reduce the SHIV and human HIV mono therapy viral load by 10,000 fold. I just can't help to think this drug is being black balled and I hope that changes in the sake of thousands of human lives over Big Pocket and control. Let me know openly and candidly off the record what I'm missing. I always thought I was an educated man but this situation leaves me not sure

Sincerely Randy Pittman

From: Woodcock, Janet [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7B0453354A9A427DB0A66A86C7A36F3D-JANET.WOODC]
Sent: 4/7/2022 6:07:57 PM
To: Raza, Mark [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5811a7d72ee34aa78ff3c8ccb59f92ee-MRaza]; Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]; Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]; Cavazzoni, Patrizia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c42abd33834044ecbaa03d075cc0a5d2-Patrizia.Ca]; Dickinson, Elizabeth (FDA) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05cb143d66ed470ebe4dba5c54a88074-EDickins]
CC: Jefferson, Erica [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0bc0bd0f8766484b803f584eb491ace6-Erica.Jeffe]
Subject: RE: Is this legal?

Our response might be more along the lines of how ill-advised this is in the face of significant evidence that it does not help COVID. Availability could make people not use highly effective treatments and have bad outcomes. jw

---

From: Raza, Mark <Mark.Raza@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:26 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Califf, Robert (b) (6)@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: RE: Is this legal?

(b) (5)

Happy to have our folks take a look.

Mark

From: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:10 PM
To: Califf, Robert < (b) (6)@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Raza, Mark <Mark.Raza@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: RE: Is this legal?

It is possible for them to do in the state I think but there is Federal preemption. Is hilarious. jw

---

From: Califf, Robert < (b) (6)@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:09 PM
To: Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Raza, Mark <Mark.Raza@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: Is this legal?

https://thehill.com/news/state-watch/3261642-tennessee-senate-passes-bill-to-allow-over-the-counter-sales-of-ivermectin/

From: Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]
Sent: 4/10/2022 4:54:52 PM
To: Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]
Subject: Fwd: Research letter on Corticosteroid/COVID-19 work published today in JAMA
Attachments: jama_bradley_2022_ld_220020_1649354358.18365.pdf

I asked them to do this analysis. Look at the south! Jw

From: Dal Pan, Gerald <Gerald.DalPan@fda.hhs.gov>
Sent: Sunday, April 10, 2022 3:25:00 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Stein, Peter <Peter.Stein@fda.hhs.gov>
Subject: Research letter on Corticosteroid/COVID-19 work published today in JAMA

Janet, Patrizia, and Peter,

Our Research Letter examining the percentage of persons with a COVID-19 diagnosis who were prescribed corticosteroids in the outpatient setting within 14 days of that diagnosis was published a few days ago in JAMA (attached). The percentages were 16.4% in Medicare and 9.4% in Sentinel.

Please let me know if you have any questions.

Gerald

Letters

RESEARCH LETTER

Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021

In June 2020, preliminary results for the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial conducted in the UK indicated benefit from dexamethasone in severely ill hospitalized patients with COVID-19 but potential harm in those not requiring oxygen.[1,2] In October 2020, the National Institutes of Health (NIH) issued COVID-19 treatment guidelines advising against systemic corticosteroid use in patients with mild to moderate COVID-19.[1] Using 2 large US health care claims databases, we examined systemic corticosteroid use among nonhospitalized patients with COVID-19.

Supplemental content

Methods | Data from Medicare fee-for-service and the US Food and Drug Administration's (FDA's) Sentinel System were used. Medicare is a federal health insurance program mostly serving those aged 65 years or older.[3] The Sentinel System comprises primarily claims data from commercially insured patients of all ages in a distributed network of data partners.[4] The Sentinel Rapid COVID-19 data source used in this analysis included 2 national insurance claims data partners and 2 integrated delivery care systems.

Nonhospitalized, noninstitutionalized patients with incident COVID-19 between April 2020 and August 2021 (July 2021 for Sentinel) were included. Incident outpatient COVID-19 was defined as a diagnosis code for COVID-19 or positive SARS-CoV-2 laboratory test (Sentinel only) recorded on an outpatient claim, including emergency department claims without subsequent hospitalization. Those with COVID-19 within the prior 183 days and those with use of systemic corticosteroids within the prior 90 days were excluded. Patients were followed up from COVID-19 diagnosis date until the earliest occurrence of a claim for a new oral or injectable corticosteroid in an outpatient setting, hospitalization, death, disenrollment, or 14 days. Demographics, clinical characteristics, and among corticosteroid initiators, corticosteroid type, timing, setting of initiation, prescriber specialty, and concomitant therapies were examined (eTable in the Supplement).

Table. Characteristics and Comorbidities of Patients With COVID-19 and Those Initiating Systemic Corticosteroids Within 14 Days of Diagnosis

	Medicare (April 1, 2020-August 31, 2021)			US FDA's Sentinel System (April 1, 2020-July 31, 2021)		
	COVID-19 diagnosis	Corticosteroid use[a]	Rate, %[b]	COVID-19 diagnosis	Corticosteroid use[c]	Rate, %[b]
Demographic and clinical characteristics						
Total No. of patients	576 885	94 781	16.4	766 105	72 124	9.4
Age, mean (SD), y	74.6 (7.2)	74.4 (6.9)		48.5 (19.9)	57.7 (16.7)	
Age group, No. (%), y						
<44				339 385 (44.3)	18 008 (25.0)	5.3
45-64				204 350 (26.7)	23 552 (32.7)	11.5
65-79	443 664 (76.9)	74 300 (78.4)	16.7	176 533 (23.0)	24 811 (34.4)	14.1
≥80	133 211 (23.1)	20 481 (21.6)	15.4	45 837 (6.0)	5753 (8.0)	12.6
Sex, No. (%)						
Male	249 044 (43.2)	42 516 (44.9)	17.1	357 697 (46.7)	32 988 (45.7)	9.6
Female	327 841 (56.8)	52 265 (55.1)	15.9	408 408 (53.3)	39 136 (54.3)	9.2
Race and ethnicity, No. (%)[d]						
Asian	9391 (1.6)	1080 (1.1)	11.5	19 210 (2.5)	1146 (1.6)	6.0
Black or African American	26 425 (4.6)	3048 (3.2)	11.5	50 417 (6.6)	4530 (6.3)	9.0
Hispanic	14 423 (2.5)	1944 (2.1)	13.5	53 420 (7.0)	4453 (6.2)	8.3
Native American	3226 (0.6)	409 (0.4)	12.7	2965 (0.4)	280 (0.4)	9.4
Native Hawaiian/other Pacific Islander				3738 (0.5)	329 (0.5)	8.8
White	500 563 (86.8)	85 302 (90.0)	17.0	298 976 (39.0)	30 797 (42.7)	10.3
Other[e]	6971 (1.2)	862 (0.9)	12.4			
Unknown	15 886 (2.8)	2136 (2.3)	13.4	390 799 (51.0)	35 042 (48.6)	9.0
US region, No. (%)[f]						
Northeast	104 929 (18.2)	8864 (9.4)	8.4	139 333 (18.2)	7284 (10.1)	5.2
Midwest	135 261 (23.5)	20 394 (21.5)	15.1	152 091 (19.9)	11 792 (16.3)	7.8
South	241 340 (41.8)	53 437 (56.4)	22.1	302 766 (39.5)	43 523 (60.3)	14.4
West	94 553 (16.4)	12 056 (12.7)	12.8	161 097 (21.0)	9167 (12.7)	5.7

(continued)

Table. Characteristics and Comorbidities of Patients With COVID-19 and Those Initiating Systemic Corticosteroids Within 14 Days of Diagnosis (continued)

	Medicare (April 1, 2020-August 31, 2021)			US FDA's Sentinel System (April 1, 2020-July 31, 2021)		
	COVID-19 diagnosis	Corticosteroid use[a]	Rate, %[b]	COVID-19 diagnosis	Corticosteroid use[c]	Rate, %[b]
Comorbidities, No. (%)						
Hematologic cancer	10 798 (1.9)	1784 (1.9)	16.5	4159 (0.5)	581 (0.8)	14.0
Congestive heart failure	40 961 (7.1)	7022 (7.4)	17.1	22 893 (3.0)	3285 (4.6)	14.3
Hospitalized acute myocardial infarction	2173 (0.4)	319 (0.3)	14.7	1147 (0.1)	85 (0.1)	10.9
Hypertension	351 427 (60.9)	59 589 (62.9)	17.0	217 346 (28.4)	30 880 (42.8)	14.2
Stroke or transient ischemic attack	1890 (0.3)	261 (0.3)	13.8	1098 (0.1)	85 (0.1)	7.7
Chronic kidney disease	65 747 (11.4)	10 770 (11.4)	16.4	40 355 (5.3)	5559 (7.7)	13.8
Diabetes	148 235 (25.7)	24 070 (25.4)	16.2	110 730 (14.5)	14 733 (20.4)	13.3
Taking immunosuppressant therapies	33 600 (5.8)	5625 (5.9)	16.7	15 702 (2.0)	2122 (2.9)	13.5
Obesity	90 793 (15.7)	17 250 (18.2)	19.0	104 244 (13.6)	15 416 (21.4)	14.8
Chronic obstructive pulmonary disease	41 908 (7.3)	9892 (10.4)	23.6	26 625 (3.5)	5581 (7.7)	21.0
Asthma	30 596 (5.3)	6706 (7.1)	21.9	32 055 (4.2)	5123 (7.1)	16.0
Rheumatologic and inflammatory conditions	37 238 (6.5)	6669 (7.0)	17.9	28 411 (3.7)	4042 (5.6)	14.2
Smoking	69 016 (12.0)	12 191 (12.9)	17.7	51 602 (6.7)	7215 (10.0)	14.0
Combined Charlson and Elixhauser comorbidity indices[g]						
Mean (SD)	0.8 (1.8)	0.8 (1.8)		0.5 (1.4)	0.7 (1.7)	
Median (IQR)	0 (0-1.0)	0 (0.1-1.0)				

[a] A total of 13 007 eligible patients (2.25%) were censored because they died, were disenrolled, or were hospitalized within 14 days after COVID-19 diagnosis.

[b] Calculated as corticosteroid use/outpatient COVID-19 diagnosis.

[c] A total of 336 eligible patients (<1%) were censored because they died or were disenrolled and 29 960 (3.9%) because they were hospitalized within 14 days after COVID-19 diagnosis.

[d] In Sentinel, race and ethnicity were separate variables, so a patient could have both a race and Hispanic ethnicity; therefore, the percentages do not equal 100%.

[e] Patients reported "other" and did not select another category.

[f] A small percentage of patients were not categorized into a region; therefore, the percentages do not equal 100%.

[g] The assessment period was 183 days prior to COVID-19 diagnosis. Additional details appear in the Supplement.

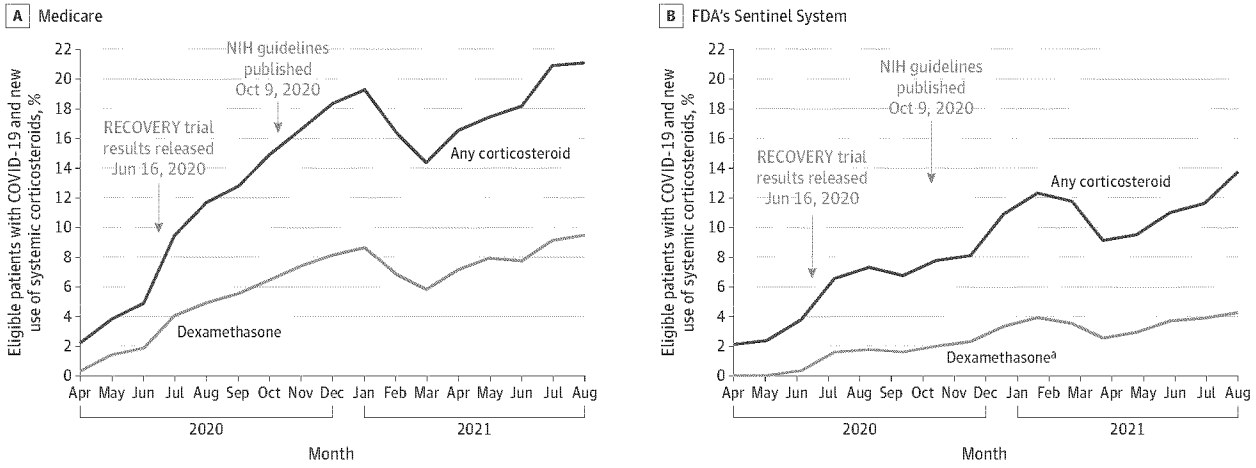
Analyses were descriptive and performed using SAS version 9.4 (SAS Institute Inc). This study was classified as public health surveillance by the FDA and exempted from review by the institutional review board in accordance with the updated Common Rule.

Results | There were 576 885 eligible patients with COVID-19 in Medicare and 766 105 in Sentinel, the mean age was 74.6 years (SD, 7.2 years) and 48.5 years (SD, 19.9 years), respectively, and the proportion of males was 43.2% and 46.7% (**Table**). Of these, 16.4% in Medicare and 9.4% in Sentinel received systemic corticosteroids in an outpatient setting within 14 days of COVID-19 diagnosis (**Figure**). The proportion of patients initiating corticosteroids in the South was higher than in any other region. Use increased with age until approximately 79 years. Corticosteroid use increased over time from 2.2% initiating in April 2020 to 21.1% in August 2021 in Medicare, and from 2.2% in April 2020 to 13.8% in July 2021 in Sentinel.

Among pharmacy dispensings, the most commonly used corticosteroids were dexamethasone in Medicare (43.8%) and prednisone in Sentinel (34.1%). The most common prescriber specialties in Medicare were internal medicine or family/general practice (39.9%) and emergency medicine (18.6%). Treatment often started on the day of COVID-19 diagnosis (58.8% for Medicare vs 51.3% for Sentinel), largely through pharmacy dispensings (70.8%-80.3%) rather than during medical encounters. On the day corticosteroid use was initiated, 24.7% in Medicare had visited the emergency department vs 22.9% in Sentinel. Azithromycin was the most common concomitant therapy (44.8% for Medicare vs 48.8% for Sentinel)—often initiated on the same date as the corticosteroid—followed by monoclonal antibodies (Medicare: 7.1%; Sentinel: 2.0%), inhaled corticosteroids (Medicare: 2.4%; Sentinel: 6.7%), ivermectin (Medicare: 3.9%; Sentinel: 3.5%), and nonoral anticoagulants (Medicare: 3.6%; Sentinel: 3.1%).

Discussion | Despite NIH recommendations, increasing numbers of nonhospitalized patients with COVID-19 were prescribed systemic corticosteroids, often on the day of diagnosis. Use appeared to be more prominent in the South and was not restricted to older patients. Limitations of the study included inability to capture date of symptom onset and indication for use, and potential for misclassifying mild to moderate COVID-19 disease due to overburdened resources and limited ability to accurately capture elements to define disease severity, including oxygen use. Given the increasing use of corticosteroids through August 2021, the potential safety signal,[2,5,6] and the lack of efficacy data in patients with mild to moderate COVID-19,[1] it is critical that prescribers consider the NIH guidelines in the therapeutic management of nonhospitalized patients with COVID-19.

Figure. Proportion of Patients With COVID-19 Initiating Systemic Corticosteroids Within 14 Days of Diagnosis



FDA indicates Food and Drug Administration; NIH, National Institutes of Health; RECOVERY, Randomised Evaluation of COVID-19 Therapy.

[a] The name of the corticosteroid was only available for pharmacy dispensings.

Marie C. Bradley, PhD, MPharm, MScPH
Silvia Perez-Vilar, PhD, PharmD
Yoganand Chillarige, MPA
Diane Dong, RN, MPH
Ashley I. Martinez, PharmD, PhD
Andrew R. Weckstein, BA
Gerald J. Dal Pan, MD, MHS

Author Affiliations: Office of Surveillance and Epidemiology, US Food and Drug Administration, Silver Spring, Maryland (Bradley, Perez-Vilar, Dal Pan); Acumen LLC, Burlingame, California (Chillarige); Department of Veterans Affairs Center for Medication Safety, Hines, Illinois (Dong); Department of Population Medicine, Harvard Medical School, Boston, Massachusetts (Martinez); Aetion Inc, New York, New York (Weckstein).

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Corresponding Author: Marie C. Bradley, PhD, MPharm, MScPH, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20903 (marie.bradley@fda.hhs.gov).

Author Contributions: Mr Chillarige and Dr Martinez had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bradley, Perez-Vilar, Chillarige, Martinez, Weckstein, Dal Pan.
Acquisition, analysis, or interpretation of data: Bradley, Perez-Vilar, Chillarige, Dong, Martinez, Weckstein.
Drafting of the manuscript: Bradley, Perez-Vilar.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Chillarige, Dong, Martinez, Weckstein.
Obtained funding: Dal Pan.
Administrative, technical, or material support: Bradley, Martinez, Weckstein, Dal Pan.
Supervision: Bradley, Perez-Vilar, Chillarige, Dal Pan.

Conflict of Interest Disclosures: Mr Chillarige reported receiving personal fees from Acumen LLC. Mr Weckstein reported being employed by and having an ownership interest (stock options or existing equity) in Aetion, a technology company that provides analytic software and services to the health care industry. No other disclosures were reported.

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Role of the Funder/Sponsor: The authors who were employees or contractors of the FDA, the CMS, or the Veterans Health Administration (VHA) played a role in the design; however, other officials at the FDA, the CMS, and the VHA had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The manuscript was subjected to administrative review before submission, but this review did not alter its content.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect those of the FDA, the CMS, the VHA, or the DHHS.

Additional Contributions: We thank David J. Graham, MD, MPH, Efe Eworuke, PhD, and Hana Lee, PhD (FDA); Jeffrey A. Kelman, MD, MSSc (CMS); Sandia Akhtar, BS, Hai Lyu, MS, and Kushal B. Naik, MBBS, MPH (Acumen LLC); and Austin Cosgrove, BS, Noelle Cocoros, DSc, MPH, and Judith Maro, PhD, MS (Department of Population Medicine, Harvard Medical School). We also thank the institutional partners that provided the data used in the Sentinel analysis: CVS Health Clinical Trial Services (an affiliate of Aetna), HealthPartners Institute, Humana Inc, and Kaiser Permanente Northwest Center. No compensation was received for this work.

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From: Woodcock, Janet [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7B0453354A9A427DB0A66A86C7A36F3D-JANET.WOODC]
Sent: 4/11/2022 12:33:33 PM
To: Cavazzoni, Patrizia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c42abd33834044ecbaa03d075cc0a5d2-Patrizia.Ca]
Subject: RE: Fluvoxamine EUA request

Agree, and yes, I think they are quite close. It is ACTIV 6 so it is a low touch trial I think they only have about 800 enrolled in this part, and it is not looking at decreasing hosp/high risk. Turns out a lot of people take antidepressants already, so accrued slower than other arms, e.g. ivermectin. If it works a bit, might be ok for low risk people to decrease sx or something. jw

From: Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>
Sent: Monday, April 11, 2022 12:13 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: FW: Fluvoxamine EUA request

I tend to agree this doesn't meet the threshold based on the data that are available right now. Is fluvoxamine in ACTIV?
Patrizia

From: Stein, Peter <Peter.Stein@fda.hhs.gov>
Sent: Monday, April 11, 2022 11:30 AM
To: Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>
Subject: Fluvoxamine EUA request

Patrizia,
The Division is planning a denial for the authorization request re fluvoxamine. I think that's a reasonable assessment/decision, but wanted to provide you some background…..

There are 4 clinical trials for fluvoxamine in COVID – outpatient treatment. The initial one (STOP COVID 1) was a very small study (~ 150 patients) done in outpatients, with telephone contact follow up – and had an endpoint of dyspnea/low O2 sat (<92%) or hospitalization. There were few events, but meeting stat significance favoring drug. A larger trial (TOGETHER, 1500 patients) was done entirely in Brazil that met stat significance for prolonged ER visit (> 6 hrs observation), stat significance was not met for hospitalization/death (but trended, with p of 0.10, and a HR of ~ 0.78). A second STOP COVID trial was done (STOP COVID 2) that was 3-4 x larger than STOP COVID 1 but with the same basic design, and failed to find stat significance or even a substantive trend (HR 0.93 with 11/274 vs 12/272 events) – not yet published. Another trial (COVID-OUT) also did not show

benefit (HR 0.90, p NS) – this was the paper that Boulware sent – although the fluvoxamine dose was lower than in the other trials (100/d vs 200/d).

The pharmacology of the drug is interesting – and there are potential mechanisms, mostly anti-inflammatory, that could be engaged at relevant clinical doses – but this has not been studied in animal models or other clinical scenarios so no evidence generated supporting the in vitro data (that does not include any data specific to COVID).

Even if we were to authorize this, I think the likelihood of NIH guidelines supporting this is very small. If we were to consider this meeting "may be effective" and "known/potential benefits…." – I would be very concerned that patients would get this instead of paxlovid or Bebto or MOL, which I see as the biggest risk here (and I am not considering cost/reimbursement issues).

I suspect this may be a notable denial given that this is a repurposed drug – with a well-known safety profile.

In summary, the preclinical data is limited, but does suggest in vitro activity that may be relevant at achieved doses, clinical data is conflicting, but with one large positive trial – overall not particularly compelling, and the risk that worries me most is redirecting patients away from effective therapies shown in appropriately done/designed RCTs.

I do support the Division's decision on this, but let me know if you want a briefing – or we could also bring this to MPPRC.

Regards, peter

From: Woodcock, Janet [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7B0453354A9A427DB0A66A86C7A36F3D-JANET.WOODC]
Sent: 3/30/2022 9:33:59 PM
To: Cavazzoni, Patrizia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c42abd33834044ecbaa03d075cc0a5d2-Patrizia.Ca]
Subject: RE: ivermectin

Thx jw

From: Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>
Sent: Wednesday, March 30, 2022 6:35 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: ivermectin

https://www.nejm.org/doi/full/10.1056/NEJMoa2115869

Patrizia

From: Cohen, C. Lee [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=96B23AF7B7D740D291E23AECACEB3D7F-CAITLIN.COH]
Sent: 4/21/2022 4:53:54 AM
To: Colonius, Tristan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2b3590c046734a2e928858bd579ed852-Tristan.Col]; Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]
Subject: Defending Advanced Manufacturing from some changes?
Attachments: Authorizers and Appropriators Supp Report 4.20.22.docx

Hello Dr. Woodcock and Tristan,

I've reconciled all the edits and sent a volley of followups that I will try to nail down later this morning. Overall, I have managed to avoid too much un-writing of the content except for one pretty big pitfall: CBER's edits (b) (5) (b) (5) (b) (5) I redrafted the section to address what I think are the ideas behind their edits while still maintaining what I hope is simple, clear, and specific language. I put in comments with extensive rationales for word choice and why I am declining some of their suggestions… but I fear that this will not go over well (they were already displeased with not being able to red-line). I attached here the most recent master draft I have ((b) (5) (b) (5)

What do you think is the best way to approach this? I haven't sent them these edits yet (except one of them in an email).

Thanks,
Lee

C. Lee Cohen, MD MBA (she/her)
Scientific Advisor, Strategic Initiatives Team, Office of the Commissioner

U.S. Food and Drug Administration
((b) (6) (cell)
Caitlin.Cohen@fda.hhs.gov

FDA COVID-19 Supplemental Supported Initiatives

April 2022

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From: Raza, Mark [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=5811A7D72EE34AA78FF3C8CCB59F92EE-MRAZA]
Sent: 4/7/2022 4:37:30 PM
To: Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]; Califf, Robert [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ad88732be1ed4912a058ee9dd9906f66-Robert.Cali]; Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; Cavazzoni, Patrizia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c42abd33834044ecbaa03d075cc0a5d2-Patrizia.Ca]; Dickinson, Elizabeth (FDA) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05cb143d66ed470ebe4dba5c54a88074-EDickins]
Subject: RE: Is this legal?

Sure thing.

From: Tierney, Julia <Julia.Tierney@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:34 PM
To: Califf, Robert (b) (6)@fda.hhs.gov>; Raza, Mark <Mark.Raza@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: RE: Is this legal?

Mark/Liz – happy to work with you on a QA that is legally accurate but accessible.

From: Califf, Robert (b) (6)@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:27 PM
To: Raza, Mark <Mark.Raza@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: Re: Is this legal?

I think its likely we'll be asked. Would be good to have an answer. What next?

rmc

From: Mark Raza <Mark.Raza@fda.hhs.gov>
Date: Thursday, April 7, 2022 at 4:25 PM
To: "Woodcock, Janet" <Janet.Woodcock@fda.hhs.gov>, Robert Califf (b) (6)@fda.hhs.gov>, Julie Tierney <Julia.Tierney@fda.hhs.gov>, Patrizia Cavazzoni <Patrizia.Cavazzoni@fda.hhs.gov>, Elizabeth Dickinson <Elizabeth.Dickinson@fda.hhs.gov>
Subject: RE: Is this legal?

(b) (5)

Happy to have our folks take a look.

Mark

From: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:10 PM
To: Califf, Robert <(b) (6)@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Raza, Mark <Mark.Raza@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: RE: Is this legal?

