Investigating pandemic drugs and vaccines

(Note: these methods are applicable outside a pandemic)

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September 21, 2023

FINANCIAL DISCLOSURES

I have received travel funds from the **European Respiratory Society** (2012), **Uppsala Monitoring Center** (2018) and **GIJN** (2023); grants from the **FDA** (through University of Maryland M-CERSI; 2020), **Laura and John Arnold Foundation** (2017-22), **American Association of Colleges of Pharmacy** (2015), **Patient-Centered Outcomes Research Institute** (2014-16), **Cochrane Methods Innovations Fund** (2016-18), and **UK National Institute for Health Research** (2011-14); was an unpaid IMEDS steering committee member at the **Reagan-Udall Foundation for the FDA** (2016-20), and is an editor at **The BMJ**. The views and opinions expressed here are those of the author/presenter and do not necessarily reflect official policy or position of the University of Maryland.

Summary

- Salary from University of Maryland & The BMJ
- Public, foundation, and non-profit funding of academic research
- Reimbursement (e.g. lodging, travel) from non-profits
- No industry funding

Early-middle 2020: search for an effective covid-19 vaccine

DESIRED ATTRIBUTES OF AN EFFECTIVE COVID-19 VACCINE

1. Use contributes to herd immunity

Requires testing ability to prevent infection and interrupt viral transmission

2. Reduce disease severity

Requires testing ability to lower risk of hospitalization, intensive care use, and death

TO DETERMINE IF A PRODUCT HAS THESE ATTRIBUTES REQUIRES CLINICAL TRIALS

… BUT IN REALITY, TRIALS WERE NOT DESIGNED TO STUDY EITHER OF THESE

Source: Doshi P. Will covid-19 vaccines save lives? Current trials aren't designed to tell us. BMJ. 2020 Oct 21;371:m4037. https://doi.org/10.1136/bmj.m4037 PMID: 33087398.

Nov 23, 2020

Moderna Chief Medical Officer Tal Zaks warns on #AxiosOnHBO to not "over-interpret" vaccine results: "They do not show that they prevent you from potentially carrying this virus...and infecting others."

But it did not actually require Moderna's CMO to acknowledge this. It was discoverable through a close reading of the trial's design.

Source: https://twitter.com/axios/status/1331090810666844161

1st question for journalists to ask:
What is a study actually studying?

- Trials do not vaguely test "how safe and effective" medicines are.
- What **specific research question** (hypothesis) does this study aim to answer?
  - Investigators define a research question in order to design the trial
  - Use the "PICO" tool to clarify the question

- After you determine the trial's research question, ask:
  - Is the trial addressing the question we need answered? (often, it's not[1])
  - What questions are not being addressed by this trial? (often, the important questions[1])
  - Are trial participants being told? (often, they're not[2])

1: Wieseler et al. New drugs: where did we go wrong and what can we do better? BMJ. 2019 Jul 10;366:l4340. https://doi.org/10.1136/bmj.l4340 **2:** Doshi et al. Informed Consent to Study Purpose in Randomized Clinical Trials of Antibiotics, 1991 Through 2011. JAMA Intern Med. 2017 Oct 1;177(10):1452-1459. https://doi.org/10.1001/jamainternmed.2017.3820.

Use “PICO” to clarify the research question	
Patients/Population *What kinds of people are being studied?*	Are these patients the ones who we think need the drug?
Intervention & **C**omparison *What is being studied and what is it being compared with? And how is the comparison constructed?*	Do the intervention and comparator comprise a pair of realistic choices people choose between? Is this a randomized trial? Is it double-blind?
Outcome(s) being studied (in particular, the “primary endpoint”) *How is efficacy being defined?*	Is this endpoint what we really want to know about?

EXAMPLE EXERCISE #1

Can Vaccine X stop the spread?

PICO	What you might expect	Reality (covid vaccine trials)
Population	Children and adults	
Intervention	vaccine	
Comparison	Inert placebo, randomized trial	
Outcome(s) of interest (endpoints)	Rate of virus transmission to contacts (e.g. family members)	

Conclusion: there's a mismatch between actual trial design and needed trial design

EXAMPLE EXERCISE #2

Can Vaccine X save lives?

PICO	What you might expect	Reality (covid vaccine trials)
Population	Highest risk (e.g. frail elderly)	
Intervention	vaccine	
Comparison	Inert placebo, randomized trial	
Outcome(s) of interest (endpoints)	Death rate	

Conclusion: there's a mismatch between actual trial design and needed trial design

Where can one determine study design?

Where	When is it available	Notes
Study protocol (ideal)	Written before trial begins	Often not publicly accessible until later (if ever)
Trial registers (e.g. ClinicalTrials.gov, ICTRP, others)	Record typically established before trial begins	May lack sufficient detail to fully clarify PICO
FDA Advisory Committee meetings & related "dockets"	48 hours before advisory committee meets	Search meeting transcripts + investor and FDA slides
Sponsor press releases and investor briefings	Before, during, after trial	See guide[1]
Financial documents (in particular SEC filings in the United States)	Filed quarterly (Form 10-Q) and Annually (Form 8K)	See guide[1]

1: Tanveer S. "**Trial transparency in real time"** https://restoringtrials.org/2020/10/18/trial-transparency-in-real-time/

TRIAL PROTOCOLS – TYPICALLY CONTAIN THE MOST DETAIL

Sample study protocol

Most comprehensive source of trial design details – but often treated by companies as commercially confidential

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in the first 360 participants	In participants receiving at least 1 dose of study intervention, the percentage of participants rep	• Local reactions (pain at the injection site, redness, and g)

Source: Pfizer. PDF p.158 https://www.nejm.org/doi/suppl/10.1056/NEJMoa2027906/suppl_file/nejmoa2027906_protocol.pdf

A lack of transparency is hard to defend

Moderna

moderna

CLINICAL STUDY PROTOCOL

Protocol Title: A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

Protocol Number: mRNA-1273-P301

Sponsor Name: ModernaTX, Inc.