It is possible for them to do in the state I think but there is Federal preemption. Is hilarious. jw

---

From: Califf, Robert <(b) (6)@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:09 PM
To: Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Raza, Mark <Mark.Raza@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: Is this legal?

https://thehill.com/news/state-watch/3261642-tennessee-senate-passes-bill-to-allow-over-the-counter-sales-of-ivermectin/

From: Adam, Stacey (FNIH) [T] [sadam@fnih.org]
Sent: 4/7/2022 7:11:11 PM
To: Kurilla, Michael G (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fa2de9594d594ed9b76b935545c26754-HHS-michael]; Erhardt, Bill A (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d795053ca625464f91fa923a0a455ac1-HHS-bill.er]; Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; Read, Sarah W (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=72ca09ea60c74100a908211e1f7c5f6a-HHS-readsa-]; Lane, Henry C (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d904337536cf41719032a9359a1ec2ab-HHS-CLANE-n]; Erbelding, Emily J (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c981f04015d64d27b1afdd9c06111071-HHS-emily.e]; Eakin, Ann E (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d126f4c08a514e12ac2e646ae79bbd20-HHS-ann.eak]; Erica Ollmann Saphire [erica@lji.org]; Stein, Peter [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d30a87acb0184261961264ba984b0a51-Peter.Stein]; Judy Currier [jscurrier@mednet.ucla.edu]; Davey Smith [d13smith@health.ucsd.edu]; Kim, Peter S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2876661346ba42d7a684f7d3ae5c5b4c-HHS-peter.k]; Neaton, Jim [neato001@umn.edu]; Lundgren, Jens (b) (6); Higgs, Elizabeth S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0ac36dd643c04994b3161baf825cbfc3-HHS-ehiggs-]; Kiley, James P (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=47964c0318054e7c98c149a93cfe6ada-HHS-kileyj-]; Goff, David C (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa2747f2f704a3ba1637f2febe8bc67-HHS-david.g]; Dr Susanna Naggie, M.D. [susanna.naggie@duke.edu]; Adrian Hernandez, M.D. [adrian.hernandez@duke.edu]; Dunsmore, Sarah E (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e3ee18c15d824f2394abe93b8a0a2064-HHS-dunsmor]; Nakela Cook [nlcook@pcori.org]; Penny Mohr [pmohr@pcori.org]; Brown, Samuel (b) (6); Barkauskas, Christina [christina.barkauskas@duke.edu]; Fessel, Josh P (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1531bbc9172747829bc72c4ce1176926-HHS-josh.fe]
CC: Carver-Roberts, Trea R (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05c1728ee14540bb9d98a6b7917c85eb-HHS-trea.ca]; Reich, Colleen [cjreich@health.ucsd.edu]; Lisbeth Jørgensen (b) (6); fnih [fnih@roseliassociates.com]; Dana Carluccio [dana.carluccio@roseliassociates.com]; Church, Elizabeth S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1feccbf65b8e4285bc6fa6ede9c44e02-HHS-elizabe]; Melencio, Cheryl L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=baa3813b343d4f4cb949f1b990023053-HHS-cmelenc]; Jabarkhail, Mina [MJabarkhail@mednet.ucla.edu]; Nesin, Mirjana (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=86ffcb8d6be149788e21229c314b60f7-HHS-Mirjana]; Holly Bunton [hbunton@pcori.org]; Fant, Annie (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=01e618455da34f0a8db87cf3fc60ff36-HHS-Annie.F]; Eisnor, Derek (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f7b89712a02b43958d5253c1e79f21a3-HHS-Derek.E]; Kelly Beazley [kelly.beazley@roseliassociates.com]; Menetski, Joseph M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d8ed7bcfcbc04f338026fde223a907ae-HHS-jmenets]; Melton, Serena [smelton@deloitte.com]; Sorosa, Alex [asorosa@deloitte.com]; Cwalina, Alex [acwalina@deloitte.com]; Laura Rodriguez [lrodriguez@pcori.org]; Parker, Ashley S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3f43b948b59f4e679535a8a3ebc91167-HHS-ashley.]; Tara Cole [tcole@pcori.org]; currierea@mednet.ucla.edu
Subject: [EXTERNAL] Summary of the ACTIV-2/-3/-6 Trial Oversight Committee Meeting
Attachments: 2022-04-06_Trial_Oversight_Committee_Meeting_Summary.pdf

Dear ACTIV-2/-3/-3B/-6 TOC Members,

Please find attached the summary of our meeting yesterday. Apologies to all for my audio difficulties, but thank you for a good discussion.

If you have any additions or amendments, please let me know.

Best,
Stacey

Stacey J. Adam, PhD (*she/her*)
Associate Vice President
Research Partnerships
Foundation for the National Institutes of Health
Direct: **(301) 435-8364** | Mobile: (b) (6)
fnih.org
11400 Rockville Pike, Suite 600, North Bethesda, MD 20852

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High-Level Meeting Summary

The ACTIV-2/-3/-6 Trial Oversight Committee (TOC) heard status updates on ACTIV-2, ACTIV-3, and ACTIV-6 trials; discussed future outpatient trial design and challenges with inpatient trial oversight; and reviewed and endorsed the ACTIV-3/3B team's plan to test Evusheld and Shionogi's protease inhibitor.

Trial Accrual Updates

ACTIV-2D has opened its first site and is approaching First Patient In. The ACTIV-3 team is currently drafting manuscripts for completed trials, while ACTIV-3B has enrolled 466 participants (although its accrual has slowed amidst declining case rates). ACTIV-6 has opened 93 sites and randomized 3,572 participants, including 1,537 to the closed low-dose ivermectin arm, 1,127 to the closed fluticasone arm, 773 to fluvoxamine, and 135 to high-dose ivermectin. ACTIV-6 enrollment has continued to skew 2:1 for ivermectin versus fluvoxamine, even after the release of the TOGETHER trial's ivermectin results.

Outpatient Trial Design

ACTIV-2 is interested in developing an ethically appropriate and rigorous outpatient trial design that can surmount the challenges of the current pandemic landscape to diversify EUA- and NDA-approved therapeutics for SARS-CoV-2. Some major challenges to this effort include the inappropriateness of placebo-controlled trials in higher-risk patients, given the current availability of effective agents; the lower event rate of currently circulating virus; and the difficulty of determining the precise treatment effect of available active comparators—and thus non-inferiority margins—in the context of this lower event rate. Once these challenges have been addressed, a study must also obtain properly labeled active comparator; although BARDA has previously agreed to provide commercial Paxlovid, its packaging would not permit blinding.

Participants agreed that a conversation among key stakeholders would help advance the effort to develop a next-generation outpatient trial. The conversation should include representatives from FDA and BARDA, ACTIV trial leads, leaders of real-world observational studies, and potentially drug companies participating in ACTIV. FNIH staff will organize such a conversation to take place after the readout from the first two arms of ACTIV-6, which is expected during the next month. Participants also identified several topics for discussion, described below.

Lessons from Ongoing Studies

The design of ACTIV-6 has pointed to two general approaches for conducting a trial in the context of evolving disease. Rather than prespecify endpoints, studies may select them near the time of analysis in order to align selected variables with the immediate decision-making context. In addition, studies may use ordinal or composite outcomes that balance granular data on both symptom improvement and clinical progression. Data from ACTIV-6's first two arms will enable a closer assessment of the performance of its specific outcome. Analysis of the data will also reveal what proportion of high-risk patients chose to obtain available approved drugs alongside the trial's investigational agents.

Several other ongoing analyses of placebo-controlled trials may help inform the design of future efforts, including the ACTIV-2 team's analysis of symptom resolution data by risk group and an ongoing analysis by FDA and NIAID of quantitative viral load as a surrogate for clinical risk reduction.

Real-Time Real-World Evidence

Drs. Janet Woodcock and John Farley suggested that careful real-time use of real-world evidence might help determine non-inferiority margins. Studies could combine data from an active comparator arm with real-world evidence of placebo event rates in order to calculate an approved drug's treatment effect, or they could use real-world evidence on the active comparator in order to impute effect size more directly. The latter approach was applied retrospectively by a recent Intermountain Healthcare study of monoclonal antibodies (mAbs) during different COVID-19 waves, but could also be applied in real time to develop a concurrent comparison for an ongoing study.

Inpatient Trial Oversight

Drs. Jens Lundgren and Jim Neaton noted that the now-closed ACTIV-3 study of Pfizer's IV infused protease inhibitor raised important questions about regulators' risk/benefit assessments of drugs with a limited safety profile but the potential to address unmet clinical need among COVID-19 inpatients. FDA halted the Pfizer study when it had accrued 58 of an intended 1,000 patients, based on concern over an increased risk of thromboembolic (TE) events. Prior to the decision, FDA took the rare step of reviewing summary data by treatment group while the trial was ongoing, which is ordinarily left to a trial's DSMB. At the time of the decision, FDA and the ACTIV-3 DSMB both had access to data showing that the study's TE event rate, at 8.6 percent, was comparable to an expected event rate of 6.0 percent, and the DSMB had recommended based on the totality of trial data that enrollment continue. No other information from outside ACTIV-3 had been reported to Pfizer's IND that would explain FDA's safety concern, although it remains unclear whether FDA may have had access to other data that affected its interpretation.

Participants agreed that a lessons learned conversation between ACTIV-3 and FDA would be valuable for the trial team and regulators alike. Dr. Woodcock noted that disagreement between oversight bodies is likely in situations of high uncertainty and that regular, thorough data sharing can help resolve that uncertainty and aid future decision-making. The ACTIV-3 team agreed that such conversations are important, in part because regulators' decisions affect the evidence base for agents under evaluation: for example, regulatory concerns about the use of mAbs in patients on high-flow oxygen have limited assessment of their potential in the U.S., but not in Britain; by contrast, concerns over aviptadil's manufacturing has slowed study of that agent in other countries but not in the U.S. They also acknowledged that regulatory decisions are often based not only on data about risk but also on a general preference for risk *aversion,* which weights risk of doing harm more than risk of failing to benefit.

The ACTIV-3 team will seek a conversation with FDA after the Day 90 follow-up on the Pfizer agent has been completed, which is anticipated this week. The team is also developing a manuscript to memorialize lessons learned.

Variants

BA.2 is becoming the dominant variant in U.S. even as cases continue to decline in most states. The declining case trend may shift, however, as it has already done in Europe.

Agent Prioritization

Dr. Stacey Adam clarified the result of a recent round of ACTIV-3/3B agent prioritization. Although the Agent Prioritization Committee agreed that prostacyclin was a good candidate for testing in ACTIV-3B, the trial team has decided to focus its efforts on testing AstraZeneca's Evusheld and thus will not launch a prostacyclin trial unless plans for Evusheld are unsuccessful.

TOC members considered and endorsed the plan to test Evusheld in either ACTIV-3B or STRIVE and to test Shionogi's oral protease inhibitor in either ACTIV-3 or STRIVE, with the choice of platform based on whether case counts surge before STRIVE has been fully launched.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Christina Barkauskas, MD, *Assistant Professor of Medicine, Duke University*
Samuel Bozzette, MD, PhD, (not in attendance) *Chief Medical Officer, NCATS*
Samuel M. Brown, MD, MS, *Principal Investigator, ACTIV-3B and Associate Professor of Medicine, University of Utah*
Elizabeth Church, PhD, (not in attendance) *Deputy Director, Therapeutics Research Program, DAIDS, NIAID*
Nakela Cook, MD, MPH, (not in attendance) *Executive Director, PCORI*
Judith Currier, MD, *Professor of Medicine, Division of Infectious Diseases, UC Los Angeles*
Sarah Dunsmore, PhD, *Program Director, Division of Clinical Innovation, NCATS*
Ann Eakin, PhD, *Senior Scientific Officer, Concept Acceleration Program, NIAID*
Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID*
William Erhardt, MD, (not in attendance) *Clinical Advisor to ACTIV-2 and CEO, Soundview Pharmaceutical Consultants*
Josh Fessel, MD, PhD, *Senior Clinical Advisor, NCATS*
David C. Goff, MD, PhD, (not in attendance) *Director, Division of Cardiovascular Sciences, NHLBI*
Adrian Hernandez, MD, *Vice Dean and Executive Director, Duke Clinical Research Institute*
Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, NIAID*
James P. Kiley, PhD, (not in attendance) *Director, Division of Lung Diseases, NHLBI*
Peter Kim, MD, (not in attendance) *Director, Therapeutics Research Program, DAIDS, NIAID*
H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*
Chris Lindsell, PhD, *Professor, Vanderbilt University Medical Center*
Jens D. Lundgren, MD, (not in attendance) *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*
Susanna Naggie, MD, (not in attendance) *Vice Dean for Clinical Research and Associate Professor of Medicine, Duke University*
James D. Neaton, PhD, *Professor of Biostatistics, University of Minnesota*
Sarah Read, MD, *Deputy Director, DAIDS, NIAID*
Erica Ollmann Saphire, PhD, (not in attendance) *Professor, La Jolla Institute for Immunology*
David (Davey) Smith, MD, (not in attendance) *Professor of Medicine, UC San Diego*
Janet Woodcock, MD, (not in attendance) *Acting Commissioner, FDA*

INVITED GUESTS

John Farley, MD, MPH, *Director, Office of Infectious Diseases, FDA*

FNIH STAFF

Stacey Adam, PhD, *Associate Vice President, Research Partnerships, FNIH*
Joseph P. Menetski, PhD, *Vice President, Research Partnerships, FNIH*

Alex Cwalina, *Business Technology Analyst, Deloitte*
Serena Melton, *Senior Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*
Caroline Yarbrough, *Analyst, Deloitte*
Jonathan Wachtel, MBA, *Manager, Deloitte*

Dana Carluccio, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Log

From Samuel Brown to Everyone 03:19 PM

I'm sure our group would be glad to replicate the analyses. Brandon Webb leads that effort. I'm happy to chat with him. We've built a very robust infrastructure. The only nuance will be capturing private-pharmacy prescribed paxlovid.

From Janet Woodcock to Everyone 03:20 PM

Yes it was very impressive. jw

From Emily Erbelding to Everyone 03:20 PM

@peterkim I can connect you with the Colorado investigators if you need an intro

From Libby Higgs NIH/USG to Everyone 03:21 PM

and delta

From Samuel Brown to Everyone 03:28 PM

Spoke w Brandon. He has about 150 treated w paxlovid in the intermountain RWE cohort. Uptake was lower than with the mabs.

From Stacey Adam to Everyone 03:57 PM

Any other things to be discussed

From Libby Higgs NIH/USG to Everyone 03:57 PM

thanks stacey, you are breaking up!

From Stacey Adam to Everyone 03:57 PM

Thanks Bye all!

From christina.barkauskas@duke.edu to Everyone 03:57 PM

Thanks Stacey!

From Libby Higgs NIH/USG to Everyone 03:58 PM

Thanks all

Sent: 4/8/2022 10:13:45 AM
Subject: FW: Authorizer/Appropriator doc for clearance
Attachments: Authorizers and Appropriators Supp Report 4.6.22.docx

From: Cohen, C. Lee <Caitlin.Cohen@fda.hhs.gov>
Sent: Thursday, April 7, 2022 7:17 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Safford, Melissa <Melissa.Safford@fda.hhs.gov>
Subject: Authorizer/Appropriator doc for clearance

Hello Dr. Woodcock, Julie, and Melissa,

At long last, attached is the Authorizers/Appropriators document that has incorporated OCA/OL/OB/OEA initial edits and I believe is ready to get sent out to the centers for clearance. OEA is concurrently working on graphics. Once this one is cleared I was planning to use that already-cleared language as the basis for the public version (with modest simplification), though if you prefer to send both at once I can get you the draft of the public version tomorrow.

I defer to you on the best process for clearance. Should I draft all the emails and send to Julie to send out? I presume that we should do this on Sharepoint with track changes and strict rules about not making it longer or more complex.

Who should clear: Because the document is now comprehensive of all of the centers that received funding and all the line items, including smaller projects, I imagine it should go through all of them.

- The offices I have been in contact with are: CFSAN (Ruth Timme and Steven Musser), CBER (Angela Granum and Marc Meyer), CDRH (Jaime Horman), CDER (they requested clearance go to the ExecSec mailbox (cderexsec@cder.fda.gov) though Sunanda Bahl had been POC), ORA (Faiad Rahaman and Myer Gribbins), CVM (Heidi Jackson), ODT (Joe Montgomery), OCET (Michael Mair).
- The offices I have not been in contact with but who received funding are: NCTR, OCC, OPLIA, OSEM, OO (for testing?), OCPP, OMHHE, and OEA.
- OCA/OL/OB/OEA will want to see it again in final form

Timeline: Ideally we would have pens down by April 20th or so for OEA to finalize the formatting/ graphics for budget hearings the following week. I imagine April 8-13 for the centers, April 14 for me to address comments (I'll try to do this in real-time, but it would be nice to have a consolidation day), and then April 15-20 for OCA/OL/OB/OEA/?OCC and anyone else you think should clear?

Thank you and sorry this has taken so long!
Lee

C. Lee Cohen, MD MBA (she/her)
Scientific Advisor, Strategic Initiatives Team, Office of the Commissioner

U.S. Food and Drug Administration
(b) (6)(cell)
Caitlin.Cohen@fda.hhs.gov
U.S. FOOD & DRUG ADMINISTRATION


I GOT MY
COVID-19
VACCINATION

FDA COVID-19 Supplemental Supported Initiatives

April 2022

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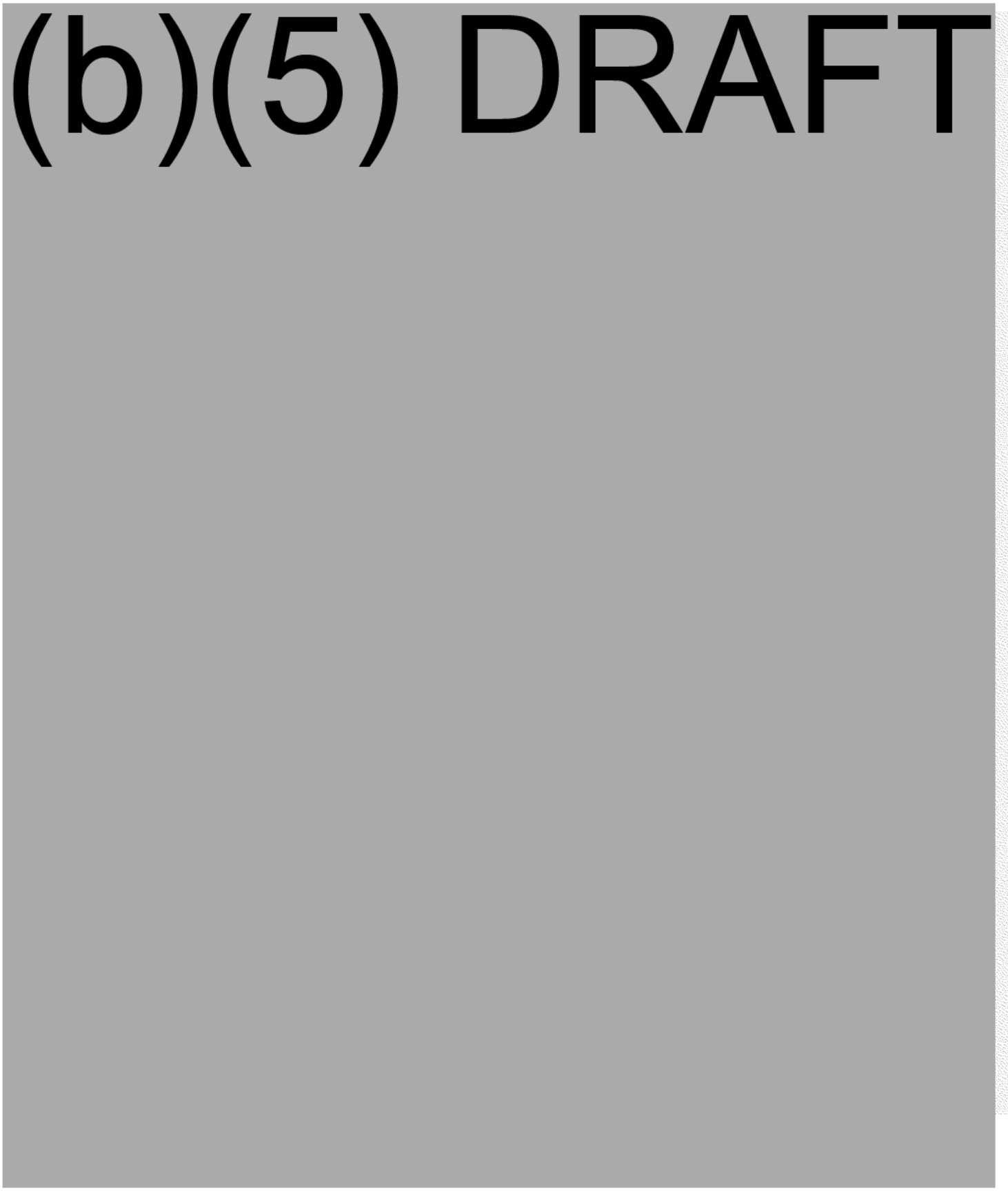
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From: Califf, Robert [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=AD88732BE1ED4912A058EE9DD9906F66-ROBERT.CALI]
Sent: 4/9/2022 12:08:45 PM
To: Raza, Mark [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5811a7d72ee34aa78ff3c8ccb59f92ee-MRaza]; Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]; Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; Cavazzoni, Patrizia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c42abd33834044ecbaa03d075cc0a5d2-Patrizia.Ca]; Dickinson, Elizabeth (FDA) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05cb143d66ed470ebe4dba5c54a88074-EDickins]
Subject: Re: Is this legal?

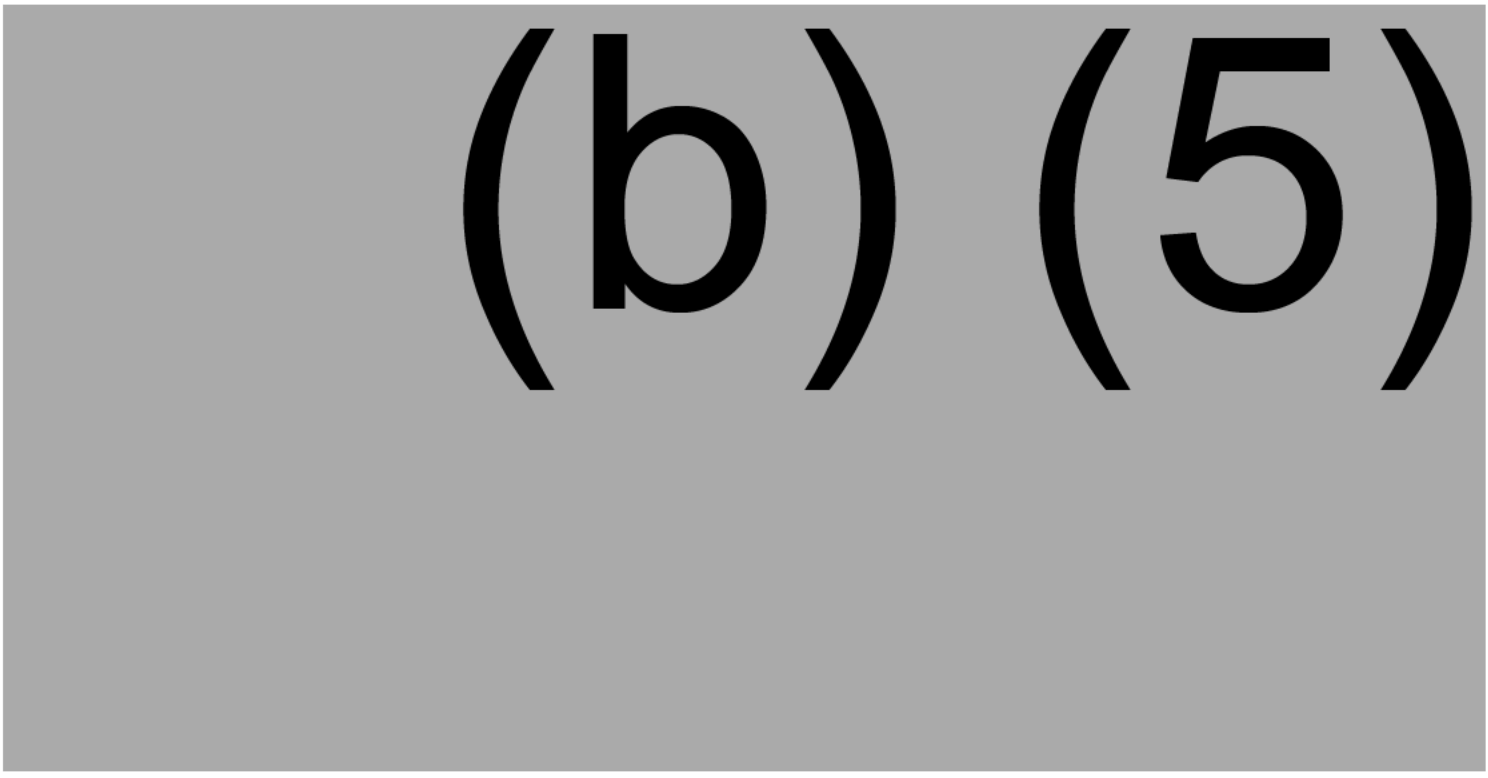
This is very helpful. Thanks. Consistent with feedback I got from Vanderbilt.

rmc

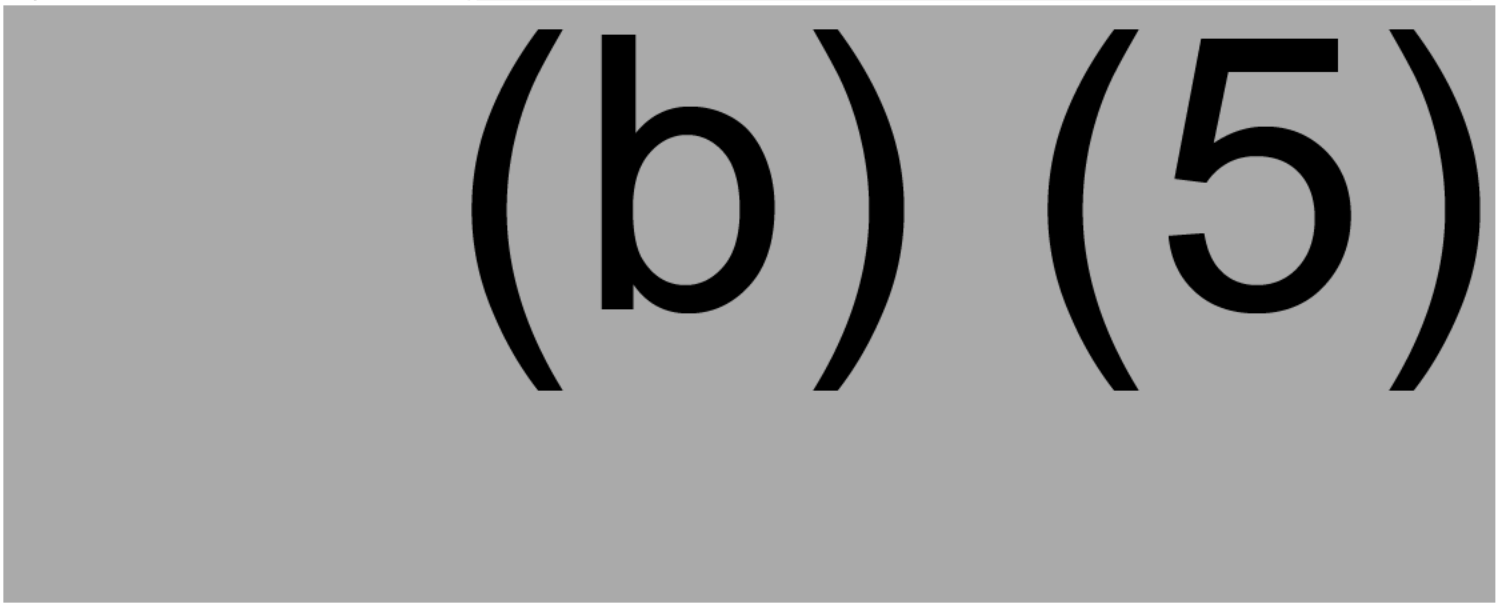
From: Raza, Mark <Mark.Raza@fda.hhs.gov>
Date: Friday, April 8, 2022 at 5:35 PM
To: Tierney, Julia <Julia.Tierney@fda.hhs.gov>, Califf, Robert <(b) (6)@fda.hhs.gov>, Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>, Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>, Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: RE: Is this legal?

Hi – to follow-up, 2 things:

1) Our initial thoughts concerning the Tennessee bill regarding ivermectin are as follows:



2) In terms of a reactive Q and A, (b) (5)



Thanks,

Mark

From: Tierney, Julia <Julia.Tierney@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:34 PM
To: Califf, Robert <(b) (6)@fda.hhs.gov>; Raza, Mark <Mark.Raza@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: RE: Is this legal?

Mark/Liz – happy to work with you on a QA that is legally accurate but accessible.

From: Califf, Robert (b) (6)@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:27 PM
To: Raza, Mark <Mark.Raza@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: Re: Is this legal?

I think its likely we'll be asked. Would be good to have an answer. What next?

rmc

From: Mark Raza <Mark.Raza@fda.hhs.gov>
Date: Thursday, April 7, 2022 at 4:25 PM
To: "Woodcock, Janet" <Janet.Woodcock@fda.hhs.gov>, Robert Califf <(b) (6)@fda.hhs.gov>, Julie Tierney <Julia.Tierney@fda.hhs.gov>, Patrizia Cavazzoni <Patrizia.Cavazzoni@fda.hhs.gov>, Elizabeth Dickinson <Elizabeth.Dickinson@fda.hhs.gov>
Subject: RE: Is this legal?

(b) (5)

Happy to have our folks take a look.

Mark

From: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:10 PM
To: Califf, Robert <(b) (6)@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Raza, Mark <Mark.Raza@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: RE: Is this legal?

It is possible for them to do in the state I think but there is Federal preemption. Is hilarious. jw

---

From: Califf, Robert <(b) (6)@fda.hhs.gov>
Sent: Thursday, April 7, 2022 4:09 PM
To: Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Raza, Mark <Mark.Raza@fda.hhs.gov>; Dickinson, Elizabeth (FDA) <Elizabeth.Dickinson@fda.hhs.gov>
Subject: Is this legal?

https://thehill.com/news/state-watch/3261642-tennessee-senate-passes-bill-to-allow-over-the-counter-sales-of-ivermectin/

From: Colonius, Tristan [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2B3590C046734A2E928858BD579ED852-TRISTAN.COL]
Sent: 4/12/2022 2:03:22 PM
To: Mayne, Susan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9e69acd84a37469aa57466a957814563-Susan.Mayne]; Cavazzoni, Patrizia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c42abd33834044ecbaa03d075cc0a5d2-Patrizia.Ca]; Shuren, Jeff [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=44335a0c2f834535bc8713dfd643905e-Jeff.Shuren]; Marks, Peter [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dfbb2b5bd38445cb9c9adca3f72df53a-MarksP]; Solomon, Steven M [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e49ac6a056dc4f299ea269945e962e82-SSOLOMON]; Yiannas, Frank [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=93cdf56a41324683ab173699c441fec8-Frank.Yiann]; McMeekin, Judith [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d824f07697784fcb9ece28cbba07102b-MCMEEKINJ]; Fristedt, Andi [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8ebcdc6531394636a5afcb391a6c0cc3-Andi.Friste]; CBER OM/PPFB/Formulation [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=groupc295713d]; CDER Executive Operations [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c68e582c3fb64e57963e510a97332f63-CDEREXSEC]; CFSANEXECSEC [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=468d52748b974fa598d4dfb4a83ab38f-OFVM-CFSAN-]; Gribbins, Myer [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a916494d855842c4ad1dd5383e661644-Myer.Gribbi]; Jackson, Heidi [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=694066ca38aa4ff5b188c4b939e0708f-HJACKSON]; Ramsey, Kathy [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=18f7bab2dc9047f38533be25624a3dbf-Eberhart]; Trzeciak, Kimberlee [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b24f98d119fa4fa1b04704e9a3a0b3f3-Kimberl.Trz]; McBride, Maren [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b65d2b38307f4b489e266d2178c46793-Maren.Kahn]; Mair, Michael [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f4511bdad7564d7fac7eadc7961467ab-Michael.Mai]; Tyler, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ddb047ff73e640b29259d7ca22611e67-James.Tyler]; Tootle, William [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0900da296e4a474da740ef1c47e6f1bd-William.Too]; Wade, Jennifer [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dbc3da04754040b6bd8107a700959e17-Jennifer.Wa]; Klimczak, Katherine [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=01a6c20534774be590c50f0d455c81de-Katherine.K]; Paulos, Lauren [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5dfb1daac9c14aab8649e6c66087f956-AubrieLaure]; Araojo, Richardae [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0474cf3e9aea4e32980ca8f3b4ad2c1e-ARAOJOR]; O'Shaughnessy, Jacqueline A [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3fcc0bbfc81941e497313b309196f28b-OSHAUGHNESS]; Black, Jodi [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=bd7b8184f4b8403bb0ebe5f4668cd143-Jodi.Black]; Desai, Vid [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=91b722d8adf748aaa8e91f77ad37a272-Vidyut.Desa]; Sigg, Jim [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=37695069dc214f5cb20e6056dd4d7cf7-sigg]; Felberbaum, Michael

[/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4819a643ca2945cdb1a2631b83e69673-Michael.Fel]; Patterson, Tucker [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=34e4b6c7b20f4c99b8691c7907864d7d-Tpatterson]; Flahive, James [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=570655c122f24177ba6e9ac768a6f731-James.Flahi]; Horman, Jaime [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=47e207dbba3f4e4aa3f22662b5418af4-Jaime.Horma]; Rahaman, Faiad [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6a370d33d1be4f8597973e9aa253a871-Faiad.Raham]; Lee, Christine (OC) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=46b2c2861a86482589389aee84448588-LEECHRI]; Hussain, Ajmal [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=58ffaade33224c82b0f60aba96200496-Ajmal.Hussa]; Roosen, Suzanne [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=67e5a1139af248699616f7f8c44f46bd-Suzanne.Roo]

CC: Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; Cohen, C. Lee [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=96b23af7b7d740d291e23aecaceb3d7f-Caitlin.Coh]; Safford, Melissa [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=662886bbfbc7441dae59de74071cec71-Melissa.Saf]

Subject: Request Clearance by COB Tuesday, 19 April - Draft Report on COVID Supplemental Spending

Attachments: Authorizers and Appropriators Supp Report 4.12.22.pdf

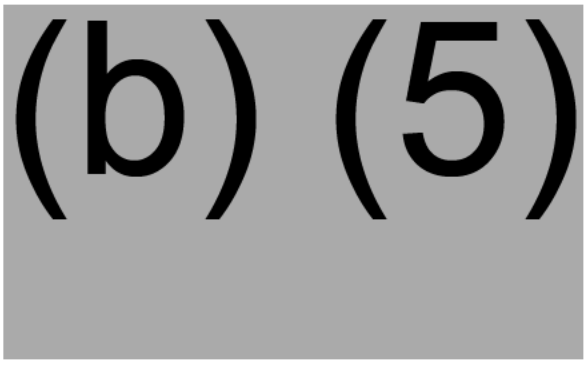
Hello Centers and Offices,

Attached is a draft report of agency's COVID-19 work funded by COVID supplementals. This document is targeted towards our authorizers and appropriators and aims to provide a plain-language background for the work, its importance and relevance for longer-term pandemic preparedness, the specific activities funded by COVID supplementals, and (where relevant) some accomplishments to date.. Those materials, plus the cleared language from this document, may be used as the basis for a public report and other materials as well in the future.

Action required by COB Next Tuesday: Please review and, if appropriate, respond to the attached document using the comments feature. Please read with a focus on factual corrections and red flags. We are not interested in copy edits or line edits at this review stage, and these will not be considered if submitted. This is a "red flags" review exercise to make sure we haven't made any factual errors or missed a significant item.

Please return the attached document with your organization's comments (or an email to indicate no comments) to C. Lee Cohen (Caitlin.Cohen@fda.hhs.gov) and myself (Tristan.Colonius@fda.hhs.gov). You may also contact us with any questions about this review process. At the end of this email is a list of the sections/pages relevant for each center/office to help your staff focus their review.

We are deeply grateful to the >100 people who have invested time and effort in crafting all the source materials for this document across your Centers and Offices, particularly our colleagues at OB and OPERM.



(b) (5)

Thank you for your time and effort in making this happen.

Best,

Tristan Colonius, DVM, MPA, DACVPM
Acting Deputy Chief of Staff
Office of the Commissioner
O: 301.796.2624 | M: (b) (6)

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA COVID-19 Supplemental Supported Initiatives

April 2022

(b)(5) DRAFT- 22 pages of this attachment were removed as DRAFT under (b)(5)

From: Melencio, Cheryl (FNIH) [T] [cmelencio@fnih.org]
on behalf of Menetski, Joseph (FNIH) [T] [jmenetski@fnih.org]
Sent: 3/29/2022 3:32:48 PM
To: Bancel, Stephane [stephane.bancel@modernatx.com]; Brodd, Lauren L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e8709bef665942aaa89ec27f79e96c9e-HHS-lauren.]; Carter, Kara (alt) [Kara.carter@evotec.com]; Cavaleri, Marco [marco.cavaleri@ema.europa.eu]; Chao, Brittany N (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ccec410dec8491985206c8694db1c15-HHS-brittan]; Cihlar, Tomas [tomas.cihlar@gilead.com]; Clevers, Hans [Hans.Clevers@roche.com]; Corey, Larry [lcorey@fredhutch.org]; Culp, Michelle A (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=93cef0f5bf33475c8e44a8b2a2516251-HHS-michell]; Victoria Davey [victoria.davey@va.gov]; Disbrow, Gary (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e0265d217b2344c6bbbaad0cbb2f0c6a-HHS-Gary.Di]; Dolsten, Mikael [mikael.dolsten@pfizer.com]; Dubin, Gary [gary.dubin@takeda.com]; Erbelding, Emily J (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c981f04015d64d27b1afdd9c06111071-HHS-emily.e]; Erck, Stan [serck@novavax.com]; Fauci, Anthony S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=759a71a9291b47a2bf83b77989d40cc3-HHS-afauci-]; Gadbois, Ellen L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=680ebce054324eff90ecfff770987437-HHS-gadbois]; Gibbons, Gary H (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0e140a10258547bfaf53da7cb7c78225-HHS-Gary.Gi]; Hudson, Thomas [thomas.hudson@abbvie.com]; James, Stephanie L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ca48852bdbe3443cb45bb640a4aa9821-HHS-sjames-]; Johnson, Robert (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9c7eb3a419464ea2917f9d1e3f6e57a4-HHS-Robert.]; Kessler, David A (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=efb6a7c634694533833de5d2f4beaee3-HHS-David.K]; Kramer, Lynn [lynn_kramer@eisai.com]; Lane, Henry C (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d904337536cf41719032a9359a1ec2ab-HHS-CLANE-n]; Lepore, John [john.j.lepore@gsk.com]; Li, Dean [dean.li@merck.com]; Mahon, Barbara (CDC) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=6ad4ef1fd0d9413d95358526dc0f9051-HHS-bdm3-cd]; Mammen, Mathai [mmammen@its.jnj.com]; Marks, Peter [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=dfbb2b5bd38445cb9c9adca3f72df53a-MarksP]; Mascola, John R (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=63aa50129c1f4d39bc0a31b3851a34c5-HHS-jmascol]; McQueen, Brig. General Anthony (b) (6) Meeker, David [dmeeker@rhythmtx.com]; Menetski, Joseph M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d8ed7bcfcbc04f338026fde223a907ae-HHS-jmenets]; Pandya, Hitesh [hitesh.pandya@astrazeneca.com]; Pangalos, Mene [mene.pangalos@astrazeneca.com]; Pao, Pfizer [William.Pao@pfizer.com]; Parker, Ashley S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3f43b948b59f4e679535a8a3ebc91167-HHS-ashley.]; Patterson, Amy P (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a842e9e8e9e84d7b8736ddaa333145d0-HHS-amy.pat]; Plenge, Robert [rplenge@celgene.com]; Reed, John [john.reed@sanofi.com]; Reese, David [dreese@amgen.com]; Rouse, Doris [rouse@rti.org]; Rutter, Joni L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0a90497bad684a6b81166a82a65e76c3-HHS-joni.ru]; Santos, Michael R (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5d410c16ad784c24a4ee47599cafec85-HHS-msantos]; Schwetz, Tara A (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3299b3dec3304ae99e54457db0320482-HHS-tara.sc]; Skovronsky, Daniel [skovronsky_daniel@lilly.com]; Stein, Peter [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d30a87acb0184261961264ba984b0a51-Peter.Stein]; Tabak, Lawrence A (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0037b2fbba164f33a24944311b80393e-HHS-Lawrenc]; Tsai, John [john.tsai@novartis.com]; Vessey, Rupert [rvessey@celgene.com]; Virgin, Skip [svirgin@vir.bio]; Wholley, David N (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group

(FYDIBOHF23SPDLT)/cn=Recipients/cn=784115e9182043d48eaa9e91761c4330-HHS-dwholle]; Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; john.young.jy3 [john.young.jy3@roche.com]; Colvis, Christine M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d3bb5ce5263c4206885ede0146e96813-HHS-christi]; Draghia-Akli, Ruxandra [rdraghia@its.jnj.com]; Hall, Matthew D (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=80fd9cb35d73417388a946a421745cbf-HHS-hallma-]; Jansen, Kathrin [kathrin.jansen@pfizer.com]; Kurilla, Michael G (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fa2de9594d594ed9b76b935545c26754-HHS-michael]; Lowy, Douglas (NCI) (b) (6) Lisa Purcell [lpurcell@vir.bio]; Read, Sarah W (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=72ca09ea60c74100a908211e1f7c5f6a-HHS-readsa-]; Adam, Stacey J (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=8de67693eab246c7946108cfd7c6d3dc-HHS-sadam-f]; Margaret Anderson [marganderson@deloitte.com]; Chen, Helen [qingchen@deloitte.com]; Connelly, Sarah [sconnelly@deloitte.com]; Copeland, Courtney [cocopeland@deloitte.com]; Culp, Michelle A (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=93cef0f5bf33475c8e44a8b2a2516251-HHS-michell]; Cwalina, Alex [acwalina@deloitte.com]; Gadbois, Ellen L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=680ebce054324eff90ecfff770987437-HHS-gadbois]; Gonzalez, Nina [ningonzalez@deloitte.com]; Larosa, Francis [flarosa@deloitte.com]; Melton, Serena [smelton@deloitte.com]; Menetski, Joseph M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d8ed7bcfcbc04f338026fde223a907ae-HHS-jmenets]; Murza, Tetyana (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c9dc1de48a104c0d8196793001a3aaab-HHS-tmurza-]; Santos, Michael R (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5d410c16ad784c24a4ee47599cafec85-HHS-msantos]; Sorosa, Alex [asorosa@deloitte.com]; Stratton, Benjamin [bstratton@deloitte.com]; Tolman, Brett [btolman@deloitte.com]; Wachtel, Jonathan [jwachtel@DELOITTE.com]; Yarbrough, Caroline [cyarbrough@deloitte.com]; Anderson, James M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e7ae7a825549453d8398a1d93d3d7d21-HHS-james.a]; Burklow, John T (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=20d9290a05474f989153cf26a5a4e669-HHS-Burklow]; Dana Carluccio [dana.carluccio@roseliassociates.com]; fnih [fnih@roseliassociates.com]; Usher, Adrienne H (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05dcba635daa4cb09ad8bdea916ac43b-HHS-adrienn]; Myles, Renate H (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=04a3e5f0ac384bd6b70bd9cdee9082f2-HHS-mylesr-]; Brooks, John T (CDC) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=def0cf9cf9f84fc6a40c4dde8c51b199-HHS-zud4-cd]; john.lepore@modernatx.com; Koroshetz, Walter J (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4d97701b01894e15a53709b9df3e08e7-HHS-koroshe]; Lerner, Andrea M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=81df9b2e44e34c81a682e5b5f5a46a14-HHS-andrea.]; Wright, Clinton B (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=65d80582eaee4fddaafcd2c8e64082ea-HHS-clinton]; Groesch, Mary E (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=78d9da4715154e1eabcf9d0178d06b88-HHS-mary.gr]

CC: Barasch, Kimberly M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4290a8d1159c480f80f059b0bfc4ffb4-HHS-kimberl]; Burke, Leslie [leslie.burke@takeda.com]; Conrad, Patricia L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e30cd6224aeb49c795844f43fd78a049-HHS-conradp]; Dimishkov, Roxanne (NIH/NHLBI) [C] (b) (6); McManus, Ayanna L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=b2bc6cf1152f4e2a9cfdc10f33a64f6c-HHS-ayanna.]; Olivarria, Frank [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c180721db774423f99990dd86e67057c-Frank.Oliva]; Protasiewicz, Ann [ann.protasiewicz@pfizer.com]; Riccobene, Kim [kriccob1@its.jnj.com]; Sheehy, Janice [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f45a6c96f5274724a1be5970eb648ff7-JSheehy]; Wood, Gretchen S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group

	(FYDIBOHF23SPDLT)/cn=Recipients/cn=e0723fb8cc6343999a70fb64f3b93cb6-HHS-gretche]; Burrus-Shaw, Cyndi R (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2a47a84f2a14441399491dbbf59467f2-HHS-Cyndi.B]; Carver-Roberts, Trea R (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05c1728ee14540bb9d98a6b7917c85eb-HHS-trea.ca]; Hughes, Karen P (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ff6551842a5f4136b70015eee83ba649-HHS-karen.h]; Melencio, Cheryl L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=baa3813b343d4f4cb949f1b990023053-HHS-cmelenc]; Simon, Dina M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=56bf2feba2384c0fb525d3c1b1439146-HHS-dina.si]; Hampton, Mary [mhampton@vir.bio]; Togashi Mah, Mieko N (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5157ec4649b145d1b673bf7b6531de7e-HHS-togashi]; Underwood, Nancy [nancy_underwood@merck.com]; VandeWalle, Mieke [mvandewa@its.jnj.com]; Zottoli, Jessica [Jessica.Zottoli@pfizer.com]
Subject:	[EXTERNAL] ACTIV Joint Executive Committee & Leadership Team Meeting: Wednesday, March 30, 2022
Attachments:	03.30.22 ACTIV EC and Leadership Team Meeting_20220330.pdf; 2022-2-23_ACTIV_Leadership_Team_and_Executive_Committee_Summary f3.docx

Dear ACTIV Leadership Team and meeting attendees:

Attached please find the slides for our meeting **Wednesday, March 30, 2022 10:30 a.m. – 12:00 p.m. Eastern U.S. Time**. The minutes from the February 23, 2022 Executive Committee/Leadership Team call are also attached to this note.

Dial-in information is located below and also is included in your calendar invite.

Join Zoom Meeting
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Meeting ID: 544 281 8826
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Dial by your location
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Best, Joe

Joseph Menetski, Ph.D.
Vice President, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6596
fnih.org
11400 Rockville Pike Suite 600 North Bethesda, MD 20852

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FNIH

Foundation for the
National Institutes of Health

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

Executive Committee and Leadership Team Meeting #24

30 March 2022

Attendees for ACTIV Leadership Meeting

INDUSTRY LEADERS

NOVARTIS	Sarah Grant John Tsai
Roche	(John Young) Hans Clevers
MERCK	Dean Li
Pfizer	Mikael Dolsten Kathrin Jansen William Pao
RHYTHM THERAPEUTICS	David Meeker
AstraZeneca	Mene Pangalos Hitesh Pandya
abbvie	Tom Hudson
Eisai	Lynn Kramer
AMGEN	David Reese
NOVAVAX	(Stan Erck)
Takeda	Gary Dubin
SANOFI	John Reed
J&J	Ruxandra Draghia Akli Mathai Mammen
Bristol Myers Squibb	(Rupert Vessey) Robert Plenge
VIR	Skip Virgin Lisa Purcell
Lilly	Dan Skovronsky
GILEAD	Tomas Cihlar
evotec	Kara Carter
gsk	(John Lepore)
moderna	(Stéphane Bancel) John Lepore

GOVERNMENT LEADERS

NIH National Institutes of Health *Turning Discovery Into Health*	Larry Tabak
NIH National Center for Advancing Translational Sciences	(Matt Hall) Joni Rutter Christine Colvis Mike Kurilla
NIH National Institute of Allergy and Infectious Diseases	Anthony Fauci Sarah Read Cliff Lane (John Mascola) Emily Erbelding
NIH NATIONAL CANCER INSTITUTE	Doug Lowy
NIH National Heart, Lung, and Blood Institute	Gary Gibbons David Goff
WHITE HOUSE COVID RESPONSE	(David Kessler)
BARDA Biomedical Advance Research and Development Authority	Gary Disbrow Robert Johnson
FDA	Janet Woodcock Peter Marks Peter Stein
EUROPEAN MEDICINES AGENCY	(Marco Cavaleri)
CDC	(Barbara Mahon) John Brooks
VA U.S. Department of Veterans Affairs	Victoria Davey
U.S. Army MEDICAL RESEARCH AND DEVELOPMENT COMMAND	Brig. Gen. Anthony McQueen

NON-PROFIT

FNIH Foundation for the National Institutes of Health	David Wholley
RTI INTERNATIONAL	Doris Rouse
FRED HUTCH CURES START HERE®	(Larry Corey)

PROGRAM MANAGEMENT

FNIH Foundation for the National Institutes of Health	Joe Menetski Stacey Adam Michael Santos Stephanie James Margaret Anderson Nina Gonzalez Serena Melton Courtney Copeland Tré LaRosa Alex Cwalina Alex Sorosa Caroline Yarbrough Brett Tolman Jonathan Wachtel

FNIH Notes: () Indicates leader not able to attend

Agenda

TIME		TOPIC	SPEAKER(S)
10:30 – 10:40 AM *10 mins*		**Introduction and General Updates on ACTIV**	Larry Tabak (NIH) William Pao (Pfizer)
10:40 – 11:25 AM *45 mins*		**Researching COVID-19 to Enhance Recovery (RECOVER) Overview** • Presentation (*30 mins*) • Discussion of partnership opportunities (*15 mins*)	Amy Patterson (NHLBI)
11:25 – 11:35 AM *10 mins*	**Working Group Updates and Q&A**	**ACTIV TRACE WG** • TRACE Updates	Lisa Purcell (Vir)
11:35 – 11:45 AM *10 mins*		**ACTIV Therapeutics Clinical WG** • Master Protocol Updates	Sarah Read (NIAID) Ruxandra Draghia-Akli (J&J)
11:45 – 12:00 PM *15 mins*		**Milestones and Discussion**	Larry Tabak (NIH) David Wholley (FNIH) William Pao (Pfizer)

Questions from 2/28 Leadership Team discussion

Given the progress of the pandemic, is it time to reassess the future direction of ACTIV?

- ACTIV focus areas have not evolved significantly from their original designs during the initial "pandemic phase" of SARS-CoV-2
- ACTIV clinical trials are continuing to examine therapeutics and combinations that are similar to others already being tested by private pharmaceutical companies in their own trials.

Changes in the SARS-CoV-2 pandemic may require focusing on a better basic understanding of the pathophysiology of the virus and the functional consequences associated with the variants.

- **Additional focus could be directed at:**
  - High-risk populations (e.g., immunocompromised people)
  - Long COVID or post-acute sequelae of SARS-CoV-2 infection [PASC].
  - Host-virus response
  - Testing better drugs or combinations of drugs

Where could a public-private partnership have the most impact?