Legal Registered Address: 200 Technology Square
Cambridge, MA 02139

Sponsor Contact and Medical Monitor: Tal Zaks, MD, PhD, Chief Medical Officer
ModernaTX, Inc.
200 Technology Square, Cambridge, MA 02139
Telephone: 1-617-209-5906
e-mail: Tal.Zaks@modernatx.com

Regulatory Agency Identifier Number(s): IND: 19745

Amendment Number: 3

Date of Amendment 3: 20 Aug 2020

Date of Amendment 2: 31 Jul 2020

Date of Amendment 1: 28 Jun 2020

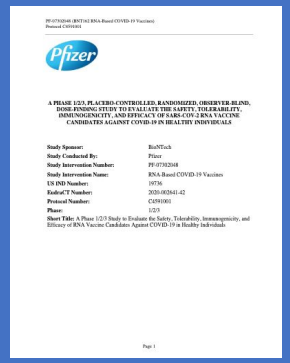
Date of Original Protocol: 15 Jun 2020

CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by ModernaTX, Inc. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed written consent of ModernaTX, Inc. The study will be conducted according to the *International Council for Harmonisation (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use. ENR2: Good Clinical Practice (GCP) Guidance.*

Confidential Page 1

Pfizer



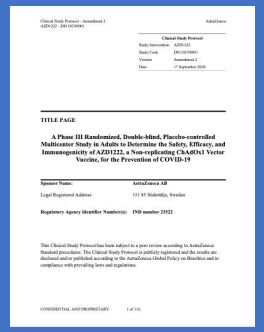
Pfizer

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor: BioNTech
Study Conducted By: Pfizer
Study Intervention Number: PF-07302048
Study Intervention Name: RNA-Based COVID-19 Vaccines
US IND Number: 19736
EudraCT Number: 2020-002641-42
Protocol Number: C4591001
Phase: 1/2/3
Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Page 1

AstraZeneca US trial



Clinical Study Protocol – Amendment 2
AZD1222 – D8110C00001

AstraZeneca

Clinical Study Protocol
Study Intervention: AZD1222
Study Code: D8110C00001
Version: Amendment 2
Date: 17 September 2020

TITLE PAGE

A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s): **IND number 23522**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

CONFIDENTIAL AND PROPRIETARY 1 of 116

Links at https://restoringtrials.org/covid-19/

New York Times, Sept 13, 2020

Vaccine Makers Keep Safety Details Quiet, Alarming Scientists

Researchers say drug companies need to be more open about how vaccine trials are run to reassure Americans who are skittish about getting a coronavirus vaccine.

New York Times, Sept 17, 2020

Moderna and Pfizer Reveal Secret Blueprints for Coronavirus Vaccine Trials

The companies hope to earn the trust of the public and of scientists who have clamored for details of the studies.

New York Times, Sept 19, 2020

AstraZeneca, Under Fire for Vaccine Safety, Releases Trial Blueprints

Experts are concerned that the company has not been more forthcoming about two participants who became seriously ill after getting its experimental vaccine.

FDA ADVISORY COMMITTEE MEETINGS

U.S. FOOD & DRUG ADMINISTRATION

Search Menu

Home / Advisory Committees / Advisory Committee Calendar / Vaccines and Related Biological Products Advisory Committee December 10, 2020 Meeting Announcement - 12/10/2020

ADVISORY COMMITTEE MEETING

Vaccines and Related Biological Products Advisory Committee December 10, 2020 Meeting Announcement

DECEMBER 10, 2020

Scheduled

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Back to Advisory Committee Calendar