Advancing Toward Recovery from Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

RECOVER Overview

ACTIV Leadership Team Meeting

March 30, 2022

RECOVER Initiative Co-Chairs

Anthony S. Fauci, MD
Director, NIAID

Gary H. Gibbons, MD
Director, NHLBI

Walter J. Koroshetz, MD
Director, NINDS

RECOVER
Researching COVID to Enhance Recovery

NIH National Institutes of Health
Researching COVID to Enhance Recovery

Anxiety

Brain Fog

Hair Loss

Depression

Headache

Decreased sense of smell, taste

Dizziness

Palpitations

Cough

Shortness of Breath

Chest or stomach pain

Disrupted Sleep

Fatigue, Malaise

Muscle Weakness

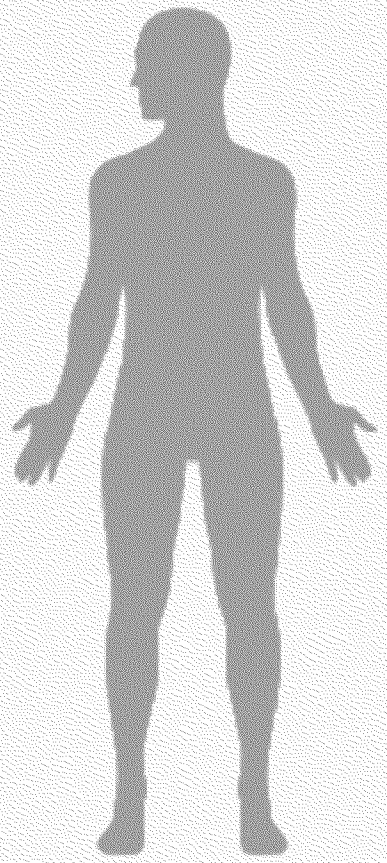
Joint Pain

Menstrual changes

Paresthesia

Rash

Examples of Symptoms



Neurologic Impairment

Mental Health Disorder

Heart Dysfunction/Damage

Lung Dysfunction/Damage

Gastro-intestinal Dysfunction

Diabetes

Kidney Damage

Reproductive System Disruption

Autonomic Dysfunction

Systems

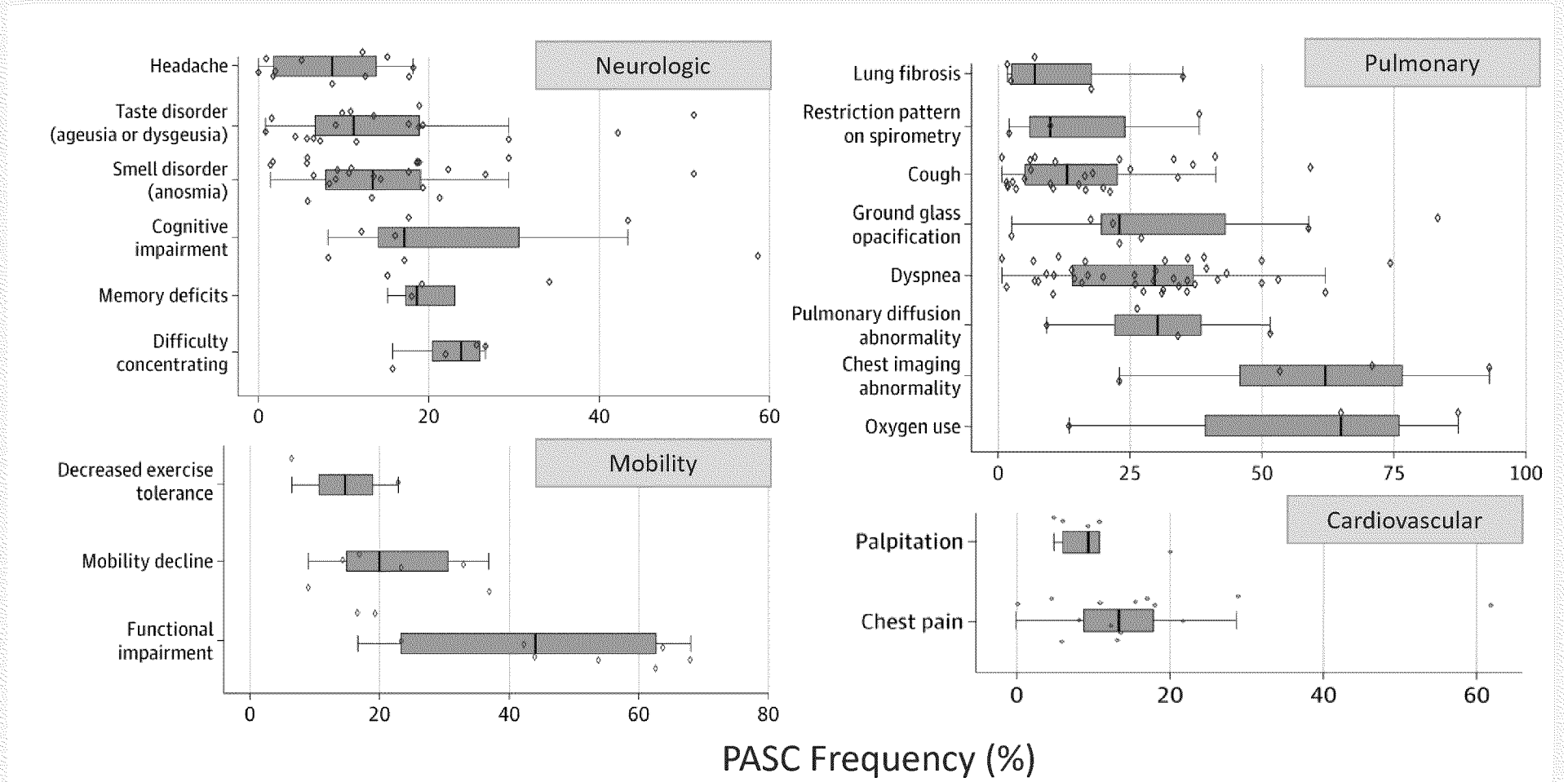
Varied Symptomatology as Multiple Systems Can be Affected in PASC:
Wide Clinical Spectrum Will Require Multi-pronged Approach to Development of Treatments

Significant Limitations in Studies to Date Hinder Understanding of PASC

Short- and Long-term Rates of Post-acute Sequelae of SARS-CoV-2 Infection: A Systematic Review
(57 studies, Total n=250,351 COVID-19 survivors assessed for PASC at 30 days and beyond after acute COVID-19)

- **Frequencies of PASC vary widely (e.g., 5-80%)**
- **Studies to date have significant design flaws that limit their utility**

JAMA Network Open



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Groff et al., *JAMA Network Open*, October 2021

NIH RECOVER Initiative

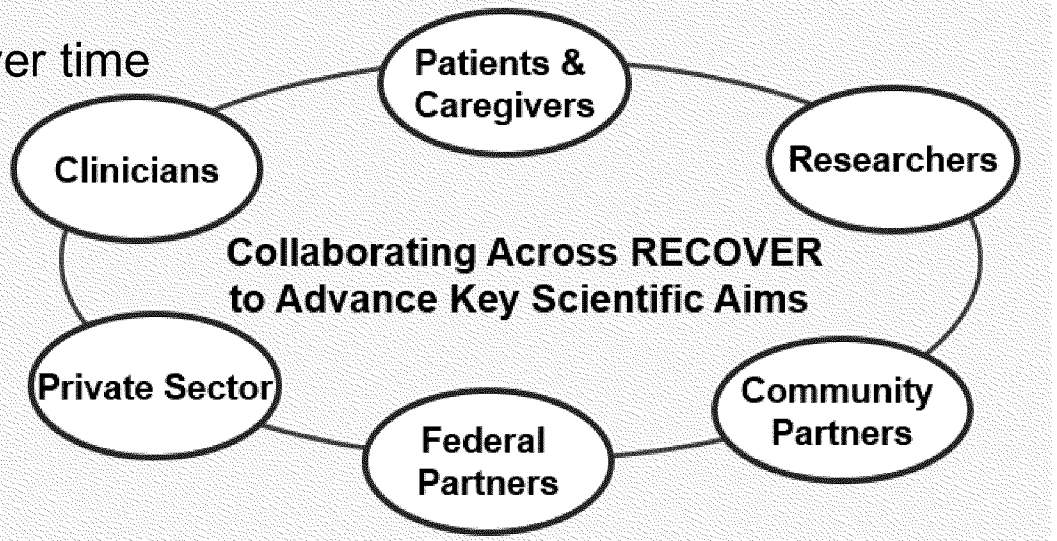
$1.15B investment

Goal

Rapidly improve our **understanding** of and ability to **predict, treat, and prevent** PASC

Key Scientific Aims

1. Understand clinical spectrum/biology underlying recovery over time
2. Define risk factors, incidence/prevalence, and distinct PASC sub-phenotypes
3. Study pathogenesis over time and possible relation to other organ dysfunction/disorders
4. Identify interventions to treat and prevent PASC



Guiding Principles

Patient-centered, participants as partners

National Scale with inclusive, **diverse** participation & community engagement

Platform protocols, standardized methodologies, and common data elements

Adaptive approaches based on emerging science

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RECOVER Study Components

RECOVER Cores

Clinical Trial Data Cord. Center	Clinical Science Core	Data Resource Core	Biorepository Core

Elements





RECOVER Clinical Trials	RECOVER Enrolling Cohorts	EHR/ Health Systems Studies	Pathobiology Studies	Tissue Pathology Studies
Adaptive Platform Multi-therapeutic domains	**~40,000** participants	**50 million+** records; **~4 million+** COVID cases	**Mechanistic studies of pathogenesis**	**50+** tissue types

Data Resources

Clinical	Imaging	Mobile and Digital Health	EHR / Other Real-World Data	Pathology

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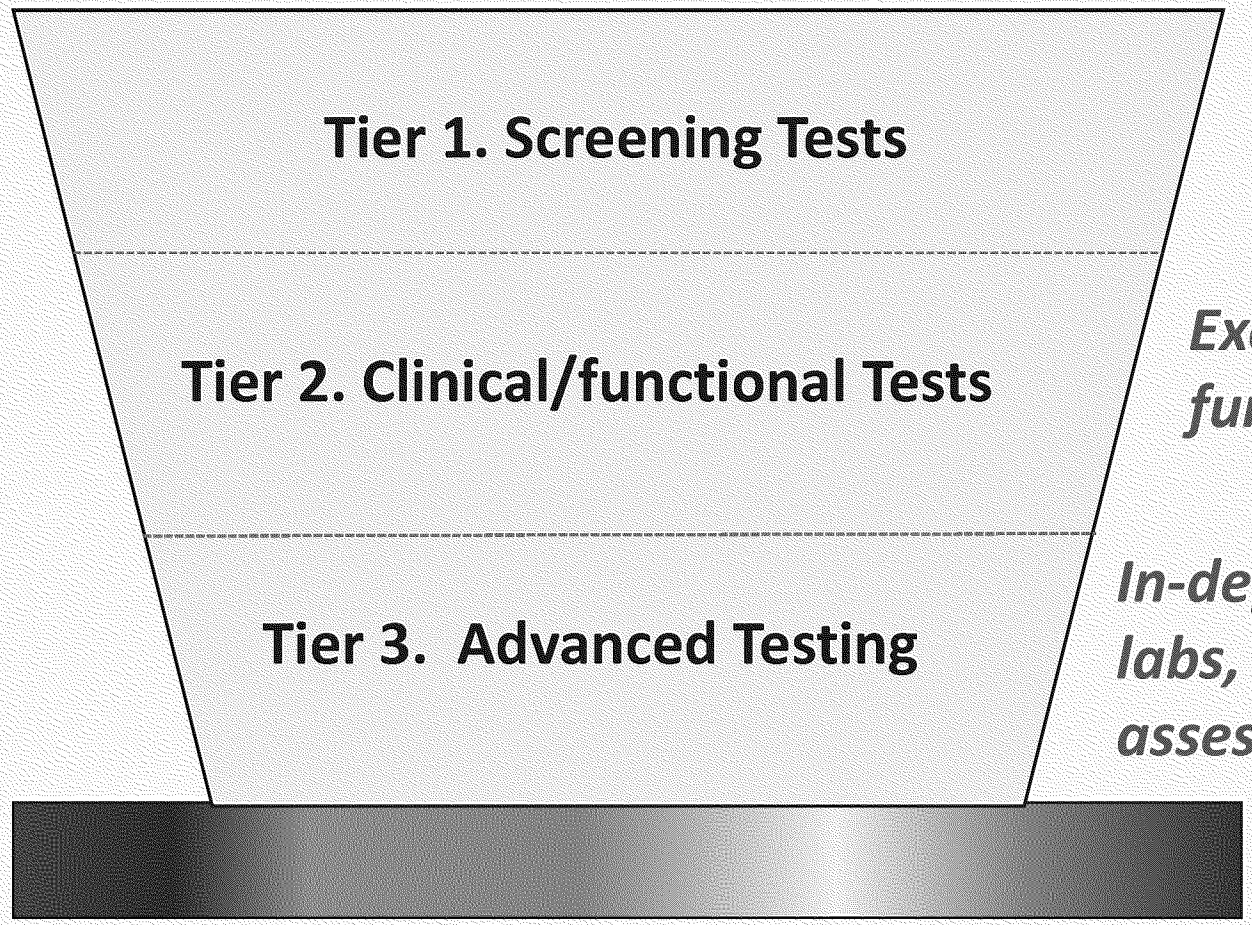
Achieving Depth and Breadth in RECOVER Cohorts

Acute and post-acute cohort studies will use platform-protocol driven tiered approach to **characterize the long-term effects of infection** and trajectory of recovery over time.

	ACUTE INFECTION COHORT	POST-ACUTE INFECTION COHORT
Overview	• Patients with confirmed acute SARS-CoV-2 infections • Prospectively followed for PASC, nested PASC cases vs. controls	• PASC patients 4+ weeks after acute SARS-CoV-2 infection • Matched PASC case-control design • Prospective and Retrospective data capture
Adults	**9k**, including 200+ pregnant persons	**9k**, including 2k pregnant persons
Children	**1k**	**18k**, including 800 with **MIS-C**

Understanding the Full Clinical Spectrum of PASC: In-depth Phenotypic Characterization through Tiered Assessments



Screening questionnaire, basic exams, and biospecimens

Exams, labs, imaging, functional assessments

In-depth phenotyping exams, labs, imaging, functional assessments

RECOVER: A National Scale Platform

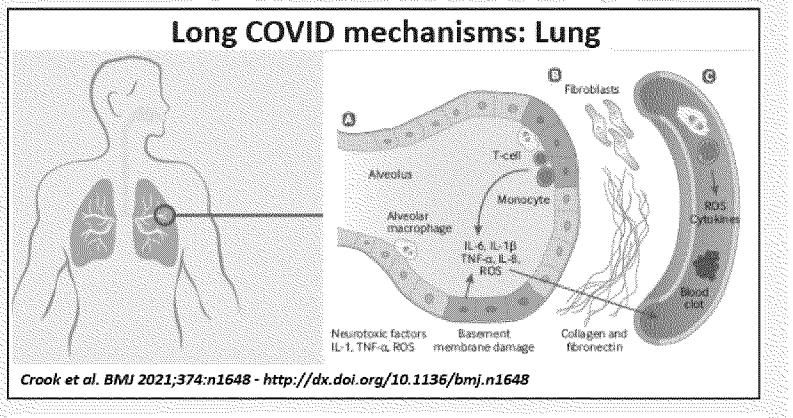
- **30 Hubs:**
  - 15 Adult Cohorts
  - 2 Pregnancy Cohorts
  - 8 Pediatric Cohorts
  - 5 Autopsy Centers
- **3 EHR Studies**
  - 50,000,000+ patient records

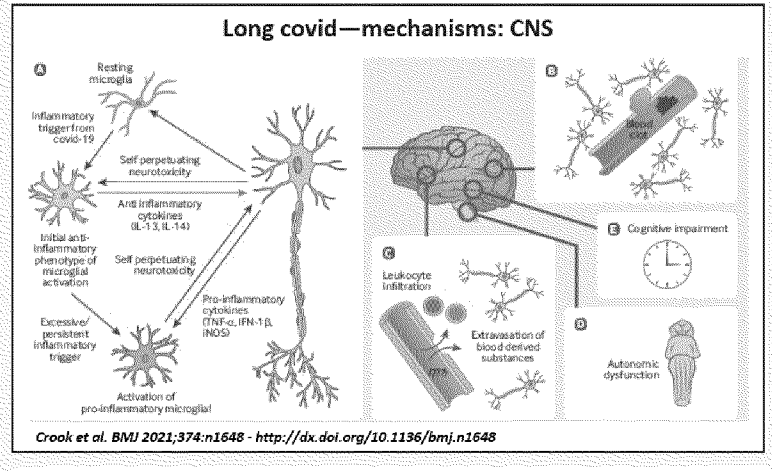
Enrolling participants from 200+ sites across the Nation

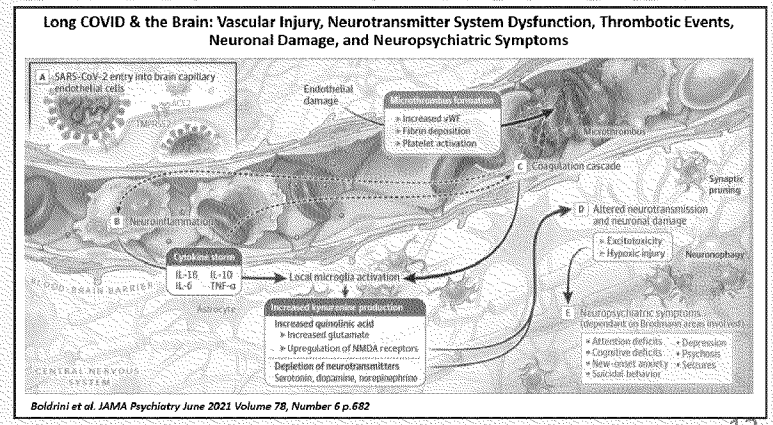
(To include Clinical Trials and Patient Registry)

Pathobiology of PASC

- **Studies from across broad extramural research community** and **RECOVER investigators** to identify:
  - Mechanisms underpinning clinical phenotypes and symptomatic manifestations
  - Pathology in multiple organ/systems that has led or will lead to clinically significant health problems
  - Potential therapeutic targets





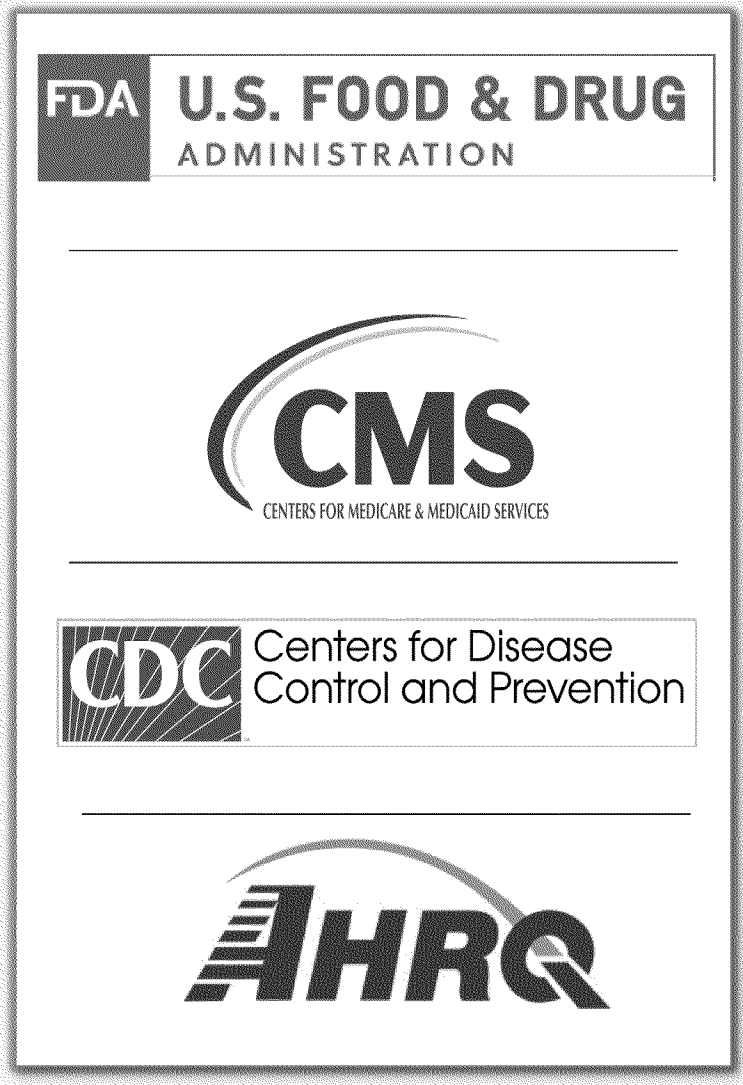


RECOVER Clinical Trials: Treatment and Prevention of PASC

- **Integral to RECOVER goals**
- **Leverage RECOVER infrastructure, expertise, data, and processes**:
  - Clinical cohorts: clinical spectrum characterized, phenotyping/sub-phenotyping
  - Input from patient engagement activities
  - Expertise of multi-disciplinary RECOVER Investigator Consortium
  - Central lab assays to further characterize and stratify patients
  - Biospecimens
  - Mobile Health platform, e-consent
  - Clinical operations infrastructure
  - Pathobiology studies/mechanistic insights
  - EHR studies
  - Patient Registry
  - Intervention Prioritization Process

PASC Research is an Integral Part of the Broader Public Health Ecosystem: Early and Ongoing Engagement with FDA, CMS, CDC, and AHRQ

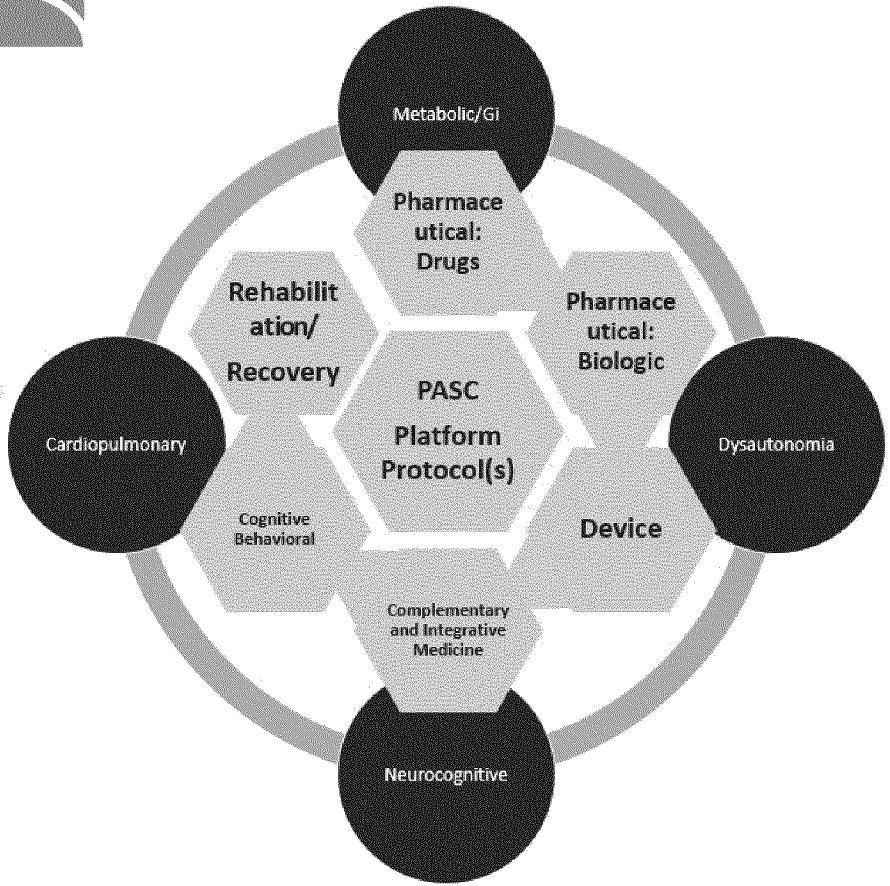
- Defining **regulatory pathway**
  - e.g., Selection on clinical endpoints
- Defining **coverage and analysis pathway**
  - e.g., Definition of PASC, evidence base to help support analyses
- Collaborating on **terminology,** sharing **approaches and emerging data**
- Providing **evidence base** for AHRQ activities in practice guideline development



Preparing for PASC Clinical Trials

PASC Interventions Prioritization

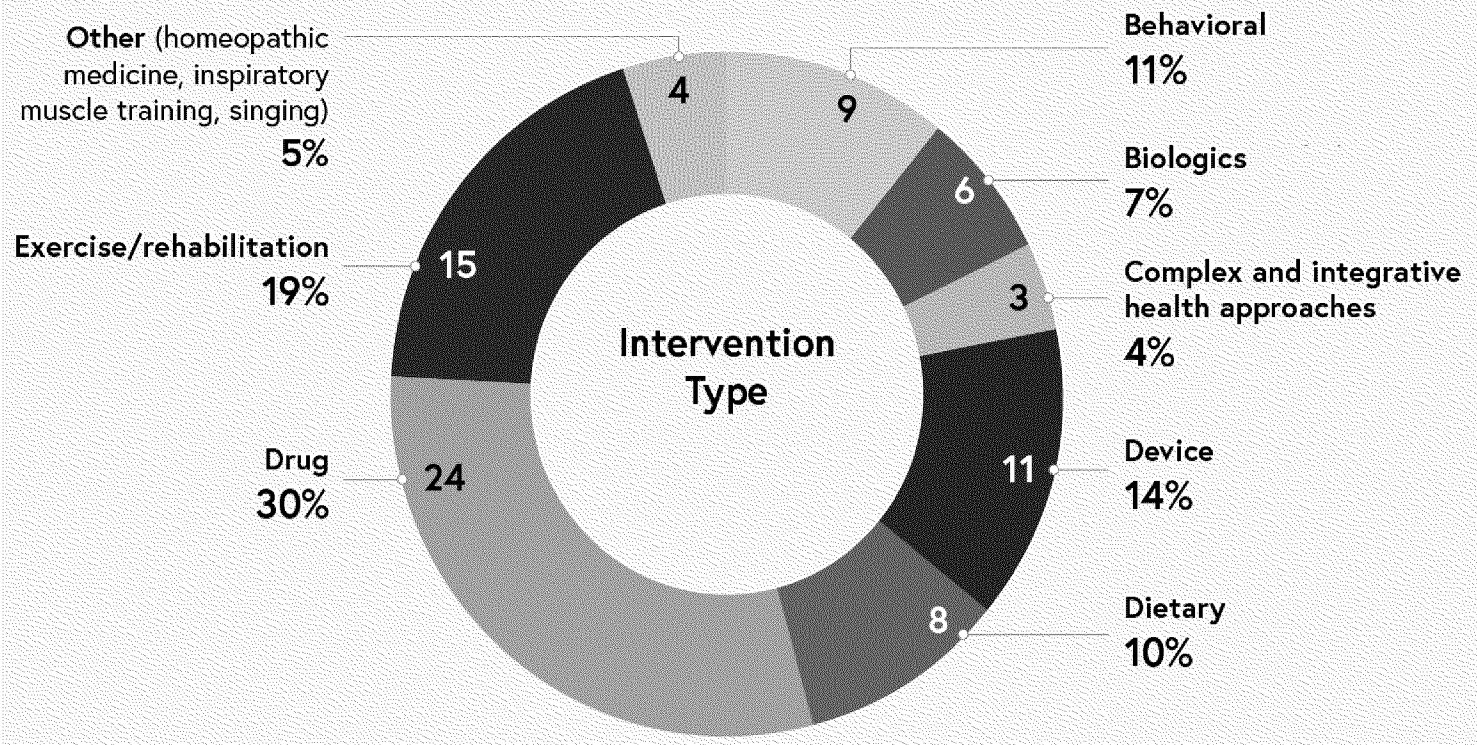
- Landscape Analysis
- Intervention & Outcomes Inventory Across RECOVER clinicians
- EHR Query of Interventions
- [Web-based Portal]