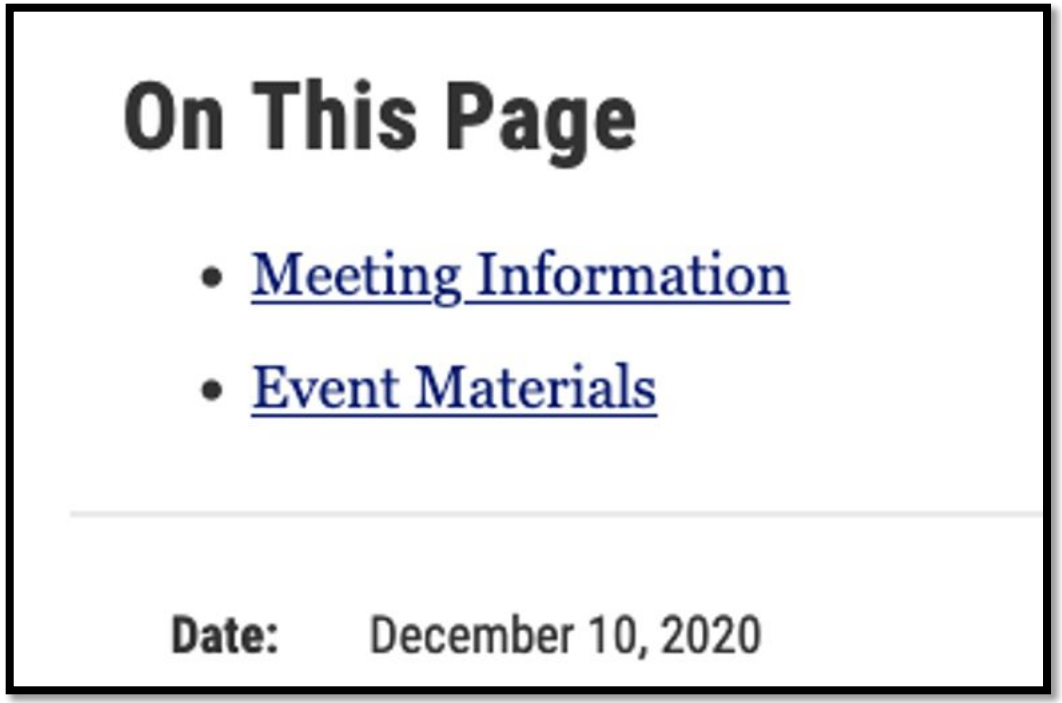
Advisory Committee Calendar

On This Page

- Meeting Information
- Event Materials

Date: December 10, 2020

Time: 9:00 AM - 6:00 PM ET



Source:
https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-com

FDA ADVISORY COMMITTEE MEETINGS

Advisory Committee Meetings

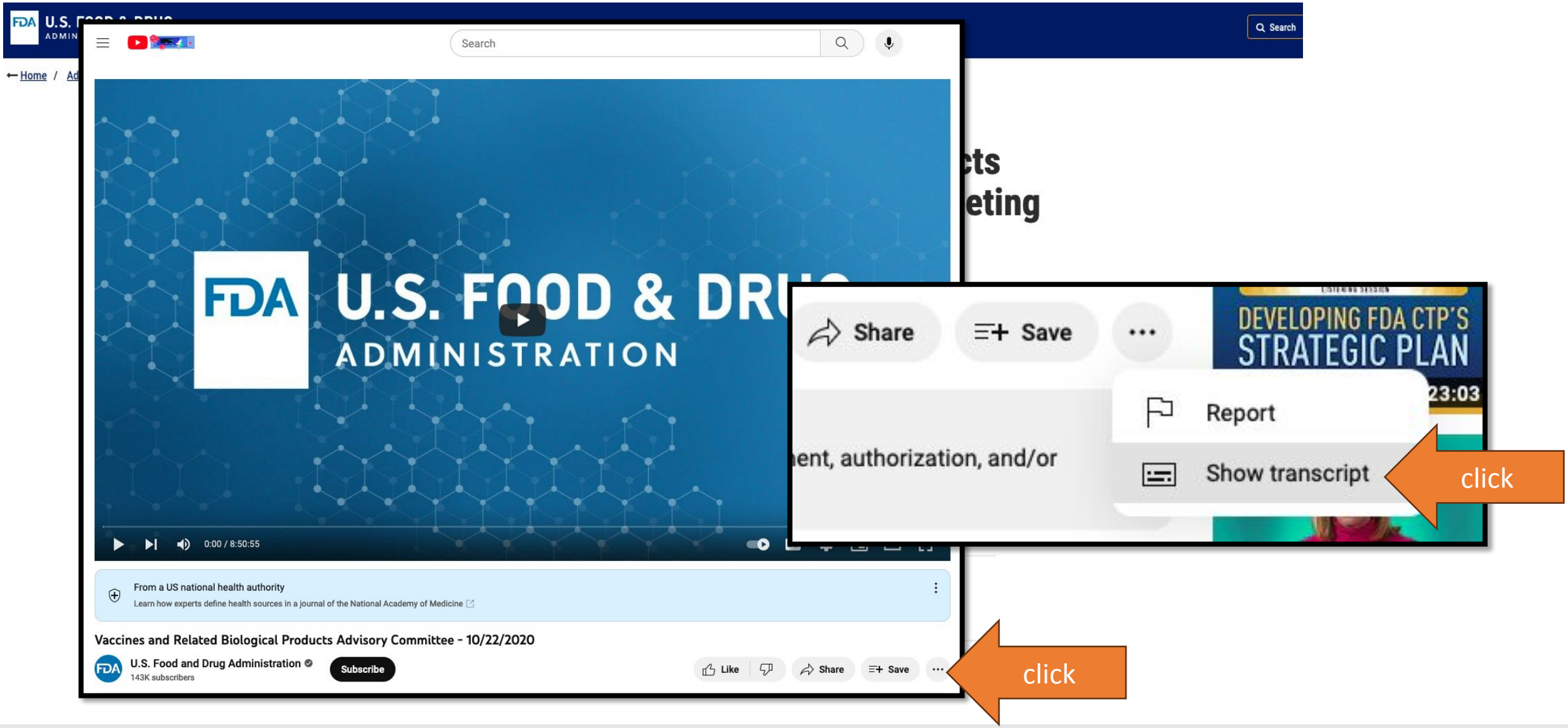
EVENT MATERIALS INCLUDE

- Meeting agendas
- FDA presentations
- Sponsor presentations
- Meeting transcripts
- and more…

Event Materials

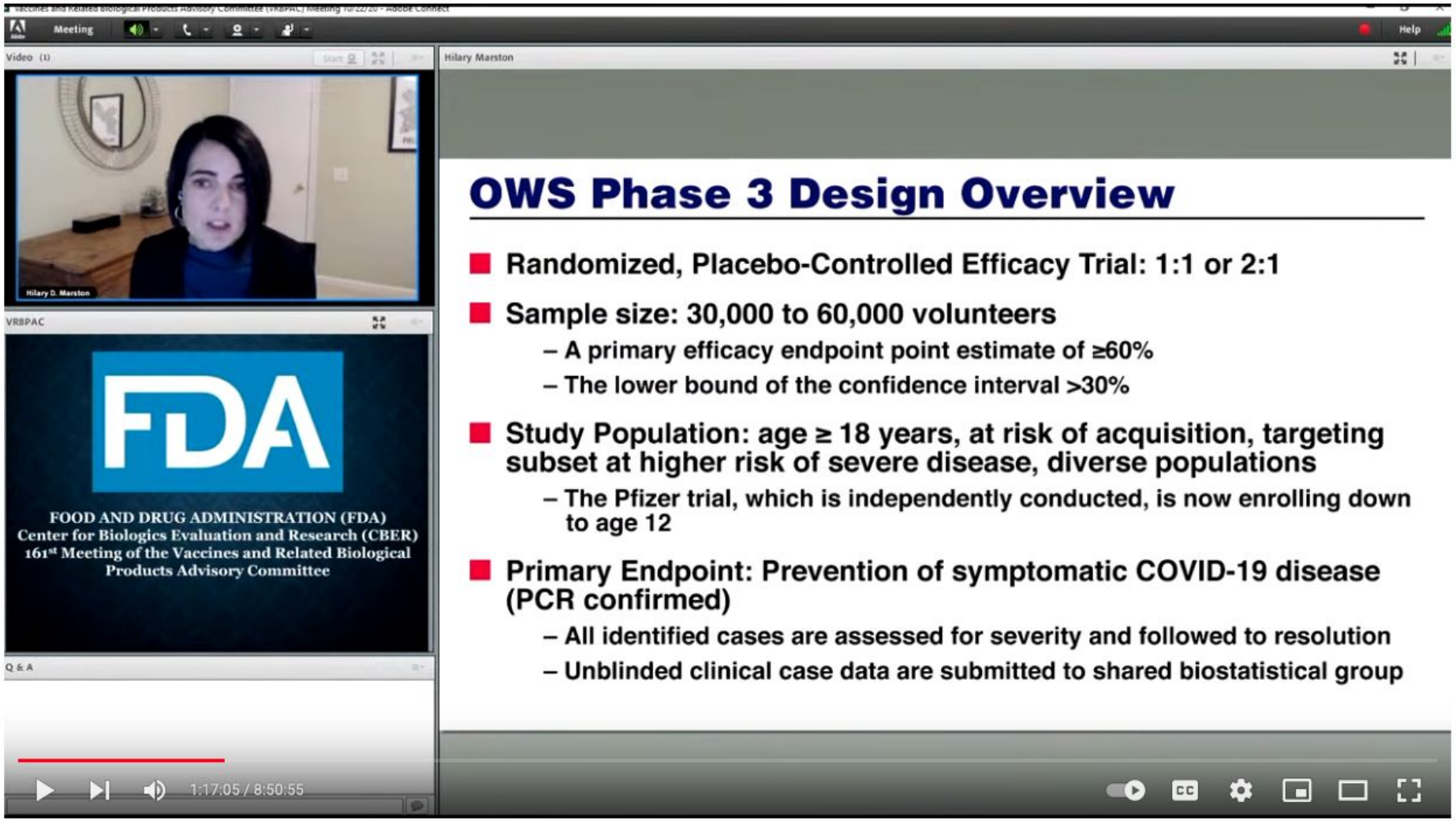
Title	File Type/Size	Source Organization
Vaccines and Related Biological Products Advisory Committee December 10, 2020 Draft Agenda	pdf (128.21 KB)	FDA
Vaccines and Related Biological Products Advisory Committee December 10, 2020 Draft Roster	pdf (291.91 KB)	FDA
Vaccines and Related Biological Products Advisory Committee December 10, 2020 Meeting Acknowledgement of Financial Interest- James Hildreth	pdf (66.06 KB)	Non-FDA
Vaccines and Related Biological Products Advisory Committee December 10, 2020 Meeting Briefing Document- FDA	pdf (1.13 MB)	FDA
Vaccines and Related Biological Products Advisory Committee December 10, 2020 Meeting Briefing Document- Sponsor	pdf (1.65 MB)	Non-FDA
Vaccines and Related Biological Products Advisory Committee December 10, 2020 Meeting Final Agenda	pdf (178.34 KB)	FDA
Vaccines and Related Biological Products Advisory Committee December 10, 2020 Meeting Final Roster	pdf (188.92 KB)	FDA
Vaccines and Related Biological Products Advisory Committee December 10, 2020 Meeting Presentation - Discussion Questions	pdf (13.99 KB)	FDA