Adaptive Platform Protocol Development

Landscape Analysis of PASC Trials

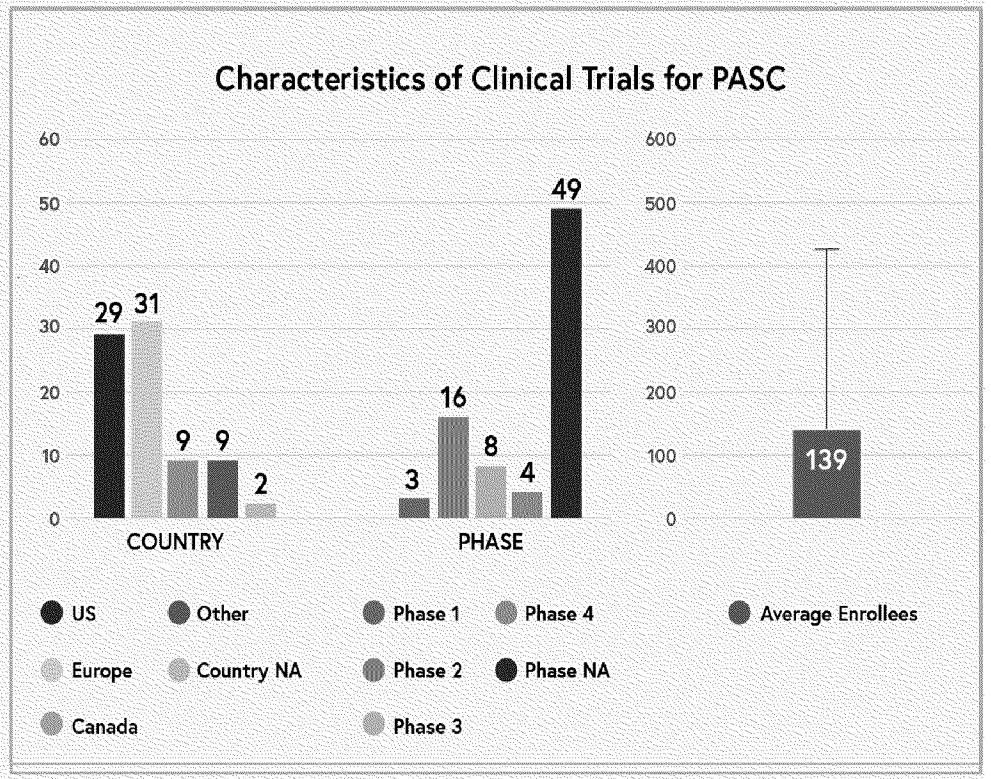
Objective: *Inform planning for PASC clinical trials*

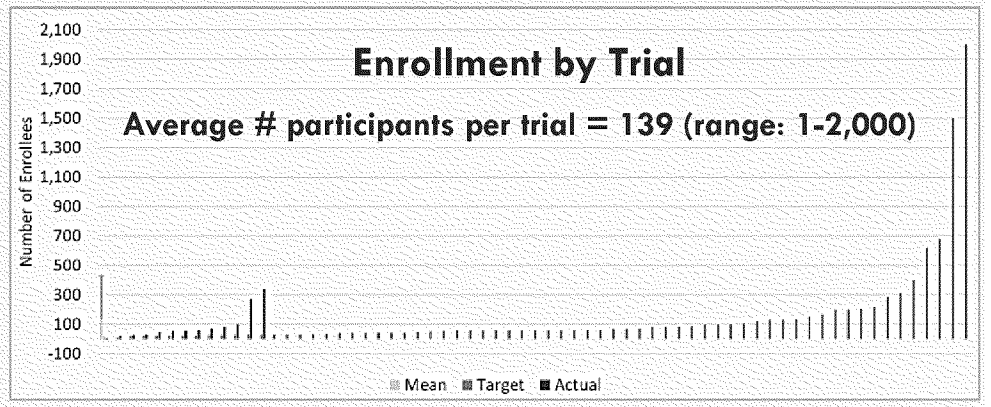


Total = 80 trials

Analysis of ct.gov conducted in January 2022

Drug/Biologic Interventions: Antivirals, immune-modulators, neuro-modulators/psychotropics/stimulants, anticoagulants, and stem cells





Hypothesized Etiologies of PASC and Implications for Potential Treatment Strategies

- PASC is very likely a set of multiple conditions with varied underlying causes

- Examples of **hypothesized** causes:
  - **Persistence or reactivation of SARS-CoV-2 virus or antigens** stimulating ongoing immune response ⇨ Antivirals
  - Viral infection setting in motion a **dysregulated immune response** affecting various organs and tissues ⇨ Immune Modulators
  - Viral infection and/or inflammatory responses cause **damage to organs and tissues** that in turn results in dysfunction (e.g., neurologic, cardiac, pulmonary, renal, metabolic, GI) ⇨ Host-tissue specific, rehab

[1] https://assets.researchsquare.com/files/rs-1139035/v1_covered.pdf?c=1640020576
[2] https://www.nature.com/articles/s41590-021-01113-x
[3] https://www.nature.com/articles/s41586-021-03631-y.pdf
[4] https://www.biorxiv.org/content/10.1101/2022.01.07.475453v1

RECOVER
Researching COVID to Enhance Recovery

Strategic Approach to PASC Clinical Trials

Intervention Selection		Features	Launch	Potential Candidate Interventions (Examples)
Informed by current etiologic hypotheses	• Intervention selection driven by patient symptoms/sx clusters • Informed by analyses of clinical practice • Informed by nascent theories regarding pathogenesis (e.g., viral persistence/reactivation, immune dysregulation, autoantibodies, host-tissue injury)	• Patient-centered outcomes as endpoints • Platform protocol(s) • Bayesian analyses	2022	• Rehabilitation and Recovery: Neuro-cog and cardiopulmonary • Cognitive behavioral therapy

		• Hard endpoints *(In addition to patient-centered outcomes)*
		• Adaptive Platform protocol(s)
		• Bayesian analyses
			2022	• Pharmacologic:
				  • Antivirals
				  • Immune modulators
				• Device: carotid body stimulation

Informed by Pathobiology Studies	• As above and • Therapeutic targets selected based on mechanisms of pathogenesis (Pathobiology Studies)	• Hard endpoints *(In addition to patient-centered outcomes)* • Adaptive Platform protocol(s) • Bayesian analyses	2023 *(earlier if possible)*	

DISCUSSION

- **Opportunities for collaboration**
- **General Q/A**

RECOVER
Researching COVID to Enhance Recovery

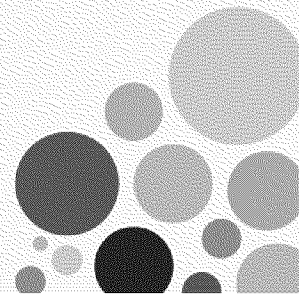
An Initiative Funded by the National Institutes of Health

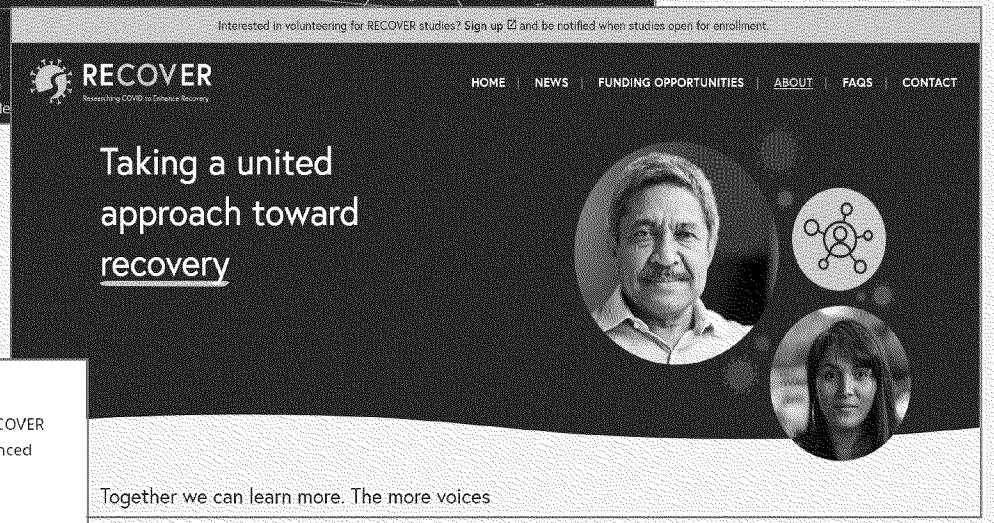
Moving the Field Forward: Potential Areas of Synergy

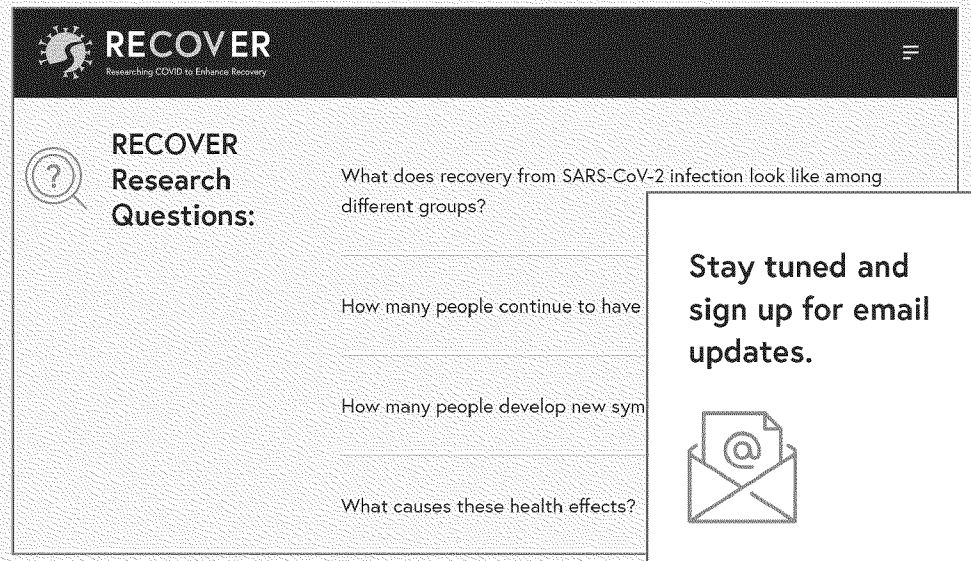
- General:
  - Accelerate and expand our understanding of PASC:
    - Elucidate targets and define patient sub-populations:
      - Additional ancillary studies, including mechanistic studies
      - Specialized assays, such as immunophenotyping, and specific functional assessments and imaging
- Specific:
  - Clinical Trials

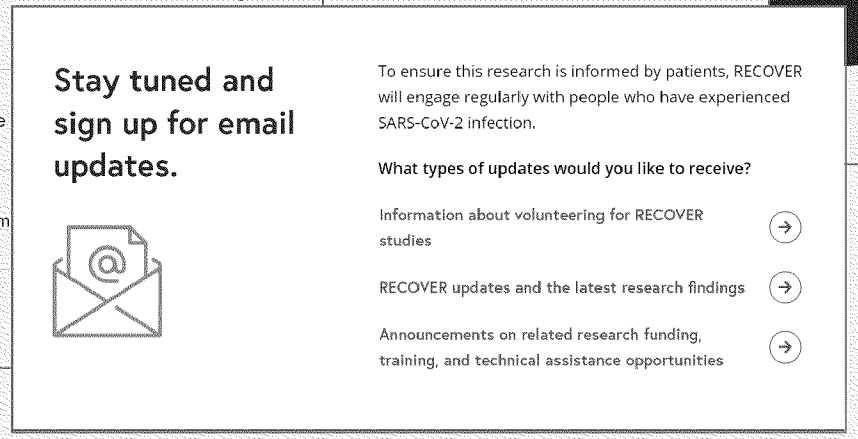
Adaptive Platform CT Investigation of Antiviral and/or Immune Modulatory Agents: Opportunity and Options for Collaborative Approach

- **Trial-specific Industry partner:**
  - Supply of drug and placebo (with appropriate labeling and packaging) and cover shipping and distribution
  - Funding for capitation
  - Funding for industry-specific requirements that go beyond FDA requirements
  - Funding for protocol/IC documents translation costs
- **NIH:**
  - Clinical trial Infrastructure
  - Clinical operations
  - Design and data analysis
  - Regulatory submissions
  - Oversight, including DSMB
  - Results sharing









RECOVER
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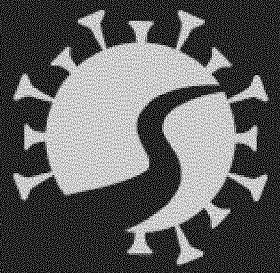
recoverCOVID.org



RECOVER

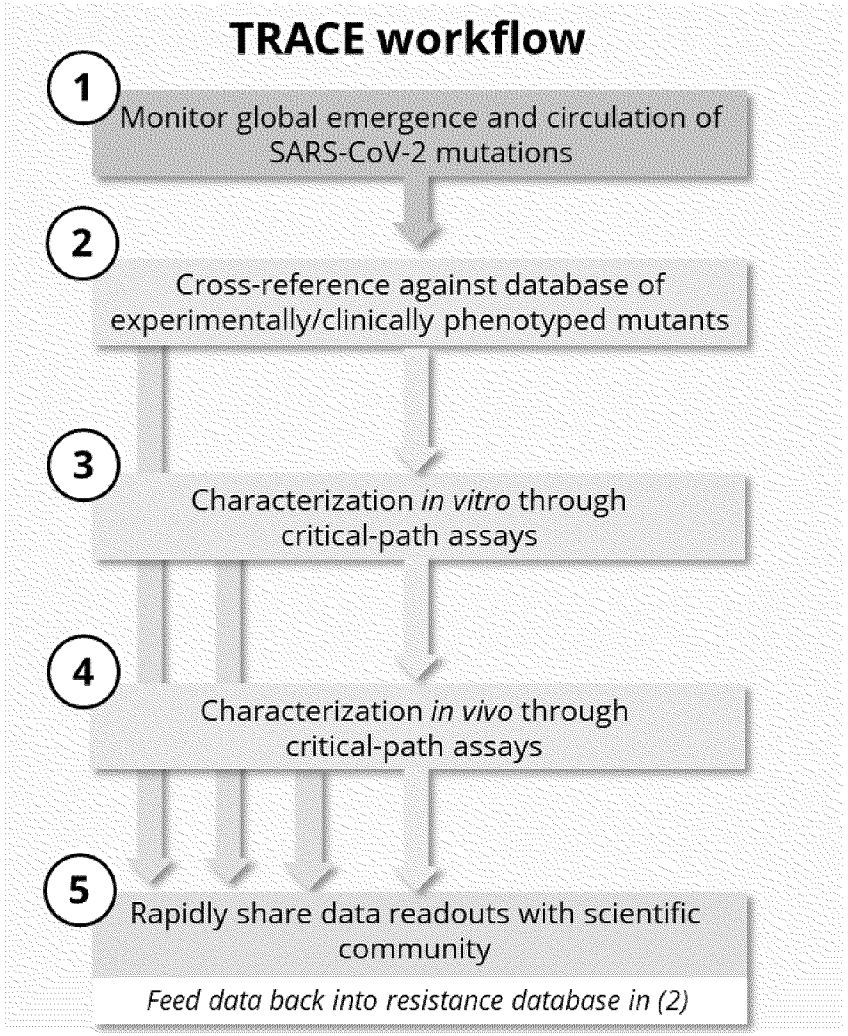
Researching COVID to Enhance Recovery

ACTIV

TRACE WORKING GROUP

Lisa Purcell, Vir

ACTIV TRACE (Tracking Resistance And Coronavirus Evolution) Workflow and Priorities



TRACE Priorities

- Publish weekly TRACE report summarizing shifting trends in emerging viral variants
- Collect available industry and government agency data on variants in one place
- Generate datasets using standardized protocols and common reference reagents

FNIH

New to the ODP & Variant Testing Updates

The ODP visualizations for VOCs now show sublineage activity data; a toggle button changes the visual from sublineage and to live virus/pseudovirus.

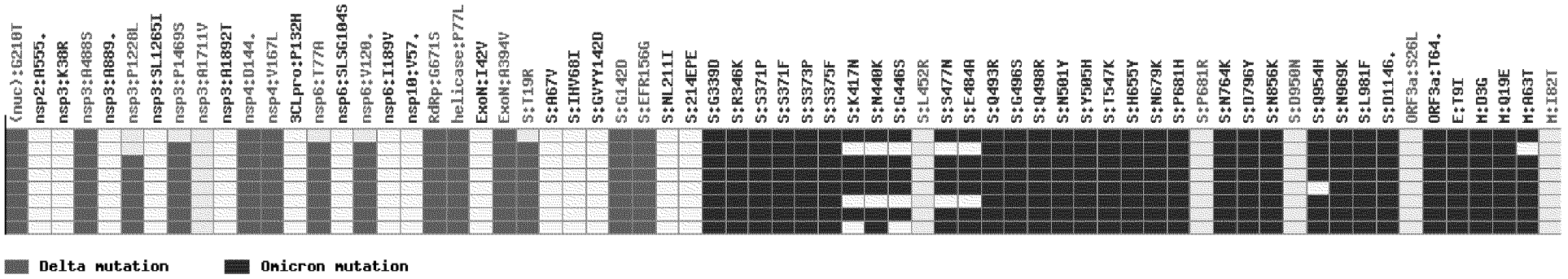
The ODP restructured the nABs to have combination therapies listed first followed by individual components to allow users to easily assess differences between agents used individually or in combination.

New NCATS standardized testing data continues to be uploaded to the ACTIV TRACE Prioritized Variant Testing Pages on the ODP.

Deltacron & Future Variants

Conducted a deep analysis of potential recombinants consistent with *Deltacron*, but prevalence is very low

- BEI is working to obtain live virus for distribution to the research community
- TRACE has setup a framework for tracking potential recombinants in the TRACE Report



The Subgroup is working to expand SARS-CoV-2 surveillance efforts to wastewater

ACTIV TRACE Effector Function Groups

Vision

- *A **collaborative initiative** to identify patterns and better inform future pandemic therapeutics and vaccines*
- *Develop an **open access repository***
- *Collect and share **effector function data***

Goal

- *Improve functional understanding to allow better drug development decision making*
- *Create a publicly accessible resource that could potentially be added to ODP*

Partnerships

Facilitators:
Galit Alter, PhD [MGH, HMS, MIT]
Annie Zumsteg, PhD [Vir]

Group Members:
Margaret Ackerman, PhD [Dartmouth]
Stelios Bournazos, PhD [Rockefeller University]
Davide Corti, PhD [Vir]
James Crowe, MD [Vanderbilt University]
Mike Diamond MD, PhD [WUSTL]
Mark Esser, PhD [AstraZeneca]
Nicole Kallewaard, PhD [Lilly]
Falk Nimmerjahn, PhD [FAU]
Erica Ollmann Saphire, PhD [LJI]
Georgia Tomaras, PhD [Duke]
Taia Wang, MD, PhD, MSCI [Stanford]

FNIH

ACTIV

THERAPEUTICS CLINICAL WORKING GROUP

Sarah Read, NIAID
Ruxandra Draghia Akli, J&J

Master Protocol | Current Status

The enrollment statuses of the open ACTIV trials are outlined below.

COMPLETED ENROLLMENT

ACTIV-1
TOPLINE RESULTS:
May 2022

ACTIV-2
TOPLINE RESULTS:
Synairgen P2: May 2022
Other Results Reported

ACTIV-5
TOPLINE RESULTS:
BET A: April 2022
BET B: June 2022
BET C: July 2022

CURRENTLY ENROLLING

ACTIV-2D

ACTIV-4A

ACTIV-4HT

ACTIV-3B

ACTIV-4C

ACTIV-6

PAUSED ENROLLMENT

ACTIV-2B/C

ACTIV-3

FNIH

Master Protocol | Recent Updates

The most recent and relevant updates from the ACTIV Trials are outlined below.

ACTIV-3B

- ✓ Agent Prioritization Committee suggested **1 agent (out of 8) to be sent to ACTIV-3B for consideration (Prostacyclin)**
- ✓ Discussing potential arm with **AZ7442 with AZ**

ACTIV-6

- ✓ Appendices for fluvoxamine/ fluticasone and montelukast submitted to FDA on March 18
- ✓ **Ivermectin 400 and Fluticasone topline results are anticipated end of April/early May**

ACTIV-2

- ✓ **Synairgen's participation in ACTIV-2 ended**
  - Exploring alternative trial platforms

ACTIV-3

- ✓ MP did not meet predefined futility criteria; data unblinded; **manuscript in preparation**
- ✓ Pfizer data readout will be published end of March
- ✓ AZ agent primary endpoint was not met.
  - **The agent did show effect on overall mortality**
  - **Manuscript submitted to NEJM**

Master Protocol | STRIVE Platform

The new inpatient platform **STRIVE (Strategies and Treatments for Respiratory & Viral Emergencies)** will serve as a master protocol platform to study interventions against respiratory infections.

- *Protocol will utilize the network of inpatient trial sites from ACTIV-1, ACTIV-3, and ACTIV-5*
- *Infections include SARS-CoV-2, influenza, and others, with therapeutic interventions being either novel or existing*

CURRENT PROGRESS

PROTOCOL DEVELOPMENT

- The STRIVE concept has been discussed with **leadership from ACTIV-3, ACTIV-1, and ACTIV-5 and with individual networks**,
- Discussions are **ongoing to incorporate sites** from ACTIV-1 and ACTIV-5

ORGANIZATIONAL STRUCTURE

Two committees that will oversee STRIVE are in development:

1. Leadership Committee
2. Scientific Steering Committee

NEXT STEPS

- Continue developing the **scientific protocol**
- Anticipate **protocol completion by summer 2022**

FNIH

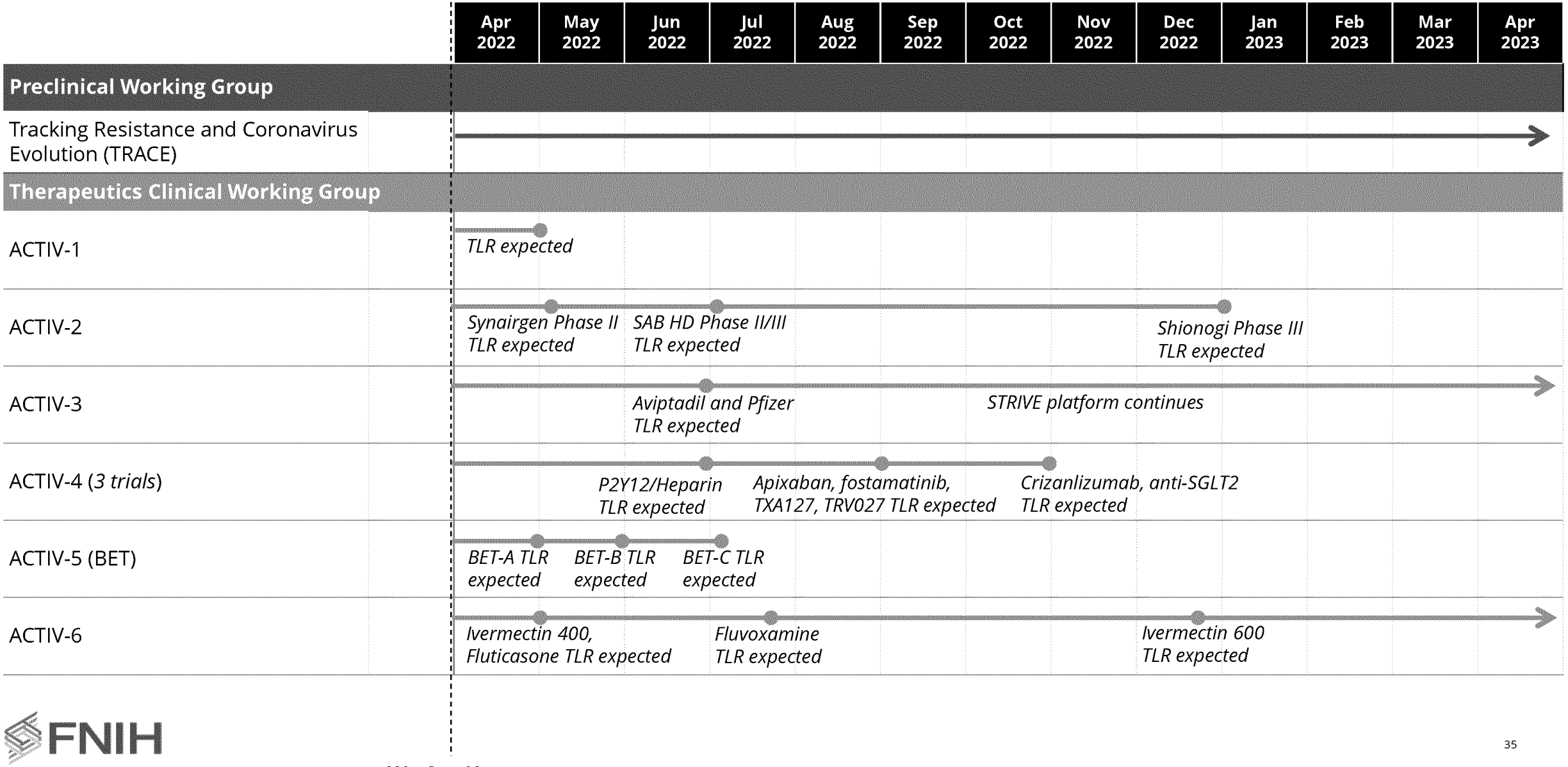
ACTIV

MILESTONES, FUTURE PLANS & DISCUSSION

William Pao, Pfizer
Larry Tabak, NIH
David Wholley, FNIH

ACTIV Milestones

Anticipated ACTIV milestones for the year ahead are outlined below.



Scheduled ACTIV EC/LT Meetings

March 30, 2022

ACTIV Executive Committee & Leadership Team Meeting

TODAY

April 20, 2022

ACTIV Executive Committee & Leadership Team Meeting

May 25, 2022

ACTIV Executive Committee & Leadership Team Meeting

FNIH

High-Level Meeting Summary

The Leadership Team and Executive Committee ("Leadership Team") guiding the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Partnership convened their 23rd meeting to review the status of current ACTIV efforts, presented by Co-Chairs of the Tracking Resistance and Coronavirus Evolution (TRACE) and Therapeutics Clinical (TX-Clinical) Working Groups (WGs), including the ongoing clinical trial of SAB-185.

Updates on Future Directions of ACTIV

David Wholley, MPhil, FNIH

Mr. Wholley provided brief updates on the status of action items from the discussion during the last Leadership Team meeting regarding potential future directions for ACTIV.

Mr. Wholley had previously sent the LT meeting participants a white paper and a slide deck summarizing the pandemic "Lessons Learned" workshop conducted through Operation Warp Speed referenced by Dr. Janet Woodcock, in which members of the ACTIV teams participated. Mr. Wholley mentioned that in addition ACTIV/NIH is collaborating with editors at *Nature* to develop a more detailed lessons learned review. NIH is also developing its own lessons learned report, which should be released in March.