FDA ADVISORY COMMITTEE MEETINGS



Source: FDA.
https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-com

FDA ADVISORY COMMITTEE MEETINGS



Transcript

1:16:37 investigators co-PIs on the trial and NIH sits on that oversight group and we are at each level of the trial

1:16:45 structure. A bit on the trials themselves, these are randomized

1:16:50 placebo-controlled trials with a one to one or 2 to 1 vaccine to

1:16:55 placebo match and sample size very somewhat but they are anywhere from 30 to

1:17:02 **60,000 volunteers the primary efficacy endpoint has a estimate requirement of greater than 60% in the lower confidence interval**

1:17:09 must be greater than 30% the

1:17:14 population individuals over 18 years of age and specifically people who are at risk of severe disease whether individuals were

1:17:21 elderly or have comorbidities from underserved minorities and one notable exception this is a Pfizer trial which is run

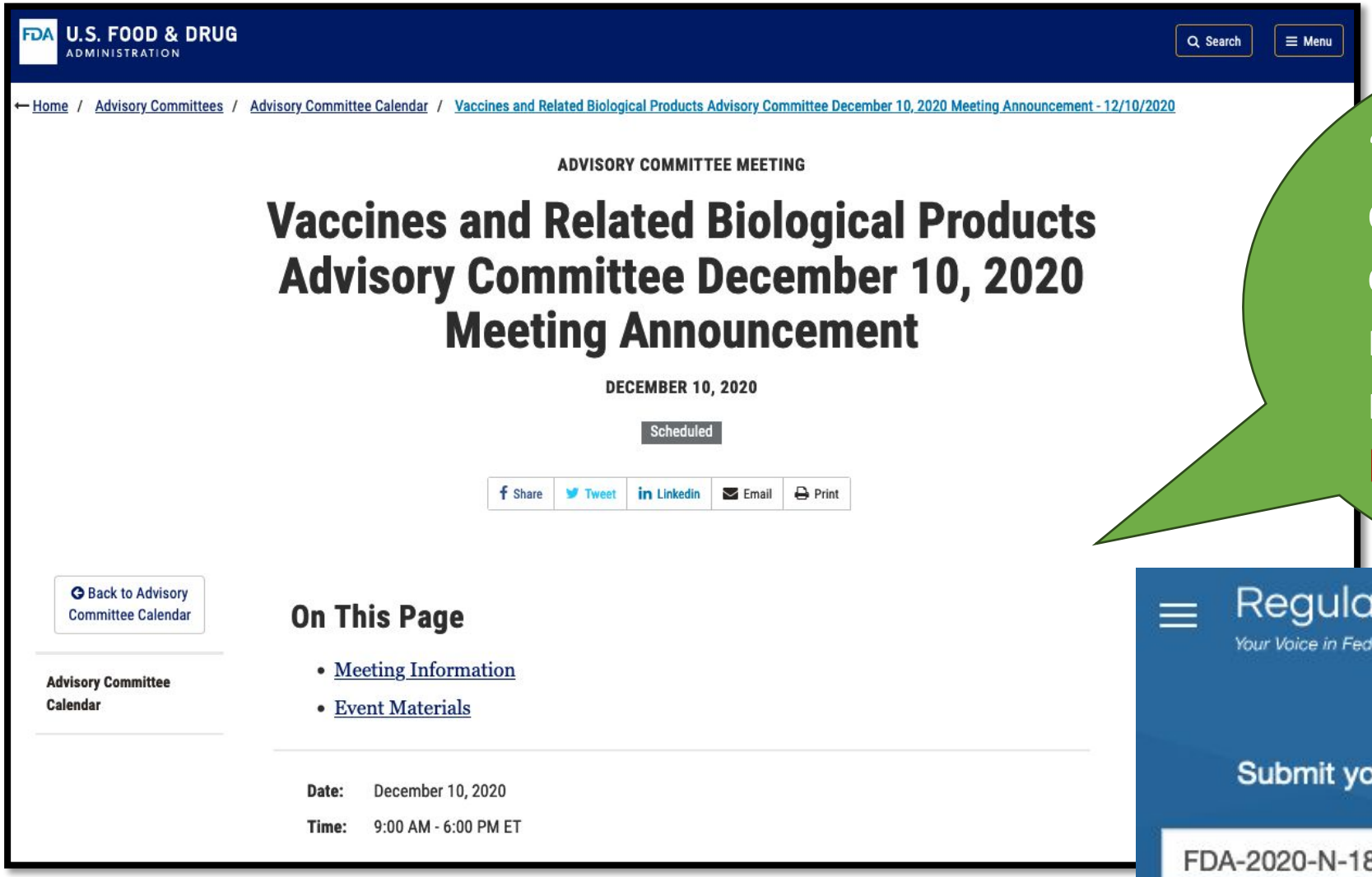
1:17:30 independently they are now enrolling age 12. The primary endpoint of the trial is

1:17:38 **COVID19 disease which PCR confirmed in portly all identified ours assess for severity and bulge resolution**

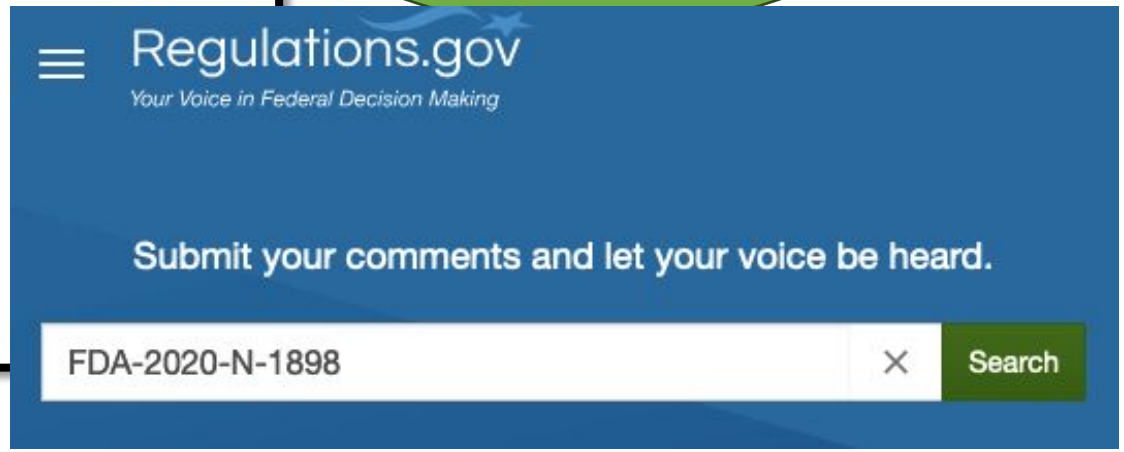
root

Source: FDA.
https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-com

"DOCKETS" for FDA ADVISORY COMMITTEE MEETINGS

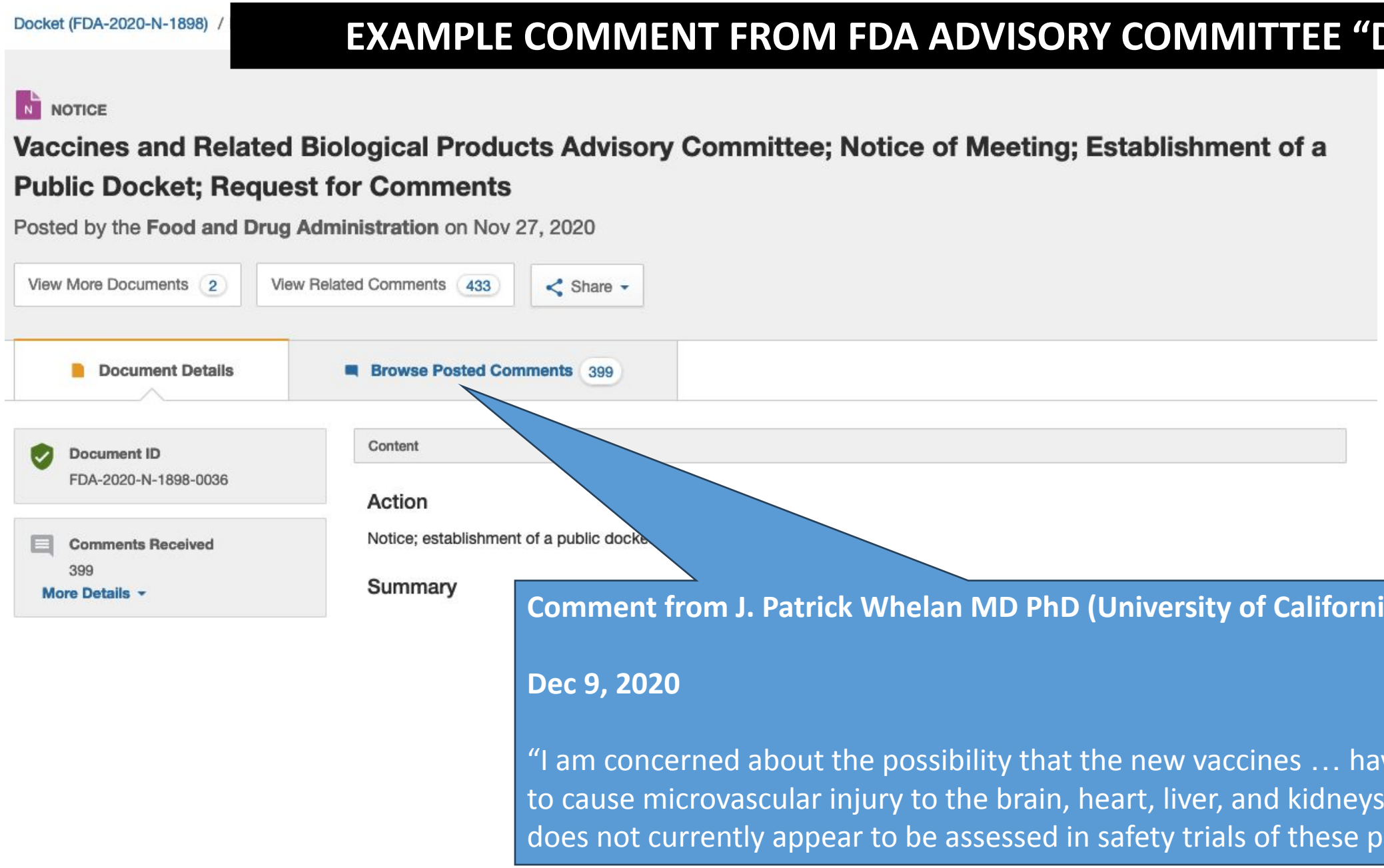


"FDA is establishing a docket for public comment on this meeting. The docket number is FDA-2020-N-1898…."