Mr. Wholley pointed out that much of ACTIV's additional ongoing effort to better prepare for future pandemics is inherent in the continued development and enhancement of the TRACE platform, which will be discussed further in today's meeting. In addition, representatives from TRACE and ACTIV are participating in a series of discussions coordinated by the Wellcome Trust on integrating global surveillance efforts to quickly identify potential future pandemics.

The LT had also asked whether the optimized structure and membership of ACTIV could be used to facilitate response to future pandemics. In response, Mr. Wholley stated that the current ACTIV infrastructure, including FNIH support, currently has clear financial support through the end of 2022, and that the group can assess the need for continued support as we get closer to the end of the year.

Additional questions by the LT focused on how to address care for "long-COVID" and critically ill patients as well as pediatric trials are to be addressed during the readout from the Therapeutics-Clinical working group today.

TRACE WG

Matthew Hall, PhD, NCATS; Kim Pruitt, PhD, NCBI

Drs. Matt Hall and Kim Pruitt provided an overview of TRACE's ongoing efforts to monitor the global emergence of SARS-CoV-2 mutations, including an overview of the Deep Sequencing Analysis Subgroup (DSAS) efforts, updates on Omicron variant sublineages, and a description of

new features in the National Center for Advancing Translational Sciences (NCATS) Open Data Portal (ODP).

Deep Sequencing Analysis Updates

DSAS focuses on ensuring that variant calls are accurate and reproducible across pipelines. DSAS evaluates partner sequences against a common set of sequencing data and identifies strategies to ensure consistent sequence results and variant calling.

DSAS has frequently encountered significant variation in sample quality and data analysis approaches across sequencing platforms. DSAS relies primarily on next generation sequencing (NGS) data submitted to the Sequence Read Archive (SRA) database. Most NGS sequences are incomplete, may be contaminated by primer sequences, and DNA from the host or other viruses. DSAS first analyzes these data to remove contaminant sequences and then aligns the NGS fragments against a reference sequence. This comparison enables DSAS to identify mutations (e.g., single nucleotide polymorphisms [SNPs], indels) and low coverage regions. Differences in data quality can be caused by multiple factors, including different sequencing platforms, software tools, sample prep strategies, and poor primer binding. Sequences from the ONT platform show greater variability than sequences from Illumina.

DSAS has instituted multiple improvements, including improved methods for removing host sequence contamination, harmonizing software tools and analyses across pipelines, and establishing consistent reporting across pipelines. These efforts have resulted in an increase in SNP call agreement from 77 percent to more than 90 percent across all participating pipelines, and an increase in indel call agreement from 16 percent to 65 percent across all participating pipelines.

Analyses of Omicron variant sequences in particular have been hampered by frequent primer failures, which often result in inconsistent read depth across the Omicron variant genome. DSAS is preparing a manuscript on Omicron variant analysis issues, which the group plans to complete by the end of March.

Shifting Trends in SARS-CoV-2 Variants

TRACE continues to track Omicron sublineages. BA.1 and BA.1.1 comprise approximately 99 percent of Omicron sequences in the United States, while BA.2 accounts for only 0.9 percent. This frequency contrasts with international sequence data, in which BA.2 comprises 20.6 percent of sequences and dominates some countries. TRACE data match CDC data on Omicron sublineages. TRACE continues to evaluate sequences reported as “Deltacron” to determine whether they are due to sequencing errors or represent a new variant.

Updated data from ODP show that bebtelovimab and sotrovimab retain activity against BA.1.1, while many other therapeutic monoclonal antibodies (mAbs) are less effective against this sublineage. Antivirals such as molnupiravir and remdesivir also retain activity against BA.1.1.

NCATS ODP Updates

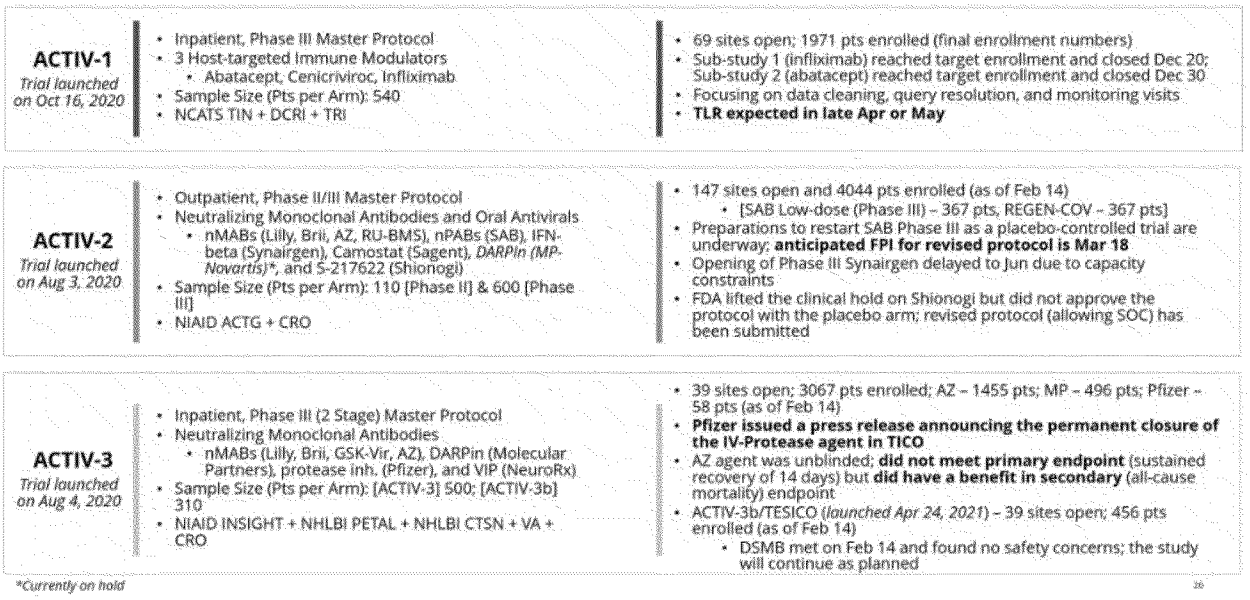
ODP has added a feature that enables users to visualize mAb effectiveness against Omicron sublineages. The ODP page now also includes a link to view and download NIH dose-response data, including fold change data, and detailed assay information for 24 variant sublineages.

Therapeutics Clinical WG

Sarah Read, MD, NIAID; Ruxandra Draghia-Akli, MD, PhD, Johnson & Johnson

Status of ACTIV Master Protocols

Dr. Read summarized the status of ACTIV's master protocols, as depicted in the screenshots below. Dr. Read also showed a table displaying the status of all agents that have undergone or are currently undergoing ACTIV testing. That table is available in the slide deck circulated for this meeting.

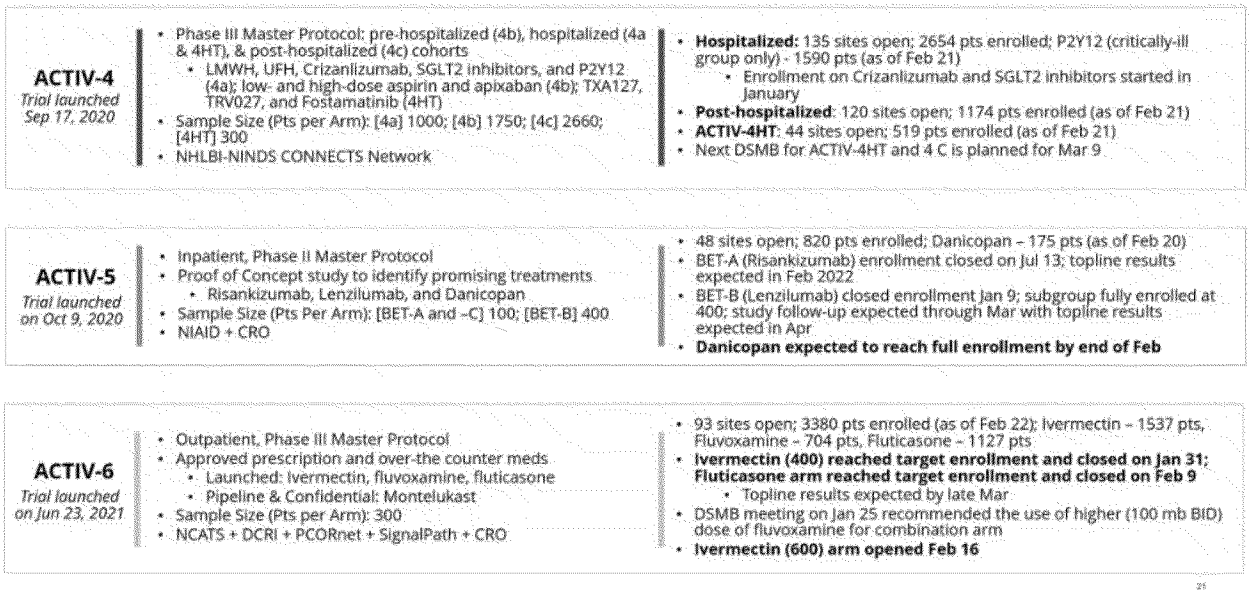


ACTIV-1 *Trial launched on Oct 16, 2020*	• Inpatient, Phase III Master Protocol • 3 Host-targeted Immune Modulators • Abatacept, Cenicriviroc, Infliximab • Sample Size (Pts per Arm): 540 • NCATS TIN + DCRI + TRI	• 69 sites open; 1971 pts enrolled (final enrollment numbers) • Sub-study 1 (infliximab) reached target enrollment and closed Dec 20; Sub-study 2 (abatacept) reached target enrollment and closed Dec 30 • Focusing on data cleaning, query resolution, and monitoring visits • **TLR expected in late Apr or May**

ACTIV-2
Trial launched on Aug 3, 2020
	• Outpatient, Phase II/III Master Protocol
	• Neutralizing Monoclonal Antibodies and Oral Antivirals
	  • nMABs (Lilly, Brii, AZ, RU-BMS), nPABs (SAB), IFN-beta (Synairgen), Camostat (Sagent), *DARPin (MP-Novartis)**, and S-217622 (Shionogi)
	• Sample Size (Pts per Arm): 110 [Phase II] & 600 [Phase III]
	• NIAID ACTG + CRO
		• 147 sites open and 4044 pts enrolled (as of Feb 14)
		  • [SAB Low-dose (Phase III) – 367 pts, REGEN-COV – 367 pts]
		• Preparations to restart SAB Phase III as a placebo-controlled trial are underway; **anticipated FPI for revised protocol is Mar 18**
		• Opening of Phase III Synairgen delayed to Jun due to capacity constraints
		• FDA lifted the clinical hold on Shionogi but did not approve the protocol with the placebo arm; revised protocol (allowing SOC) has been submitted

ACTIV-3
Trial launched on Aug 4, 2020
	• Inpatient, Phase III (2 Stage) Master Protocol
	• Neutralizing Monoclonal Antibodies
	  • nMABs (Lilly, Brii, GSK-Vir, AZ), DARPin (Molecular Partners), protease inh. (Pfizer), and VIP (NeuroRx)
	• Sample Size (Pts per Arm): [ACTIV-3] 500; [ACTIV-3b] 310
	• NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO
		• 39 sites open; 3067 pts enrolled; AZ – 1455 pts; MP – 496 pts; Pfizer – 58 pts (as of Feb 14)
		• **Pfizer issued a press release announcing the permanent closure of the IV-Protease agent in TICO**
		• AZ agent was unblinded; **did not meet primary endpoint** (sustained recovery of 14 days) but **did have a benefit in secondary** (all-cause mortality) endpoint
		• ACTIV-3b/TESICO (*launched Apr 24, 2021*) – 39 sites open; 456 pts enrolled (as of Feb 14)
		  • DSMB met on Feb 14 and found no safety concerns; the study will continue as planned

**Currently on hold*



Next Generation ACTIV Trials

As noted in previous meetings, the TX-Clinical WG has reorganized ACTIV clinical trials into three subgroups: inpatient trials, outpatient trials, and coordination with the NIH-sponsored RECOVER study of long COVID.

The Inpatient Subgroup met on February 9 and discussed three priorities: 1) opening the Strategies and Treatments for Respiratory Infectious Viral Emergencies (STRIVE) platform (described in more detail below) to evaluate therapeutic agents and combinations; 2) leveraging currently active clinical trial networks, including potentially adding ACTIV-1 and ACTIV-5 sites to the ACTIV-3 network, to support future clinical trials; and 3) reviewing 6-7 agents for potential inclusion in ACTIV-3.

Within the Outpatient Subgroup, the ACTIV-2B/C team is designing a blinded Phase II and Phase III study with Paxlovid as the active control. ACTIV-6 is seeking to open a combination arm based on Agent Prioritization Committee scoring. The Outpatient Subgroup is also actively discussing additional approaches for examining therapeutic combinations for outpatient use.

The Coordination with RECOVER Subgroup continues to follow up with ACTIV trial participants to assess long-term outcomes. This Subgroup is also discussing ways to use the ACTIV trial network to support RECOVER's interventional trials.

The TX-Clinical WG will also meet with Novartis on March 3 to discuss approaches for increasing pediatric trials and pediatric-specific therapeutics for SARS-CoV-2 and other infectious diseases.

Discussion

Dr. Dolsten expressed concern that the orientation of many ACTIV focus areas have not evolved from their original designs during the initial "pandemic phase" of SARS-CoV-2, and that the ACTIV clinical trials are continuing to examine therapeutics and combinations that are similar to

others already being tested by private pharmaceutical companies in their own trials. While the initial focus of ACTIV and the field on survival was necessary and understandable, continuing changes in the SARS-CoV-2 pandemic may require focusing on a better basic understanding of the pathophysiology of the virus and its functional changes, particularly in high-risk populations (e.g., immunocompromised people) and those with "long COVID" (or post-acute sequelae of SARS-CoV-2 infection [PASC]. Is there an appropriate focus on host-virus response? Are there better drugs or combinations of drugs that could be studied beyond those currently under consideration? Where could a public-private partnership approach have the most impact?

Dr. Draghia-Akli noted that many of the ACTIV trials currently being considered by the TX-Clinical Working Group are combination trials that examine different patient populations and levels of disease severity. Furthermore, the TX-Clinical WG's plans include efforts to enable ACTIV to retain its existing clinical trial infrastructure for future trials on SARS-CoV-2 and other infectious diseases. These will be discussed further during the report of the TX-Clinical WG which follows this discussion.

Dr. Tabak noted that PASC is likely a spectrum of pathologies with a large degree of interpersonal variation. Post-mortem analyses of patients with PASC have found SARS-CoV-2 virus in multiple tissues, and the specific tissues affected may differ between patients. Dr. Tabak suggested inviting representatives from the National Institute of Neurological Diseases and Stroke (NINDS) and National Heart, Lung, and Blood Institute (NHLBI) to the next Leadership Team meeting to provide an overview of the NIH's RECOVER project, which includes substantial efforts to examine PASC risk factors and pathophysiology, as well as eventually interventional therapeutic trials.

Mr. Wholley also asked Dr. Dolsten if he and other company members would be willing to allow their agents that are now approved under Emergency Use Authorization (like Paxlovid) to be used within the ACTIV trials. This will allow for more novel and progressive combinations to be studied to address some of the concerns raised. Dr Dolsten suggested that these agents could be made available for trials if the proposed trial includes relevant populations that would be informative and not already tested by the company (e.g., immunocompromised individuals), or that was not covered in the original trials (e.g., PASC).

STRIVE: A Potential Next Generation ACTIV In-Patient Platform

Wesley Self, MD, Vanderbilt University

The ACTIV-3 team is developing STRIVE, a next-generation ACTIV platform and infrastructure that can be used to study COVID-19 and other infectious diseases. STRIVE seeks to consolidate inpatient ACTIV trial networks into a singular platform that leverages lessons learned from previous ACTIV clinical trials.

STRIVE will have a shared coordinating center, data collection tools, and consent procedures, and will also have shared control groups within randomization domains (e.g., among patients requiring mechanical ventilation). STRIVE's framework will also be usable across different types of therapeutic interventions, including investigational agents, repurposed agents, and

supportive care strategies. To study effectiveness throughout disease progression, STRIVE will use sequential randomizations across stages of infection and recovery. Dr. Self presented an example of sequential randomizations for patients based on clinical stage at admission, which is illustrated in the presentation slides. Effective sequential randomizations would likely require greater understanding of a disease's pathophysiology and biomarkers for disease progression and immune response.

Results of Phase II Study on SAB-185

Babafemi Taiwo, MBBS, Northwestern University

SAB-185 is a transchromosomic, bovine-derived polyclonal antibody (pAb) with evidence of in-vitro activity against multiple SARS-CoV-2 variants, including Omicron. The ACTIV-2 Phase II clinical trial examined two doses of SAB-185: low-dose (3,840 units/kg), and high-dose (10,240 units/kg). The sample size for each dose group was 220 (110 SAB-185 and 110 pooled placebo). The study initially enrolled participants at high-risk of progression to hospitalization or death but protocol eligibility was changed to low-risk persons only after EUA COVID-19 treatments became available for high-risk persons. The study defined three primary outcome measures: Nasopharyngeal (NP) SARS-CoV-2 RNA < lower limit of quantification (LLoQ), time to improvement in targeted symptoms, and safety through day 28. Secondary outcomes included quantitative NP SARS-CoV-2 RNA. Results from the low-dose group only were presented at CROI and here.

The median age was 38, 68% had symptoms for 5 days or less, 11% had higher risk of progression to hospitalization or death and 23% were COVID vaccinated. Although proportion with NP SARS-CoV-2 below limits of quantitation was higher at days 3 and 7 in the SAB-185 arm compared to placebo, the difference was not significant on those days or overall for days 3, 7, and 14 combined. At Day 3, median NP RNA levels for SAB-185 and placebo were 2.38 vs. 3.14 log10 copies/ml, respectively, (difference in medians = -0.76 log10 copies/ml favoring SAB-185, p=0.10). There appears to be greater antiviral effects in those with 5 or less days of symptoms before study entry. Time to symptom improvement for 2 days was not different between SAB-185 and placebo (11 versus 10 days). There were no severe infusion reactions, hypersensitivity reactions or drug related serious AEs.

The conclusions were that 1) SAB-185 was safe, and 2) while no significant differences to placebo were seen in symptom duration or proportion of participants with NP SARS-CoV-2 RNA <LLoQ, quantitative RNA assessments showed a trend towards virologic efficacy at day 3.

The DSMB evaluated interim data from this study and concluded that both low and high doses of SAB-185 met pre-specified criteria for efficacy. Low dose SAB was subsequently selected for advancement to phase 3 evaluation.

Redesigning ACTIV-2/A5401 for the Omicron Variant

Kara Chew, MD, UCLA

In September 2021, ACTIV-2 began enrolling participants for a non-inferiority trial comparing SAB-185 against the casirivimab/imdevimab cocktail. However, in vitro studies showed that casirivimab and imdevimab are not likely to be clinically effective against the Omicron variant, leading the FDA to request an enrollment pause in January 2022. By that point, ACTIV had already enrolled 734 participants for this trial.

Following discussions with the FDA, ACTIV-2 amended its protocol to complete the SAB-185 Phase III trial as a blinded, placebo-controlled superiority study. Participants will be permitted to receive standard of care (SOC) therapies *after* enrollment, but only if they sought and did not receive SOC therapies at the time of enrollment. ACTIV-2 has more than 200 sites across the world, and SOC therapies remain limited at many of these sites.

The primary analysis population will be comprised of participants with documented (by sequencing) or suspected (by time of enrollment) Omicron infection enrolled to SAB-185 or casirivimab under protocol version 7 and all participants enrolled to SAB-185 vs placebo. ACTIV-2 researchers are currently analyzing SARS-CoV-2 sequences for all ACTIV-2 participants; sequencing data are currently limited due to an initial lag in sequencing.

In the new trial design, ACTIV-2 researchers are comparing hospitalizations and deaths between the placebo and SAB-185 arms. Participants who previously received the casirivimab/ imdevimab cocktail are assumed to have received a "functional placebo" for Omicron infection with respect to clinical efficacy. The total sample size is 1200 participants, which is equally divided between the two study arms. The statistical power in the revised study design may be impacted by multiple events, including decreased hospitalizations and deaths in the placebo control group, differential efficacy of SAB-185 in conjunction with SOC treatments, and loss to follow-up. The ACTIV-2 team is actively collaborating with the DSMB to monitor these potential impacts on statistical power and study feasibility. The DSMB may recommend early termination of study enrollment due to safety concerns, evidence of efficacy favoring SAB-185, evidence of limited efficacy of SAB-185, and operational futility.

ACTIV-2's challenges highlight difficulties in planning and executing non-inferiority studies as new variants arise, any of which may threaten the constancy assumption fundamental to the design of NI studies. Most available therapeutics were developed and tested prior to the Omicron variant, making it difficult to select a different active comparator for a non-inferiority study at this time.

Discussion

Dr. Virgin expressed concern about including participants treated with the casirivimab/imdevimab cocktail in the placebo control group of the newly designed ACTIV-2 study, since these antibodies may still retain some degree of activity against Omicron within participants. He noted that in vitro levels of mAbs in neutralization studies should be compared to pharmacokinetic levels of these mAbs in patients following administration. Dr. Chew noted that binding of casirivimab and imdevimab to Omicron spike is limited. Furthermore, the FDA has approved analysis of casirivimab/imdevimab as a functional placebo.

Dr Dolsten pointed to the mild effect of the SAB therapeutic in the phase 2 portion of the trial and asked what criteria was used to approve the agent moving into a phase 3 trial. The team responded that the pre-specified criteria for moving to phase 3 was met and thus the agent moved on. These criteria were designed by the protocol writing team and the decision was based on the interim analysis of the data.

Adjourn

The Leadership Team's next meeting will be held on March 30, and the following meeting will be on April 20.

Appendix A: Participants List

William Pao, PhD, *Head of Pharma Research and Early Development, Roche (Session Co-Leader)*
Lawrence Tabak, DDS, PhD, *Director, NIH (Session Co-Leader)*

Stéphane Bancel, ME, MBA, (not in attendance) *CEO, Moderna*
Kara Carter, PhD, *Dewpoint Therapeutics*
Marco Cavaleri, (not in attendance), *Head of Office, Anti-infectives and Vaccines, EMA*
Tomas Cihlar, PhD, (not in attendance), *VP and Head of Virology, Gilead*
Christine Colvis, PhD, *Director for Drug Development Partnership Programs, NCATS*
Larry Corey, MD, *President and Director Emeritus, Fred Hutchison Cancer Research Center*
Michelle Culp, MPH, (not in attendance), *Office of Science Policy, Office of the Director, NIH*
Victoria Davey, PhD, MPH, *Chief Officer of Public Health and Environmental Hazards, VA*
Ruxandra Draghia-Akli, MD, PhD, *Global Head, Global Public Head R&D, Johnson & Johnson*
Mikael Dolsten, MD, PhD, *CSO and President, Worldwide R & D, Pfizer*
Betsy Desrosiers, MS, PMP, (not in attendance), *Executive Director, Clinical Sciences and Study Management, Merck*
Gary Disbrow, PhD, *Acting Director, BARDA*
Emily Erbelding, MD, MPH, (not in attendance*), Director, Division of Microbiology and Infectious Diseases, NIAID*
Stanley Erck, MBA, (not in attendance) *President and CEO, Novavax*
Anthony Fauci, MD, (not in attendance), *Director, NIAID*
Ellen Gadbois, PhD, *Office of Science Policy, Office of the Director, NIH*
Gary H. Gibbons, MD, (not in attendance), *Director, NHLBI*
Sarah Grant, MD, *Strategic Assistant to Head Global Drug Development, Novartis*
Matthew Hall, PhD, *Director, Early Transition Branch, NCATS*
Thomas J. Hudson, MD, (not in attendance), *Vice President of Oncology Discovery and Early Development, AbbVie*
Kathrin Jansen, PhD, (not in attendance) *Senior Vice President, Head of Vaccine Research and Development, Pfizer*
Robert Johnson, PhD, *Director, Division of Influenza and Emerging Infectious Diseases, BARDA, ASPR, HHS*
David Kessler, MD, (not in attendance), CSO, *White House COVID Response*
Lynn Kramer, MD, (not in attendance), *Chief Clinical Officer, Neurology Business Group, Eisai Company Ltd*
Michael Kurilla, MD, PhD, (not in attendance) *Director, Division of Clinical Innovation, NCATS*
H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*
John Lepore, MD, (not in attendance), *Senior Vice President, Head of Research, GlaxoSmithKline*
Dean Li, MD, PhD, *Executive Vice President & President, Merck*
Doug Lowy, MD, (not in attendance), *Principal Deputy Director, NCI*

Barbara Mahon, MD, *Medical Epidemiologist, CDC*

Peter Marks, MD, PhD, (not in attendance), *Director, CBER, FDA*

John Mascola, MD, (not in attendance) *Director, Vaccine Research Center, NIAID*

David Meeker, MD, (not in attendance), *KSQ Therapeutics (formerly Genzyme)*

Hitesh Pandya, MD, *Medical Science Director, AstraZeneca*

Mene Pangalos, PhD, (not in attendance), *Executive Vice President, BioPharmaceuticals R&D, AstraZeneca*

Ashley Parker, PhD, *Health Science Policy Analyst, NIH*

Robert Plenge, MD, PhD, (not in attendance), *Senior Vice President & Head of Immunology, Cardiovascular and Fibrosis Thematic Research Center, Head of Translational Medicine, Bristol Myers Squibb*

Lisa Purcell, PhD, (not in attendance), *Vice President of Microbiology and Virology, Vir Biotechnology*

Sarah Read, MD, *Deputy Director, Division of AIDS, NIAID*

John C. Reed, MD, PhD, (not in attendance) *Executive Vice President, Global Head of Research & Development, Sanofi*

David Reese, MD, (not in attendance), *Executive Vice President Research & Development, Amgen*

Doris J. Rouse, PhD, *VP, Global Health Technologies, RTI International*

Daniel M. Skovronsky, MD, PhD, (not in attendance) *Senior Vice President and Chief Scientific Officer, Eli Lilly and Company*

Peter Stein, MD, (not in attendance) *Director of Office of New Drugs, CDER, FDA*

Paul Stoffels, MD, (not in attendance), *Vice Chairman of the Executive Committee and Chief Scientific Officer, Johnson & Johnson*

Brig. Gen. Michael Talley, (not in attendance), *Commanding General, US Army Medical Research and Development Command*

John Tsai, MD, *Head, Global Drug Development and CMO, Novartis*

Rajeev Venkayya, MD, (not in attendance), *President, Global Vaccine Business Unit, Takeda*

Rupert Vessey, DPhil, (not in attendance), *President of Research and Early Development, Bristol Meyers Squibb*

Tonya Villafana, PhD, MPH, (not in attendance) *Vice President and Global Franchise Head, Infection, AstraZeneca*

Herbert (Skip) Virgin, MD, PhD, *EVP Research and CSO, Vir Biotechnology*

Janet Woodcock, MD, (not in attendance), *Principal Deputy Commissioner, FDA*

John Young, PhD, *Global Head, Infectious Diseases and Vice President, Roche*

INVITED PARTICIPANTS

Brittany Chao, PhD, *Scientific Special Assistant to the NIH Principal Deputy Director, Office of the Director, NIH*

Kara Chew, MD, *Associate Clinical Professor, University of California Los Angeles (UCLA)*

David Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, NHLBI*

Mathai Mammen, MD, PhD, *Executive Vice President, Pharmaceuticals, R&D, Johnson & Johnson*
Kim Pruitt, PhD, *Chief, Information Engineering Branch, NCBI, NLM*
Joni Rutter, PhD, *Acting Director, NCATS, NIH*
Wesley Self, MD, *Associate Professor of Medicine, Vanderbilt University*
Tara Schwetz, PhD, *Acting Principal Deputy Director, NIH*
Babafemi Taiwo, MBBS, *Chief of Infectious Diseases in the Department of Medicine, Northwestern University*

STAFF

Stacey Adam, PhD, *Associate VP of Research Partnerships, FNIH*
Cheryl Melencio, *Administrative Manager, FNIH*
Michael Santos, PhD, *VP of Science, FNIH*
David Wholley, MPhil, *Interim President and Executive Director, FNIH*

Margaret Anderson, MA, *Managing Director, Deloitte*
Serena Melton, *Senior Consultant, Deloitte*
Courtney Copeland, PhD, *Senior Consultant, Deloitte*
Francis Larosa, *Consultant, Deloitte*
Alex Cwalina, *Consultant, Deloitte*
Alex Sorosa, *Consultant, Deloitte*
Jonathan Wachtel, MBA, *Manager, Deloitte*
Caroline Yarbrough, *Consultant, Deloitte*

Gina Castelvecchi, PhD, *Writer, Rose Li and Associates, Inc.*

Appendix B: Zoom Chat Transcript

13:24:33 From William Pao To Everyone:
I had a comment re Deltacron [answered in discussion and below]

13:28:24 From Matt Hall To Everyone:
William I could have mentioned that for the deltacron sequences the TRACE team have been evaluating, they all contain the omicron RBD

13:28:48 From William Pao To Everyone:
Thanks, Matt

13:45:22 From Skip Virgin (he-him-his) To Everyone:
The basic understanding of the pathophysiology of the different outcomes is very rudimentary to me. I think that we can all benefit from a deeper understanding of the disease(s) and outcomes that will afflict our populations hereinafter. This is a super urgent need that can transform us.