Sources:
https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-com

EXAMPLE COMMENT FROM FDA ADVISORY COMMITTEE "DOCKET"



Comment from J. Patrick Whelan MD PhD (University of California, Los Angeles)

Dec 9, 2020

"I am concerned about the possibility that the new vaccines … have the potential to cause microvascular injury to the brain, heart, liver, and kidneys in a way that does not currently appear to be assessed in safety trials of these potential drugs."

Source: https://www.regulations.gov/document/FDA-2020-N-1898-0246

INVESTOR BRIEFINGS

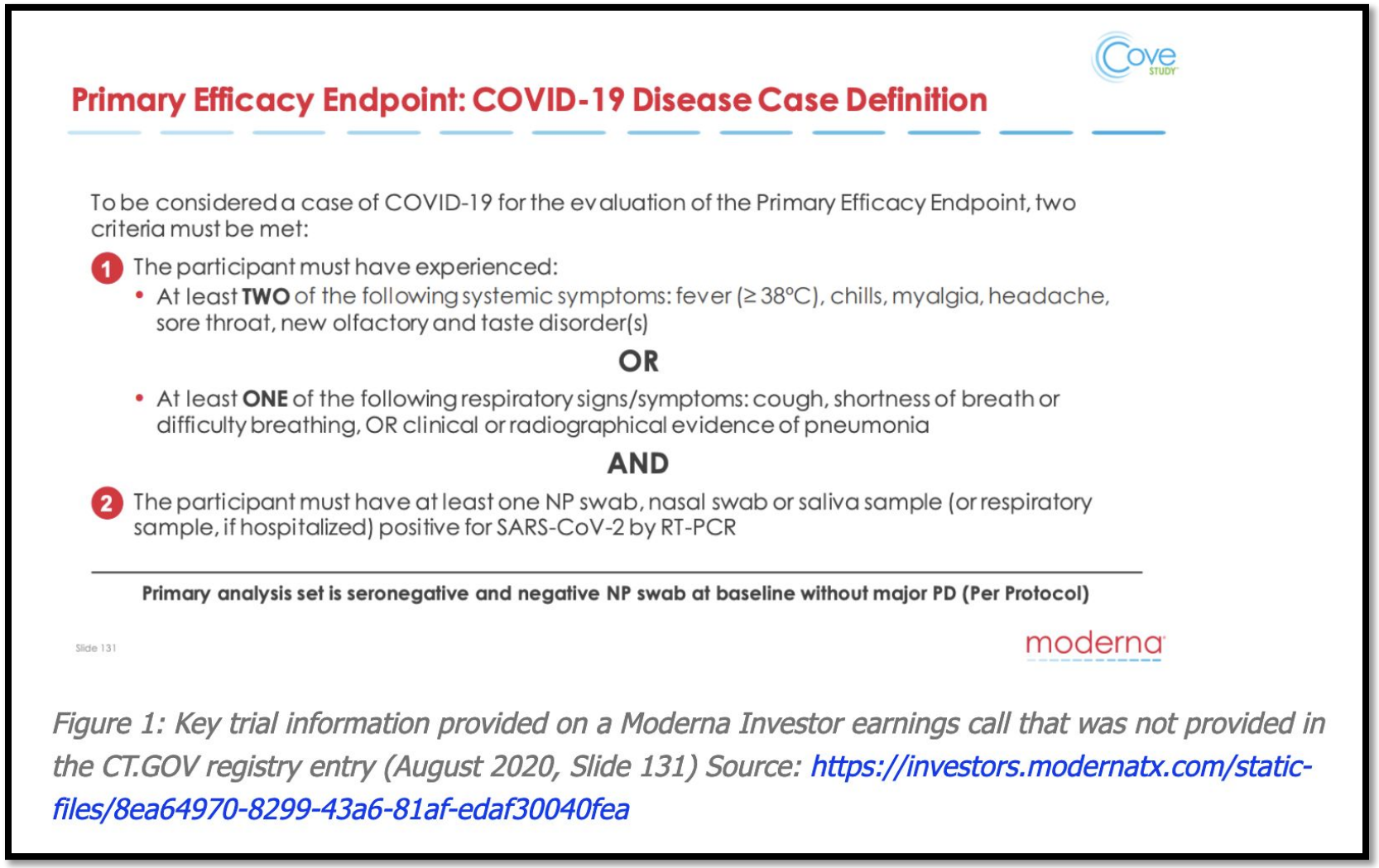
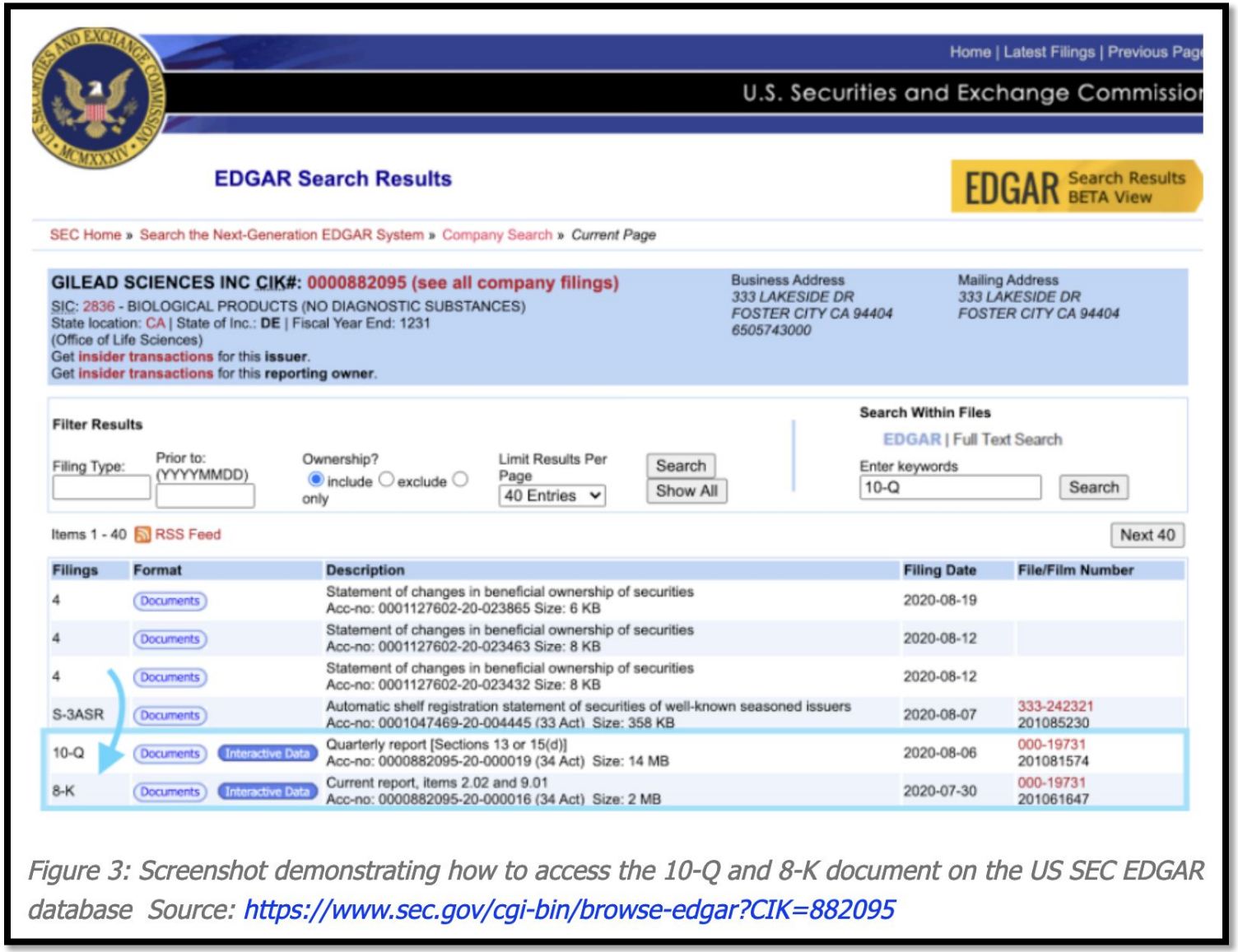


Figure 1: Key trial information provided on a Moderna Investor earnings call that was not provided in the CT.GOV registry entry (August 2020, Slide 131) Source: https://investors.modernatx.com/static-files/8ea64970-8299-43a6-81af-edaf30040fea

Source: From "Trial transparency in real time" how-to guide at https://restoringtrials.org/2020/10/18/trial-transparency-in-real-time/ showing a slide shown on a Moderna investors' call.

FINANCIAL FILINGS TO THE SEC (SECURITIES AND EXCHANGE COMMISSION)



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U.S. Securities and Exchange Commission

EDGAR Search Results

EDGAR Search Results BETA View

SEC Home » Search the Next-Generation EDGAR System » Company Search » *Current Page*

GILEAD SCIENCES INC CIK#: 0000882095 (see all company filings)

SIC: 2836 - BIOLOGICAL PRODUCTS (NO DIAGNOSTIC SUBSTANCES)
State location: CA | State of Inc.: DE | Fiscal Year End: 1231
(Office of Life Sciences)
Get insider transactions for this issuer.
Get insider transactions for this reporting owner.

Business Address
333 LAKESIDE DR
FOSTER CITY CA 94404
6505743000

Mailing Address
333 LAKESIDE DR
FOSTER CITY CA 94404

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Search Within Files
EDGAR | Full Text Search
Enter keywords: 10-Q | Search

Items 1 - 40 RSS Feed | Next 40

Filings	Format	Description	Filing Date	File/Film Number
4	Documents	Statement of changes in beneficial ownership of securities Acc-no: 0001127602-20-023865 Size: 6 KB	2020-08-19	
4	Documents	Statement of changes in beneficial ownership of securities Acc-no: 0001127602-20-023463 Size: 8 KB	2020-08-12	
4	Documents	Statement of changes in beneficial ownership of securities Acc-no: 0001127602-20-023432 Size: 8 KB	2020-08-12	
S-3ASR	Documents	Automatic shelf registration statement of securities of well-known seasoned issuers Acc-no: 0001047469-20-004445 (33 Act) Size: 358 KB	2020-08-07	333-242321 201085230
10-Q	Documents Interactive Data	Quarterly report [Sections 13 or 15(d)] Acc-no: 0000882095-20-000019 (34 Act) Size: 14 MB	2020-08-06	000-19731 201081574
8-K	Documents Interactive Data	Current report, items 2.02 and 9.01 Acc-no: 0000882095-20-000016 (34 Act) Size: 2 MB	2020-07-30	000-19731 201061647

Figure 3: Screenshot demonstrating how to access the 10-Q and 8-K document on the US SEC EDGAR database Source: https://www.sec.gov/cgi-bin/browse-edgar?CIK=882095

Source: From "Trial transparency in real time" how-to guide at
https://restoringtrials.org/2020/10/18/trial-transparency-in-real-time/ showing a slide shown on a Moderna investors' call.

AFTER REGULATORY AUTHORIZATION/LICENSURE

Locating trial data/documents, including results

- Regulators
  - Drugs@FDA (https://www.fda.gov/drugsatfda)
  - FDA Advisory Committees (https://www.fda.gov/advisory-committees)
  - Health Canada portal (https://clinical-information.canada.ca)
  - EMA Clinical Data Publication portal (https://clinicaldata.ema.europa.eu)
  - Japan PMDA (English & 日本語) (https://www.pmda.go.jp/)
- Supplemental files for trial publications (for protocol and statistical analysis plan)

See "**How to access clinical trial data**" guide at https://restoringtrials.org/accessing-trial-data/

Thank you

Contact
pdoshi@bmj.com
pdoshi@rx.umaryland.edu

FDA U.S. FOOD & DRUG ADMINISTRATION

The Drug Development Process

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Step 1
Discovery and Development

Discovery and Development

Research for a new drug begins in the laboratory.

More Information

Step 2
Preclinical Research

Preclinical Research

Drugs undergo laboratory and animal testing to answer basic questions about safety.

More Information

Step 3
Clinical Research

Clinical Research

Drugs are tested on people to make sure they are safe and effective.

More Information

Step 4
FDA Review

FDA Review

FDA review teams thoroughly examine all of the submitted data related to the drug or device and make a decision to approve or not to approve it.

More Information

Step 5
FDA Post-Market Safety Monitoring

FDA Post-Market Safety Monitoring

FDA monitors all drug and device safety once products are available for use by the public.