13:46:43 From Skip Virgin (he-him-his) To Everyone:
Appreciate Mikael asking the provocative question.

13:47:26 From Tom Hudson To Everyone:
Mikael: I think that your comments are appropriate and that any future study should be selected based on a higher bar in regards to the scientific understanding of the disease.

13:47:49 From dolstem To Everyone:
thanks

13:52:10 From Skip Virgin (he-him-his) To Everyone:
Would 10 experimental medicine trials defining outcome mechanisms save more lives than 2 clinical efficacy trials and cost the same?

13:54:04 From William Pao To Everyone:
I had a separate maybe controversial question re: ACTIV-6. I understand the rationale for testing those agents but I assume there'll be a lot of interest in the outcomes as most scientists would probably say they'd be negative. Is the team prepared for the media coverage on these studies? [answered below]

13:59:34 From Joni Rutter To Everyone:
@William - yes we are thinking of this. You may have seen the JAMA Internal Medicine paper on a recent trial (I-TECH), which was negative. ACTIV6 topline results are not out yet, but it did use the same dose as this trial. The trial PIs are ready for the media coverage and have been doing interviews over the course of the trial.

14:05:57 From William Pao To Everyone:

Thanks - sounds like you have it under control!

14:23:11 From Skip Virgin (he-him-his) To Everyone:
I have a question for this speaker.....

14:24:21 From Matt Hall To Everyone:
My question ; how will sequencing not be available? I think sequencing & variant ID for each study participant is critical in trials. [answered in discussion]

14:28:03 From dolstem To Everyone:
didn't this look like a failed phase 2...why to go to phase 3 [answered in discussion]

14:28:56 From Skip Virgin (he-him-his) To Everyone:
I am not sure if there is time for a question. I think inclusion of mAb treated persons as placebos (did I get that right) is quite concerning. The Cmax for the mAbs may be in excess of the concentrations for a mAb in serum or tissue. So assuming that a large loss in neutralization potency is equivalent to a placebo is not appropriate to me without assessment of the PK of the mAbs. [answered in discussion]

From: Thomas, Jacqueline [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3a2c3bbc2bd0426bb3dd8e1ef7ec3686-Jacqueline.]
Sent: 3/29/2022 7:40:56 PM
To: Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]
CC: Helms Williams, Emily [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=873be46f1b1a4d2b8df3fe67137cbdc8-HELMSWILLIA]; Sheehy, Janice [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f45a6c96f5274724a1be5970eb648ff7-JSheehy]; Olivarria, Frank [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c180721db774423f99990dd86e67057c-Frank.Oliva]; Copeland, Jakea [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7fe05ed233c42b68be990b12ae2c8c8-Jakea.Copel]; Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]; Colonius, Tristan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2b3590c046734a2e928858bd579ed852-Tristan.Col]; Flowers, Susan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9418b62ec07642d7bc53c564e008f5ce-Susan.Flowe]
Subject: Read-Aheads for Wednesday, March 30, 2022
Attachments: 03.30.22 ACTIV EC and Leadership Team Meeting_20220330.pdf; 2022-2-23_ACTIV_Leadership_Team_and_Executive_Committee_Summary f3.docx; MM HU Flowchart.pdf; Briefing Memo - stemcells (CBER 3.24.22) (004).docx; CaliffR HCTP stem cells (CBER 3.24.22)oes.pptx; Agenda for OEA Weekly Comms Mtg 3-30-22.docx; FW: [EXTERNAL] Article - USA today on Rare Diseases

Read-Aheads for Wednesday, March 30, 2022

- **10:30 a.m.** - [EXTERNAL] ACTIV Leadership Team Meeting #24 – *2 documents attached*
- **1:00 p.m.** - Commissioner Informational Briefing: HCT/Ps including stem cells – *3 documents (briefing materials) attached*
- **4:15 p.m.** - Agenda for OEA Weekly Communications Forecast meeting – *1 document attached*

Reading Material

- [EXTERNAL] Article – USA Today on Rare Disease – *email attached*

Jacqueline Thomas
Executive Assistant
Immediate Office, Office of the Principal Deputy Commissioner
U.S. Food and Drug Administration
Mobile: (b) (6)
Email: Jacqueline.Thomas@fda.hhs.gov

From: Goldie, Christina [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4511e64a9fcd44db933f961260de0f42-Christina.G]
Sent: 3/29/2022 6:24:58 PM
To: Thomas, Jacqueline [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3a2c3bbc2bd0426bb3dd8e1ef7ec3686-Jacqueline.]
Subject: FW: [EXTERNAL] Article - USA today on Rare Diseases
Attachments: Screen Shot 2022-03-29 at 2.10.58 PM.png

From: Claire Murphy <Claire.Murphy@terrapinn.com>
Sent: Tuesday, March 29, 2022 6:20 PM
To: Hatch, Shannon <Shannon.Hatch@fda.hhs.gov>; Goldie, Christina <Christina.Goldie@fda.hhs.gov>
Cc: Grant, April <April.Grant@fda.hhs.gov>; Felberbaum, Michael <Michael.Felberbaum@fda.hhs.gov>
Subject: Re: [EXTERNAL] Article - USA today on Rare Diseases

Hi all,

I've attached the correct screenshot of the print article in USA today.

Thank you,
Claire

From: Claire Murphy <Claire.Murphy@terrapinn.com>
Sent: Tuesday, March 29, 2022 3:05 PM
To: Hatch, Shannon <Shannon.Hatch@fda.hhs.gov>; Goldie, Christina <Christina.Goldie@fda.hhs.gov>
Cc: Grant, April <April.Grant@fda.hhs.gov>; Felberbaum, Michael <Michael.Felberbaum@fda.hhs.gov>
Subject: Re: [EXTERNAL] Article - USA today on Rare Diseases

Hi all,

The USA Today article featuring Dr. Janet Woodcock is finally out! The attached screenshot is a PDF version of the physical article in the print copies of USA Today.

Link to Online Article: https://www.futureofpersonalhealth.com/rare-diseases/why-its-an-exciting-time-in-rare-disease-drug-development/

Please feel free to share on social as you see fit. We are blasting this out today on our channels as well.

Thank you to Dr. Woodcock for contributing as a thought leader to this piece.

Let me know if you have any questions.

Best,
Claire

From: Claire Murphy <Claire.Murphy@terrapinn.com>
Sent: Wednesday, February 23, 2022 4:43 PM
To: Hatch, Shannon <Shannon.Hatch@fda.hhs.gov>
Cc: Grant, April <April.Grant@fda.hhs.gov>; Felberbaum, Michael <Michael.Felberbaum@fda.hhs.gov>
Subject: Re: [EXTERNAL] Article - USA today on Rare Diseases

Hi Shannon,

Received! Thank you for helping to coordinate this internally. We look forward to incorporating Dr. Woodcock's input for this article.

Best reguards,
Claire

From: Hatch, Shannon <Shannon.Hatch@fda.hhs.gov>
Sent: Wednesday, February 23, 2022 4:19 PM
To: Claire Murphy <Claire.Murphy@terrapinn.com>
Cc: Grant, April <April.Grant@fda.hhs.gov>; Felberbaum, Michael <Michael.Felberbaum@fda.hhs.gov>
Subject: RE: [EXTERNAL] Article - USA today on Rare Diseases

Dear Claire,
I'm writing to provide Dr. Woodcock's responses for your article on rare diseases. You can download a photo of Dr. Woodcock here: https://www.flickr.com/photos/fdaphotos/albums/72157632027269586. Kindly reply-all to confirm receipt of this e-mail.

The following responses can be attributed to **Janet Woodcock, M.D., Principal Deputy Commissioner, U.S. Food and Drug Administration**:
=======
I've been involved in rare disease drug development for over 30 years. Things have changed a lot in that time. The 1980-2000 period brought increased awareness and hope, but limited progress. The genomics revolution brought new understanding to many rare diseases and true optimism about cures.

What is exciting about the future?
The new tools that are on the horizon—gene therapies, cellular therapies, gene editing technologies—will let us attack the causes of many rare diseases in ways we couldn't even imagine previously. These tools could help us treat the cause of the diseases rather than just help the symptoms, bringing people longer and healthier lives.

Why does it take more than 6 years for the average rare disease to be diagnosed?
Medicine still relies a lot on the "see one, do one, teach one" paradigm. If you've never seen one diagnosed, you probably won't recognize one when you do see it. We need to use more information technology in diagnosis, not just rely on standard diagnostics, they often don't reveal the rare disorder.

How to make rare disease drug development more equitable?
Most of drug development is done by for-profit companies. They have to stay in business, so they need to have successful programs and get a return on investment. FDA operates incentive programs like Orphan Drug exclusivity to sweeten the pot, and we also give out grants to help with development costs. Patient groups that help stake development costs have been successful in some diseases. FDA works with patient groups to develop knowledge about the disease, its progression, and the kinds of problems it causes, and this can give developers a head start on their programs, incentivize investment and potentially create more competition in the field.
=======

Best regards,
Shannon

Shannon P. Hatch
Media Relations Director

Office of Media Affairs
Office of External Affairs
U.S. Food and Drug Administration
Mobile: 202-510-1973

From: Claire Murphy <Claire.Murphy@terrapinn.com>
Sent: Monday, February 7, 2022 5:54 PM
To: Goldie, Christina <Christina.Goldie@fda.hhs.gov>
Cc: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Subject: [EXTERNAL] Article - USA today on Rare Diseases

Dear both,

The World Orphan Drug Congress USA is collaborating with MediaPlanet for a massive article for Rare Disease Day in USA Today print and several digital publications.

Dr. Woodcock, would you be interested in providing a quote for the prompts below? Here is a list of questions and information on the article:

Questions:

1. What is the most important medical advancement in rare diseases in the last 5 years?
2. What do you think is most exciting about the future of rare disease drug development?
3. Why do rare diseases take 6 years on average to diagnose? How can this be improved?
4. What challenges do we need to overcome to make rare disease drug development more equitable?

Kindly let me know by Thursday 2/10 if this would be of interest.

World Orphan Drug Congress USA 2022| Editorial Contribution Overview & Guidelines

Final Content Deadline: February 23rd

Word Count: 50-100 words per answer*

- 2 questions per Panelist will be featured in print, extended answers and all questions to be featured digitally

Photo: Headshot required - to be shown next to quotes

Exposure: Article will run within print campaign (150k minimum copies within USA Today) and will be featured indefinitely on digital campaign site featured on Future of Personal Health (100k monthly unique visitors, health-interested consumers)

Development: Article written by Mediaplanet journalists/WODC to get responses from experts

Happy to answer any questions!

Best,
Claire

Claire Murphy

Production Director

Terrapinn Inc.

110 William St, 25th Fl. | New York, NY 10038

T | +1 646 619 1784

E | claire.murphy@terrapinn.com

W | www.terrapinn.com

From: Adam, Stacey (FNIH) [T] [sadam@fnih.org]
Sent: 3/21/2022 12:33:24 PM
To: Kurilla, Michael G (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fa2de9594d594ed9b76b935545c26754-HHS-michael]; Erhardt, Bill A (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d795053ca625464f91fa923a0a455ac1-HHS-bill.er]; Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; Read, Sarah W (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=72ca09ea60c74100a908211e1f7c5f6a-HHS-readsa-]; Lane, Henry C (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d904337536cf41719032a9359a1ec2ab-HHS-CLANE-n]; Erbelding, Emily J (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c981f04015d64d27b1afdd9c06111071-HHS-emily.e]; Eakin, Ann E (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d126f4c08a514e12ac2e646ae79bbd20-HHS-ann.eak]; Erica Ollmann Saphire [erica@lji.org]; Stein, Peter [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d30a87acb0184261961264ba984b0a51-Peter.Stein]; Judy Currier [jscurrier@mednet.ucla.edu]; Davey Smith [d13smith@health.ucsd.edu]; Kim, Peter S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2876661346ba42d7a684f7d3ae5c5b4c-HHS-peter.k]; Neaton, Jim [neato001@umn.edu]; Lundgren, Jens (b) (6); Higgs, Elizabeth S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0ac36dd643c04994b3161baf825cbfc3-HHS-ehiggs-]; Kiley, James P (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=47964c0318054e7c98c149a93cfe6ada-HHS-kileyj-]; Goff, David C (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa2747f2f704a3ba1637f2febe8bc67-HHS-david.g]; Dr Susanna Naggie, M.D. [susanna.naggie@duke.edu]; Adrian Hernandez, M.D. [adrian.hernandez@duke.edu]; Dunsmore, Sarah E (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e3ee18c15d824f2394abe93b8a0a2064-HHS-dunsmor]; Nakela Cook [nlcook@pcori.org]; Penny Mohr [pmohr@pcori.org]; Brown, Samuel (b) (6); Barkauskas, Christina [christina.barkauskas@duke.edu]; Fessel, Josh P (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1531bbc9172747829bc72c4ce1176926-HHS-josh.fe]
CC: Carver-Roberts, Trea R (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05c1728ee14540bb9d98a6b7917c85eb-HHS-trea.ca]; Reich, Colleen [cjreich@health.ucsd.edu]; Lisbeth Jørgensen (b) (6) fnih [fnih@roseliassociates.com]; Dana Carluccio [dana.carluccio@roseliassociates.com]; Church, Elizabeth S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1feccbf65b8e4285bc6fa6ede9c44e02-HHS-elizabe]; Melencio, Cheryl L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=baa3813b343d4f4cb949f1b990023053-HHS-cmelenc]; Jabarkhail, Mina [MJabarkhail@mednet.ucla.edu]; Nesin, Mirjana (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=86ffcb8d6be149788e21229c314b60f7-HHS-Mirjana]; Holly Bunton [hbunton@pcori.org]; Fant, Annie (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=01e618455da34f0a8db87cf3fc60ff36-HHS-Annie.F]; Kelly, William (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5238754dfa034c159efd8e749c2739a6-HHS-William]; Eisnor, Derek (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f7b89712a02b43958d5253c1e79f21a3-HHS-Derek.E]; Kelly Beazley [kelly.beazley@roseliassociates.com]; Menetski, Joseph M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d8ed7bcfcbc04f338026fde223a907ae-HHS-jmenets]; Melton, Serena [smelton@deloitte.com]; Sorosa, Alex [asorosa@deloitte.com]; Cwalina, Alex [acwalina@deloitte.com]; Laura Rodriguez [llrodriguez@pcori.org]; Parker, Ashley S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3f43b948b59f4e679535a8a3ebc91167-HHS-ashley.]; Tara Cole [tcole@pcori.org]; Chao, Brittany N (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ccec410dec8491985206c8694db1c15-HHS-brittan]; Martins, Karen (OS)

	[/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=16144aa45fbf4fe58775e7340f4c8c82-HHS-Karen.M]
Subject:	[EXTERNAL] Summary of the ACTIV-2/-3/-6 Trial Oversight Committee Meeting
Attachments:	2022-03-16_Trial_Oversight_Committee_Meeting_Summary.pdf

Dear ACTIV-2/-3/-3B/-6 TOC Members,

Please find attached the summary of our meeting last week. If you have any additions or amendments, please let me know.

Thanks,
Stacey

Stacey J. Adam, PhD (*she/her*)
Associate Vice President
Research Partnerships
Foundation for the National Institutes of Health
Direct: **(301) 435-8364** | Mobile: (b) (6)
fnih.org
11400 Rockville Pike, Suite 600, North Bethesda, MD 20852

For 18 years, Charity Navigator has recognized the FNIH as an organization that exceeds industry standards.

High-Level Meeting Summary

The ACTIV-2/-3/-6 Trial Oversight Committee (TOC) heard status updates on ACTIV-2, ACTIV-3, and ACTIV-6 trials; the emerging SARS-CoV-2 variant landscape; and the outcomes of a recent agent prioritization meeting for ACTIV-3/-3b.

Trial Accrual Updates

ACTIV-2

ACTIV-2 has closed enrollment, having opened 147 sites and enrolled 734 patients (including 367 each to SAB low dose and REGEN-COV) in the Phase III study under Version 7 of the master protocol. In total, ACTIV-2 enrolled 4,044 patients, including 1,079 to Lilly and 624 to Brii Bio for its Phase III study, as well as 319 to Lilly, 222 to Brii Bio, 94 to AZ IV, 164 to AZ IM, 167 to Camostat, 163 to Synairgen, 149 to SAB (high dose), 156 to SAB (low dose), and 173 to RU/BMS for its Phase II study.

The ACTIV-2 team is working on a letter of amendment for Version 8 of the master protocol, with a focus on following up with participants who have already enrolled in the trial.

Synairgen had previously met graduation criteria for ACTIV-2 but will not be moving forward. Dr. Stacey Adam forecasted that the next TOC meeting on March 30 may include discussion about the potential onboarding of Synairgen in ACTIV-6.

ACTIV-2b/-2c/-2d

The ACTIV-2b team continues to work with Molecular Partners/Novartis to launch the Phase II evaluation of their DARPin agent in low-risk individuals. Though currently pursuit of this trial is on hold pending the outcome of government appropriations decisions.

The ACTIV-2d team continues to move quickly toward launch with the Shionogi agent, pending feedback from FDA. FPI is anticipated in the last week of March or first week in April.

ACTIV-3

ACTIV-3 has closed enrollment, having registered 53 sites, opened 39 sites, and enrolled a total of 3,067 patients. At the next TOC meeting on March 30, the ACTIV-3 team will present unblinded data for the Pfizer and Molecular Partners/Novartis agents, which enrolled a total of 58 and 496 patients, respectively. The ACTIV-3 team is analyzing safety data through Day 28 in an effort to understand the divergent recommendations from the DSMB and FDA regarding continued enrollment in the study. In addition, the team has decided to expand its overall report on the Pfizer agent to include data from 90 days of follow-up.

The ACTIV-3 team has continued to collaborate with the ACTIV-1 and ACTIV-5 teams to develop a new trial platform, which would involve 80-90 sites in the United States and Latin America.

ACTIV-3b

The ACTIV-3b sub-study has registered 43 sites, opened 39 sites, and enrolled 465 participants. Dr. Samuel Brown noted that none of the trial sites currently have COVID-19 patients in the ICU.

Trial Expansion

The ACTIV-3b team has been meeting with AstraZeneca (AZ) to discuss the potential expansion of TESICO to include additional study of its monoclonal antibody (mAb) cocktail, Evusheld, following the agent's promising performance in TICO. In addition, the Agent Prioritization Committee met last week to review nine other candidates for potential entry into ACTIV-3/-3b. The committee recommended only one reviewed candidate, prostacyclin, for further consideration, in light of recent data on its use for COVID-19 ARDS. Dr. Brown acknowledged that prostacyclin has a long history of use in ARDS patients and would therefore be familiar to hospital staff, but contrasted its relatively involved route of administration with the ease of administering the AZ mAb. The committee similarly agreed that onboarding the AZ agent into ACTIV-3b would be a better selection than prostacyclin. FNIH will share with the TOC the full Agent Prioritization Committee review of all nine considered candidates.

VATICO

Enrollment to VATICO has been stopped due to VATICO's reliance on randomization of patients to TICO. Although VATICO likely did not enroll enough patients for a full analysis, the trial team plans to write a manuscript based on lessons learned to inform future similar trials.

ACTIV-6

ACTIV-6 has opened 93 sites and enrolled 3,477 participants, including 740 to fluvoxamine and 73 to ivermectin 600; the ivermectin 400 and fluticasone arms completed accrual with final totals of 1,537 and 1,127 participants, respectively (note: enrollment numbers do not include shared placebo controls). As with other ACTIV trials, weekly accrual has slowed for ACTIV-6, and the DSMB canceled its meeting scheduled for next week due to insufficient new enrollment. However, ivermectin enrollment continues to outpace fluvoxamine enrollment due to both participant preference and DDI-related eligibility criteria for fluvoxamine. Nonetheless, ACTIV-6 has reached 75 percent of its target enrollment for the shared placebo in the fluvoxamine arm. Diversity among enrolled participants remains a challenge for ACTIV-6, which has recently seen a slight decrease in enrollment of Black participants and a slight increase in enrollment of Latinx participants.

Final follow-ups for the closed ivermectin 400 and fluticasone arms have been completed and data analysis is underway, with unblinding anticipated in April and topline results shortly thereafter. The ivermectin 400 results will be announced separately from the fluticasone results per a request from GSK. The ACTIV-6 team is planning a stakeholder meeting that will include the trial's community engagement partners to solicit feedback on the results dissemination plan.

The ACTIV-6 team is also working to finalize trial arms for the combination of fluticasone and fluvoxamine as well as montelukast. The team has fulfilled a request from GSK to provide a

restatement of the rationale for the proposed combination as well as the decision to increase the dose of fluvoxamine relative to the current fluvoxamine-only trial arm. The combination arm is expected to launch in late April or early May, pending finalization of contracts and shipment of drug supply. For the montelukast arm, drug supply has been received by the drug depot and is ready for distribution, pending acquisition of a placebo agent. The ACTIV-6 team is negotiating with Thermo Fisher to manufacture the placebo, which may take 6-8 weeks.

Emerging SARS-CoV-2 Variants

The frequency of the BA.2 sublineage of Omicron continues to increase in the EU and is suspected to have been the predominant variant in a recent Hong Kong outbreak. CDC wastewater surveillance has revealed a rise in overall positivity rates despite the lack of a corresponding increase in reported cases, suggesting that this milder variant is present in the United States; whether rates of BA.2 will rise domestically is unclear. Overall SARS-CoV-2 case rates are declining in the United States, whereas trends in the UK have been harder to interpret. Differences across countries in both case rates and in ways of counting cases make it difficult to know what direction variants like BA.2 are headed.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Christina Barkauskas, MD, *Assistant Professor of Medicine, Duke University*
Samuel Bozzette, MD, PhD, (not in attendance) *Chief Medical Officer, NCATS*
Samuel M. Brown, MD, MS, *Principal Investigator, ACTIV-3B and Associate Professor of Medicine, University of Utah*
Elizabeth Church, PhD, *Deputy Director, Therapeutics Research Program, DAIDS, NIAID*
Nakela Cook, MD, MPH, (not in attendance) *Executive Director, PCORI*
Judith Currier, MD, *Professor of Medicine, Division of Infectious Diseases, UC Los Angeles*
Sarah Dunsmore, PhD, *Program Director, Division of Clinical Innovation, NCATS*
Ann Eakin, PhD, *Senior Scientific Officer, Concept Acceleration Program, NIAID*
Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID*
William Erhardt, MD, (not in attendance) *Clinical Advisor to ACTIV-2 and CEO, Soundview Pharmaceutical Consultants*
Josh Fessel, MD, PhD, *Senior Clinical Advisor, NCATS*
David C. Goff, MD, PhD, *Director, Division of Cardiovascular Sciences, NHLBI*
Adrian Hernandez, MD, (not in attendance) *Vice Dean and Executive Director, Duke Clinical Research Institute*
Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, NIAID*
James P. Kiley, PhD, (not in attendance) *Director, Division of Lung Diseases, NHLBI*
Peter Kim, MD, (not in attendance) *Director, Therapeutics Research Program, DAIDS, NIAID*
H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*
Jens D. Lundgren, MD, (not in attendance) *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*
Susanna Naggie, MD, (not in attendance) *Vice Dean for Clinical Research and Associate Professor of Medicine, Duke University*
James D. Neaton, PhD, *Professor of Biostatistics, University of Minnesota*
Sarah Read, MD, *Deputy Director, DAIDS, NIAID*
Erica Ollmann Saphire, PhD, (not in attendance) *Professor, La Jolla Institute for Immunology*
David (Davey) Smith, MD, *Professor of Medicine, UC San Diego*
Janet Woodcock, MD, (not in attendance) *Acting Commissioner, FDA*

OTHER INVITED ATTENDEES

Brittany Chao, PhD, *Scientific Special Assistant to the NIH Principal Deputy Director, Office of the Director, NIH*
Ashley Parker-Gordon, PhD, *Health Science Policy Analyst, NIH*
Erin Holve, PhD, *Chief Research Infrastructure Officer, PCORI*

FNIH STAFF

Stacey Adam, PhD, *Associate Vice President, Research Partnerships, FNIH*
Joseph P. Menetski, PhD, *Vice President, Research Partnerships, FNIH*

Alex Cwalina, *Business Technology Analyst, Deloitte*
Serena Melton, *Senior Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*
Caroline Yarbrough, *Analyst, Deloitte*

Caroline Sferrazza, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Log

From Samuel Brown to Everyone at 3:24 PM

Glad to think about it. It's in common clinical use.

From christina.barkauskas@duke.edu to Everyone at 3:25 PM

Results of a recent study of prostacyclin use in COVID ARDS are in AJRCCM. PubMed: 34813414

From Samuel Brown to Everyone at 3:27 PM

e 28-day mortality was 21.9% versus 43.6% in the prostacyclin and the placebo groups, respectively (risk ratio, 0.50; 95% CI, 0.24 to 0.96; P = 0.06)

From: Cohen, C. Lee [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=96B23AF7B7D740D291E23AECACEB3D7F-CAITLIN.COH]
Sent: 4/11/2022 5:02:27 PM
To: Colonius, Tristan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2b3590c046734a2e928858bd579ed852-Tristan.Col]; Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]; Safford, Melissa [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=662886bbfbc7441dae59de74071cec71-Melissa.Saf]
Subject: RE: Authorizer/Appropriator doc for clearance
Attachments: Public version Supp report example 3.10.22.docx

Thank you!

Tristan, I sent you a time to catch up tomorrow morning. Julie, I totally understand your reservations on talking about any expedited process, and glad to hear any suggestions. Dr Woodcock, thank you for your FDA-speak translation, I am a non-native speaker and google translate has not yet created that service 😊

One question for Dr. Woodcock: when you say "this will work well for the public doc" does that mean that you do not wish to also do a separate document for a general audience? In parallel I've been working on a ~10pg simpler-language version for a general public audience with white space/graphics/text boxes, though I was waiting for the cleared approp/authorizer version to finish the wording. A rough draft of that version is attached here. OEA has already started doing some of the graphical work on this because the design will take a lot of time, so if we don't think it's useful to do two versions (a general audience version and authorizer/appropriator version) let me know.

Thank you again,
Lee

From: Colonius, Tristan <Tristan.Colonius@fda.hhs.gov>
Sent: Monday, April 11, 2022 1:46 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Cohen, C. Lee <Caitlin.Cohen@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Safford, Melissa <Melissa.Safford@fda.hhs.gov>
Subject: RE: Authorizer/Appropriator doc for clearance

Yes – why don't you mention at Exec Comm tomorrow and I will help to set this in motion afterwards. Lee – let's find time to connect and talk more.

From: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Sent: Monday, April 11, 2022 1:35 PM
To: Cohen, C. Lee <Caitlin.Cohen@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Safford, Melissa <Melissa.Safford@fda.hhs.gov>; Colonius, Tristan <Tristan.Colonius@fda.hhs.gov>
Subject: RE: Authorizer/Appropriator doc for clearance

I think this is a great document! Love the format since it really calls out how the supplementals are, well, supplemental to base approps! This will work well for the public doc. I imagine clearance will be a nightmare. I have edited the document to conform more with FDA-speak about things, hopefully this will help. After incorporating the edits, I would send to the various Center Directors (or their exec sec) and other appropriate people you mention below such as the OCS folks, OPPLIA and so forth and give them a hard deadline such as a week. I'm not sure Sharepoint will work, maybe just ask them for edits, since each will concentrate on different parts. Then once we have reconciled the comments (I can help on this), we can re-clear thru OC. Ask them please no line edits unless there is a mistake, people will want to re-

write the whole thing. OCC should get a look now, as well, since they typically take a long time. Tristan can you help Lee with getting this out for clearance. I can mention tomorrow at Exec Comm. jw

---

From: Cohen, C. Lee <Caitlin.Cohen@fda.hhs.gov>
Sent: Thursday, April 7, 2022 7:17 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Safford, Melissa <Melissa.Safford@fda.hhs.gov>
Subject: Authorizer/Appropriator doc for clearance

Hello Dr. Woodcock, Julie, and Melissa,

At long last, attached is the Authorizers/Appropriators document that has incorporated OCA/OL/OB/OEA initial edits and I believe is ready to get sent out to the centers for clearance. OEA is concurrently working on graphics. Once this one is cleared I was planning to use that already-cleared language as the basis for the public version (with modest simplification), though if you prefer to send both at once I can get you the draft of the public version tomorrow.

I defer to you on the best process for clearance. Should I draft all the emails and send to Julie to send out? I presume that we should do this on Sharepoint with track changes and strict rules about not making it longer or more complex.

Who should clear: Because the document is now comprehensive of all of the centers that received funding and all the line items, including smaller projects, I imagine it should go through all of them.

- The offices I have been in contact with are: CFSAN (Ruth Timme and Steven Musser), CBER (Angela Granum and Marc Meyer), CDRH (Jaime Horman), CDER (they requested clearance go to the ExecSec mailbox (cderexsec@cder.fda.gov) though Sunanda Bahl had been POC), ORA (Faiad Rahaman and Myer Gribbins), CVM (Heidi Jackson), ODT (Joe Montgomery), OCET (Michael Mair).
- The offices I have not been in contact with but who received funding are: NCTR, OCC, OPLIA, OSEM, OO (for testing?), OCPP, OMHHE, and OEA.
- OCA/OL/OB/OEA will want to see it again in final form

Timeline: Ideally we would have pens down by April 20th or so for OEA to finalize the formatting/ graphics for budget hearings the following week. I imagine April 8-13 for the centers, April 14 for me to address comments (I'll try to do this in real-time, but it would be nice to have a consolidation day), and then April 15-20 for OCA/OL/OB/OEA/?OCC and anyone else you think should clear?

Thank you and sorry this has taken so long!
Lee

C. Lee Cohen, MD MBA (she/her)
Scientific Advisor, Strategic Initiatives Team, Office of the Commissioner

U.S. Food and Drug Administration
(b) (6) (cell)
Caitlin.Cohen@fda.hhs.gov

(b)(5) DRAFT--12 pages of this attachment have been removed under (b)(5) DRAFT

From: Adam, Stacey (FNIH) [T] [sadam@fnih.org]
Sent: 4/22/2022 10:36:41 AM
To: Kurilla, Michael G (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fa2de9594d594ed9b76b935545c26754-HHS-michael]; Erhardt, Bill A (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d795053ca625464f91fa923a0a455ac1-HHS-bill.er]; Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; Read, Sarah W (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=72ca09ea60c74100a908211e1f7c5f6a-HHS-readsa-]; Lane, Henry C (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d904337536cf41719032a9359a1ec2ab-HHS-CLANE-n]; Erbelding, Emily J (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=c981f04015d64d27b1afdd9c06111071-HHS-emily.e]; Eakin, Ann E (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d126f4c08a514e12ac2e646ae79bbd20-HHS-ann.eak]; Erica Ollmann Saphire [erica@lji.org]; Stein, Peter [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d30a87acb0184261961264ba984b0a51-Peter.Stein]; Judy Currier [jscurrier@mednet.ucla.edu]; Davey Smith [d13smith@health.ucsd.edu]; Kim, Peter S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2876661346ba42d7a684f7d3ae5c5b4c-HHS-peter.k]; Neaton, Jim [neato001@umn.edu]; Lundgren, Jens [jens. (b) (6) Higgs, Elizabeth S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0ac36dd643c04994b3161baf825cbfc3-HHS-ehiggs-]; Kiley, James P (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=47964c0318054e7c98c149a93cfe6ada-HHS-kileyj-]; Goff, David C (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1fa2747f2f704a3ba1637f2febe8bc67-HHS-david.g]; Dr Susanna Naggie, M.D. [susanna.naggie@duke.edu]; Adrian Hernandez, M.D. [adrian.hernandez@duke.edu]; Dunsmore, Sarah E (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=e3ee18c15d824f2394abe93b8a0a2064-HHS-dunsmor]; Nakela Cook [nlcook@pcori.org]; Penny Mohr [pmohr@pcori.org]; Brown, Samuel (b) (6); Barkauskas, Christina [christina.barkauskas@duke.edu]; Fessel, Josh P (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1531bbc9172747829bc72c4ce1176926-HHS-josh.fe]
CC: Carver-Roberts, Trea R (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=05c1728ee14540bb9d98a6b7917c85eb-HHS-trea.ca]; Reich, Colleen [cjreich@health.ucsd.edu]; Lisbeth Jørgensen [(b) (6); fnih [fnih@roseliassociates.com]; Dana Carluccio [dana.carluccio@roseliassociates.com]; Church, Elizabeth S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1feccbf65b8e4285bc6fa6ede9c44e02-HHS-elizabe]; Melencio, Cheryl L (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=baa3813b343d4f4cb949f1b990023053-HHS-cmelenc]; Jabarkhail, Mina [MJabarkhail@mednet.ucla.edu]; Nesin, Mirjana (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=86ffcb8d6be149788e21229c314b60f7-HHS-Mirjana]; Holly Bunton [hbunton@pcori.org]; Fant, Annie (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=01e618455da34f0a8db87cf3fc60ff36-HHS-Annie.F]; Kelly, William (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5238754dfa034c159efd8e749c2739a6-HHS-William]; Eisnor, Derek (OS) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f7b89712a02b43958d5253c1e79f21a3-HHS-Derek.E]; Kelly Beazley [kelly.beazley@roseliassociates.com]; Menetski, Joseph M (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d8ed7bcfcbc04f338026fde223a907ae-HHS-jmenets]; Melton, Serena [smelton@deloitte.com]; Sorosa, Alex [asorosa@deloitte.com]; Cwalina, Alex [acwalina@deloitte.com]; Laura Rodriguez [llrodriguez@pcori.org]; Parker, Ashley S (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3f43b948b59f4e679535a8a3ebc91167-HHS-ashley.]; Tara Cole [tcole@pcori.org]; Chao, Brittany N (NIH) [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ccec410dec8491985206c8694db1c15-HHS-brittan]; Martins, Karen (OS)

	[/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=16144aa45fbf4fe58775e7340f4c8c82-HHS-Karen.M]
Subject:	[EXTERNAL] Summary of the ACTIV-2/-3/-6 TOC Meeting and FDA Letter for Review
Attachments:	2022-04-20_Trial_Oversight_Committee_Meeting_Summary.pdf; ACTIV TOC Recommendation Letter to FDA 042022v2.docx
Importance:	High

Dear ACTIV-2/-3/-6 TOC Members,

Please find attached the summary of our meeting on Wednesday. If you have any additions or amendments, please let me know.

In addition, as discussed at the meeting and reflected in the summary, Cliff and I have worked on a draft for the letter that the TOC would like to have sent to the FDA on their behalf expressing their concern about the current stance on outpatient protocol design. **Please review and send to me as redlines and comments in the document any revisions you would like to suggest.** Cliff and I will then work to finalize and transmit the letter to John Farley, as discussed.

Thanks,
Stacey

Stacey J. Adam, PhD (*she/her*)
Associate Vice President
Research Partnerships
Foundation for the National Institutes of Health
Direct: **(301) 435-8364** | Mobile: (b) (6)
fnih.org
11400 Rockville Pike, Suite 600, North Bethesda, MD 20852

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High-Level Meeting Summary

The ACTIV-2/-3/-6 Trial Oversight Committee (TOC) heard status updates on ACTIV-2, ACTIV-3, and ACTIV-6 trials; and discussed the implications of FDA's request to not enroll patients eligible for PAXLOVID treatment into ACTIV-2d, as well as the BA.2 status in the United States.

Trial Accrual Updates

The main ACTIV-2 study has ended and ACTIV-2b, -2c, and -2d are on hold per direction from FDA. ACTIV-3 has not enrolled new patients or incorporated new drugs into its pipeline since the previous TOC meeting. ACTIV-3b has enrolled 467 participants. ACTIV-6 has activated 91 sites and enrolled a total of 3,665 participants (1,537 to the low dose ivermectin arm, 813 to the fluvoxamine arm, 1,127 to the fluticasone arm, and 208 to the high dose ivermectin arm). The low dose ivermectin and fluticasone arms have completed enrollment and topline results are expected soon. The ACTIV-6 team continues to improve enrollment of participants from diverse and underrepresented populations.

ACTIV-2 Updates

The ACTIV-2 team met with FDA today to discuss the ACTIV-2d trial design. During this meeting, FDA requested that ACTIV-2d pause enrollment into the Shionogi study, which was open but had not yet enrolled its first patient. FDA explained that individuals eligible to receive PAXLOVID within the United States are no longer eligible for enrollment in placebo-controlled trials such as ACTIV-2d, regardless of whether or not those individuals actually seek to obtain PAXLOVID treatment. This change is a result of PAXLOVID's increasing availability within the United States, which makes it unethical to withhold standard of care treatment. This decision likely precludes ACTIV-2d's ability to conduct any trial of Shionogi's product within the United States, because the product has known drug-drug interactions with PAXLOVID that would prevent the use of PAXLOVID as a standard of care treatment. In addition, the patient population eligible for PAXLOVID in the United States is very broad according to NIH guidelines and thus the remaining population ineligible for PAXLOVID treatment—and eligible for the trial—would be very small. FDA also imposed an additional requirement that the ACTIV-2D patient population include only individuals who are ineligible to receive PAXLOVID and required these individuals to receive remdesivir or another effective standard of care antiviral treatment. Thus, ACTIV-2d will likely need to focus on ex-U.S. enrollment to complete its study. The implications of FDA's direction will likely begin to affect other placebo-controlled trials, including ACTIV-6.

Discussion

Participants noted that the FDA's request removes patients' autonomy to choose whether they wish to enter a clinical trial: even patients who do not wish to seek PAXLOVID treatment are now ineligible for most trials because of their sheer eligibility to obtain PAXLOVID. Participants noted that the NIH guidelines regarding PAXLOVID are very broad and reiterated that guidelines do not constitute standard of care.

Dr. Cliff Lane suggested requesting an ethics consult from the NIAID Bioethics department regarding the FDA request. Dr. Peter Kim noted that when ACTIV made a similar request for another study, the NIAID Bioethics department offered a different opinion than FDA but that opinion did not ultimately alter FDA's decision.

Dr. Lane suggested drafting a TOC recommendation letter requesting review by the FDA Advisory Committee of the FDA's request; Dr. Janet Woodcock recused herself from discussion and next steps regarding this topic. Dr. Emily Erbelding seconded Dr. Lane's suggestion and thus Drs. Lane and Stacey Adam will draft a recommendation letter on the TOC's concerns regarding the FDA's recent request to preclude PAXLOVID-eligible individuals from enrolling in the ACTIV-2d trial; the draft letter will be shared with TOC members for review before being submitted to Dr. John Farley. If needed, the letter will subsequently be escalated to CDER and CBER leadership.

Participants noted that some studies have shown that some patients exhibit symptom worsening after PAXLOVID, indicating that a better understanding of the necessary duration of PAXLOVID treatment may be needed.

Dr. Kim expressed ethical concerns regarding the need to focus on ex-U.S. enrollment now that a placebo-controlled trial for the Shionogi product cannot be conducted in the United States. Participants seconded these concerns, noting that the patient populations must be enrolled in regions where the tested agent will eventually be broadly available for treatment, given the ACTIV-2 requirement that studied agents be made broadly available in enrolling regions after the ACTIV study concludes. Dr. Erbelding recommended that the ACTIV-2 team engage with its Community Advisory Board to discuss this topic.

ACTIV-3/3b Updates

The VATICO study has closed and the Evaluation of Point of Care (EPOC) study will open soon. The ACTIV-3 team is working to finalize the STRIVE master protocol by early May and to submit it for FDA review by the end of May. The team is in discussions with Shionogi and AstraZeneca to include their agents in the first two STRIVE study arms. During the previous TICO study on the AstraZeneca agent, the ACTIV-3 team identified a patient subgroup that exhibited more therapeutic benefit than others. This subgroup, which included patients that required high-flow nasal cannula/non-invasive mechanical ventilation oxygen supplementation, will be the focus of the AstraZeneca STRIVE study arm.

ACTIV-3b has enrolled 367 patients. The ACTIV-3b team is ready to activate sites in Brazil, with enrollment to begin in July, and is working to train site staff and ship agent to sites.

Discussion

Dr. Adam confirmed that the TOC will provide oversight for the new STRIVE master protocol. Because STRIVE will include sites previously included in the ACTIV-1 and -5 networks, representatives from those master protocols will be invited to join the TOC.

ACTIV-6 Updates

ACTIV-6 is currently enrolling into its fluvoxamine and high dose ivermectin study arms. The ACTIV-6 team will unblind data from the low dose ivermectin arm on April 22 and soon after will unblind data from the fluticasone arm. Manuscripts on the results from the low dose ivermectin and fluticasone studies have been drafted and are awaiting the final unblinded data before submission. Press releases organized by the team and NCATS will be released shortly after the data unblinding for both study arms.

The ACTIV-6 team continues to work to open a dual fluvoxamine/fluticasone arm and a montelukast arm. The fluvoxamine/fluticasone protocol was submitted to FDA on March 18 and all contracts have been executed. The team is now working to reevaluate the budget for the montelukast study arm.

Variant Updates

BA.2 continues to be the dominant SARS-CoV-2 variant within the United States, accounting for approximately 60-70 percent of cases.

Appendix A: Participants List

TRIAL OVERSIGHT COMMITTEE MEMBERS

Christina Barkauskas, MD, *Assistant Professor of Medicine, Duke University*
Samuel Bozzette, MD, PhD, (not in attendance) *Chief Medical Officer, NCATS*
Samuel M. Brown, MD, MS, *Principal Investigator, ACTIV-3B and Associate Professor of Medicine, University of Utah*
Elizabeth Church, PhD, (not in attendance) *Deputy Director, Therapeutics Research Program, DAIDS, NIAID*
Nakela Cook, MD, MPH, (not in attendance) *Executive Director, PCORI*
Judith Currier, MD, *Professor of Medicine, Division of Infectious Diseases, UC Los Angeles*
Sarah Dunsmore, PhD, *Program Director, Division of Clinical Innovation, NCATS*
Ann Eakin, PhD, (not in attendance) *Senior Scientific Officer, Concept Acceleration Program, NIAID*
Emily Erbelding, MD, MPH, *Director, Division of Microbiology and Infectious Diseases, NIAID*
William Erhardt, MD, (not in attendance) *Clinical Advisor to ACTIV-2 and CEO, Soundview Pharmaceutical Consultants*
Josh Fessel, MD, PhD, (not in attendance) *Senior Clinical Advisor, NCATS*
David C. Goff, MD, PhD, (not in attendance) *Director, Division of Cardiovascular Sciences, NHLBI*
Adrian Hernandez, MD, (not in attendance) *Vice Dean and Executive Director, Duke Clinical Research Institute*
Elizabeth (Libby) Higgs, MD, MIA, DTM&H, *Global Health Science Advisor, NIAID*
James P. Kiley, PhD, *Director, Division of Lung Diseases, NHLBI*
Peter Kim, MD, *Director, Therapeutics Research Program, DAIDS, NIAID*
H. Clifford Lane, MD, *Deputy Director for Clinical Research and Special Projects, NIAID*
Chris Lindsell, PhD, (not in attendance) *Professor, Vanderbilt University Medical Center*
Jens D. Lundgren, MD, *Professor of Viral Diseases, University of Copenhagen and Executive Committee Member, INSIGHT*
Susanna Naggie, MD, *Vice Dean for Clinical Research and Associate Professor of Medicine, Duke University*
James D. Neaton, PhD, *Professor of Biostatistics, University of Minnesota*
Sarah Read, MD, *Deputy Director, DAIDS, NIAID*
Erica Ollmann Saphire, PhD, (not in attendance) *Professor, La Jolla Institute for Immunology*
David (Davey) Smith, MD, *Professor of Medicine, UC San Diego*
Janet Woodcock, MD, *Acting Commissioner, FDA*

INVITED PARTICIPANTS

Brittany Chao, PhD, *Scientific Special Assistant to the NIH Principal Deputy Director, Office of the Director, NIH*
Erin Holve, PhD, *Chief Research Infrastructure Officer, PCORI*
Karen Martins, PhD, *Acting Branch Chief, BARDA*

FNIH STAFF

Stacey Adam, PhD, *Associate Vice President, Research Partnerships, FNIH*
Alex Cwalina, *Business Technology Analyst, Deloitte*
Serena Melton, *Senior Consultant, Deloitte*
Alex Sorosa, *Business Analyst, Deloitte*
Caroline Yarbrough, *Analyst, Deloitte*
Bethany Stokes, MS, *Writer, Rose Li and Associates, Inc.*

Appendix B: Chat Log

From Sarah Dunsmore to Everyone 03:17 PM

Thanks for the heads up Davey, Judy, ACTIV-2 team!

From Dr. Susanna Naggie (she/her) to Everyone 03:20 PM

Yes thank you ACTIV-2. Sorry to hear about this.

From Davey Smith to Everyone 03:25 PM

Less than half my patients finish their Paxlovid course…

Thanks for the discussion and effort. Very helpful

From Currier, Judith S. to Everyone 03:25 PM

Agree with Davey- thanks very much for the support and actions.

From: Tierney, Julia [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1160d300bc4248b790ded292a082e9a8-Julia.Tiern]
Sent: 4/22/2022 10:29:24 PM
To: Woodcock, Janet [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7b0453354a9a427db0a66a86c7a36f3d-Janet.Woodc]; Cohen, C. Lee [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=96b23af7b7d740d291e23aecaceb3d7f-Caitlin.Coh]; Colonius, Tristan [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2b3590c046734a2e928858bd579ed852-Tristan.Col]
Subject: RE: Clean copy of Supp report
Attachments: Authorizers and Appropriators Supp Report 4.22.22 (jct).docx

Just to echo, Janet, this is really quite impressive. Thank you so much for this hard work.

I have some edits attached. Also, would you mind providing me with the clearance legend since I wasn't on those chains. I'd like to make sure that we've gotten review by everyone who needs to and be able to answer any questions if asked.

On hand sanitizers, I hate the thought of you trying to recreate the wheel. I would be very surprised if there wasn't already a summary in an issue paper, perhaps kept by OL, on this topic. Whatever we present to Dr. Califf, I think the takeaway isn't just what we did, but the fact that FDA lacks mandatory drug recall authority, and so our response, although valiant, was somewhat hampered - we could have acted more quickly with that authority. Perhaps you could ask CDER or OCC to add a sentence or two on that.

From: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>
Sent: Friday, April 22, 2022 9:51 PM
To: Cohen, C. Lee <Caitlin.Cohen@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Colonius, Tristan <Tristan.Colonius@fda.hhs.gov>
Subject: RE: Clean copy of Supp report

Lee I think this is truly fabulous. You have accomplished what we tried to do without success for a year! I have one small comment on the document, put in a bubble. Really clear explication and gives an appreciation of the scope of our efforts. BRAVO! jw

---

From: Cohen, C. Lee <Caitlin.Cohen@fda.hhs.gov>
Sent: Friday, April 22, 2022 7:19 PM
To: Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Tierney, Julia <Julia.Tierney@fda.hhs.gov>; Colonius, Tristan <Tristan.Colonius@fda.hhs.gov>
Subject: Clean copy of Supp report

Hello All,

Attached is a clean copy of the supp report, cleared by all, including OCC and OEA. The only thing not finished is tallying the totals in the charts and cross-linking to the index (I'll do tomorrow) and design work by OEA (in progress, they'll fill it in when "pens down").

- Julie, would you like to read through and give me any final edits?
- I will cut-paste the highlights into 1-2 pages for Dr. Califf and send it to you and OCA *first thing tomorrow morning*. I drafted a paragraph using mostly pre-cleared language on the methanol poisoning issue as per Dr. Cavazzoni and Dr. Califf's request on today's budget hearing briefing, and asked CDER/ORA/OCC to clear it, but that probably will not happen until Monday. The draft of that is cut-pasted below.

Thank you,
Lee

Thanks,
Lee

Methanol Poisoning from Hand Sanitizers:
The below language is ***not yet cleared*** by the centers, but I drafted it using mostly *pre-cleared language in italics*, borrowed from this press alert. Non-italicized points/data are from the FDA historian.

In June 2020 FDA received over 700 reports of poisonings, including at least 17 deaths,* from *hand sanitizer products that were labeled to contain ethanol (also known as ethyl alcohol) but tested positive for methanol contamination. Methanol, or wood alcohol, is a substance that can be toxic when absorbed through the skin and life-threatening when ingested. The FDA's analyses of alcohol-based hand sanitizers imported from Mexico found 84% of the samples analyzed by the agency from April through December 2020 were not in compliance with the FDA's regulations.* The agency responded by proactively working with over 3000 manufacturers to ascertain the scope of the problem, *issuing a guidance, encouraging retailers to remove violative products*, and providing safety toolkits in multiple languages to consumers and health care professionals. The FDA coordinated directly with Mexican government to issue *14 warning letters* and *work with companies to recall over 250 violative products.* In January 2021, FDA issued an import alert for all alcohol-based hand sanitizers manufactured in Mexico, *the first time the FDA has issued a countrywide import alert for any category of drug product.*

*[[Dr. Cavazzoni on today's briefing mentioned 20 deaths, there are popular media reports of FDA spokesperson stating 17 deaths as of October 2020, and CDC/MMWR journal articles citing 4-5 at a time, but if there's a more recent acceptable citation for that number it would be good to include]]

C. Lee Cohen, MD MBA (she/her)
Scientific Advisor, Strategic Initiatives Team, Office of the Commissioner

U.S. Food and Drug Administration
(b) (6) (cell)
Caitlin.Cohen@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA COVID-19 Supplemental Supported Initiatives

April 2022

[PAGE * MERGEFORMAT]

(b)(5) DRAFT-removed 24 pages of this attachment under (b)(5) DRAFT