More Information

Source: FDA. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

FDA U.S. FOOD & DRUG ADMINISTRATION

"Before filing a marketing application, a developer must have adequate data from two large, controlled clinical trials."

"Length of Study: 1 to 4 years"

Source: FDA. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research

Research

Original Investigation

Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012

Nicholas S. Downing, AB; Jenerius A. Aminawung, MD, MPH; Nilay D. Shah, PhD; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

IMPORTANCE Many patients and physicians assume that the safety and effectiveness of newly approved therapeutic agents is well understood; however, the strength of the clinical trial evidence supporting approval decisions by the US Food and Drug Administration (FDA) has not been evaluated.

OBJECTIVES To characterize pivotal efficacy trials (clinical trials that serve as the basis of FDA approval) for newly approved novel therapeutic agents.

DESIGN AND SETTING Cross-sectional analysis using publicly available FDA documents for all novel therapeutic agents approved between 2005 and 2012.

MAIN OUTCOMES AND MEASURES Pivotal efficacy trials were classified according to the following design features: randomization, blinding, comparator, and trial end point. Surrogate outcomes were defined as any end point using a biomarker expected to predict clinical benefit. The number of patients, trial duration, and trial completion rates were also determined.

RESULTS Between 2005 and 2012, the FDA approved 188 novel therapeutic agents for 206 indications on the basis of 448 pivotal efficacy trials. The median number of pivotal trials per indication was 2 (interquartile range, 1-2.5), although 74 indications (36.8%) were approved on the basis of a single pivotal trial. Nearly all trials were randomized (89.3% [95% CI, 86.4%-92.2%]), double-blinded (79.5% [95% CI, 75.7%-83.2%]), and used either an active

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Author Video Interview at jama.com

Related articles pages 378 and 385

Supplemental content at jama.com

188 novel agents
16% orphan
84% non-orphan

Downing et al. JAMA. 2014;311(4):368-377.
doi:10.1001/jama.2013.282034

Rhetoric	Reality (non-orphan drugs)
• **Long (1 – 4 years)**	• **Short.** 7% had at least 1 trial ≥12 months; **67% approved with no pivotal trial ≥6 months**
• **2 pivotal trials**	• **33% of indications approved on single pivotal trial** (median 2; IQR 1 to 3)

What do we know about a drug at time of approval?
Answer: far less than many assume

Health Affairs Scholar, 2023, **1(2)**, 1–3
https://doi.org/10.1093/haschl/qxad028
Advance access publication: July 19, 2023
Brief Report

Health Affairs Scholar
EMERGING & GLOBAL HEALTH POLICY
OXFORD

Food and Drug Administration novel drug decisions in 2017: transparency and disclosure prior to and 5 years following approval

Robert M. Kaplan[1,*], **Amanda J. Koong**[2], **Veronica Irvin**[3]

[1]Clinical Excellence Research Center, Stanford University School of Medicine, Stanford, CA 94305, United States
[2]University of Texas Health Science Center at Houston, McGovern School of Medicine, Houston, TX 77030, United States
[3]College of Health, Oregon State University, Corvallis, OR 97331, United States

*Corresponding author: Clinical Excellence Research Center, Stanford University School of Medicine, CAM Building, First Floor, Stanford, CA 94305, United States. Email: bob.kaplan@stanford.edu

Abstract

The Food and Drug Administration (FDA) approved 46 novel drugs in 2017. We reviewed availability of results prior to and during the 5 years following each approval. Using the FDA website and ClinicalTrials.gov, we recorded trials cited as evidence for the approval, total number of studies registered in ClinicalTrials.gov, number started and completed before approval, and the frequency and timing of reporting results. The 46 drugs approved in 2017 were evaluated in 1149 studies. The number of studies used to evaluate the 46 drugs ranged from 2 to 165 (mean: 24.98; SD = 28.95). Among these, an average of 9.22 studies (SD = 9.21) were started and 5.82 studies (SD = 6.89) were completed before the approval. A single trial justified approval for 19 of 46 (41%) of the approved products. Public posting of results prior to the FDA approval was available for an average of only 1.42 studies (SD = 3.12). No results were publicly reported before approval for 9 of the 46 drugs (20%). Health care providers and consumers depend on complete and transparent reporting of information about FDA-approved medications. Only a fraction of evidence from completed studies was available before approval and a substantial portion of research evidence remained undisclosed after 5 years.

Key words: FDA; regulatory science; evidence-based medicine; evidence standards.

https://academic.oup.com/healthaffairsscholar/article/1/2/qxad028/7226406

"A single trial justified approval for 19 of 46 (41%) of the approved products."

Feature » BMJ Investigation

Did the FDA break its own rules in approving the antibiotic Recarbrio?

BMJ 2023 ; 381 doi: https://doi.org/10.1136/bmj.p1048 (Published 15 May 2023)
Cite this as: *BMJ* 2023;381:p1048

Linked Commentary

The decline of science at the FDA has become unmanageable

Peter Doshi, senior editor

Author affiliations

pdoshi@bmj.com

FDA scientists said that they couldn't draw any inferences from the clinical trials for a new combination antibiotic from Merck—but the agency approved Recarbrio anyway. **Peter Doshi** investigates

Since the 1960s, in the wake of the thalidomide tragedy, the US has required drug makers to provide "substantial evidence" that drugs are effective. This evidence, says the law, must consist of "adequate and well-controlled

https://www.bmj.com/content/381/bmj.p1048

STAT REPORTS

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Failed trial, successful drug: How a negative readout can lead to FDA approval

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ADD TO CART

A failed late-stage clinical trial is bad news for patients, the drugmaker, and investors who made a bet that the product would be successful. But it doesn't always mean the end of the road for a new drug.

https://reports.statnews.com/products/failed-trial-successful-drug?variant=40178917245031

The New York Times

24 August 2020

OPINION

A Vaccine That Stops Covid-19 Won't Be Enough

The best vaccines don't just prevent a disease; they also prevent the pathogen causing the disease from being transmitted. So why aren't we focusing more on those?

"One cannot assume that a vaccine that prevents the development of Covid-19 in a patient will necessarily also limit the risk that the patient will transmit SARS-CoV-2 to other people."

Source: Finn A, Malley R. "A Vaccine That Stops Covid-19 Won't Be Enough" https://nyti.ms/2Fwr098

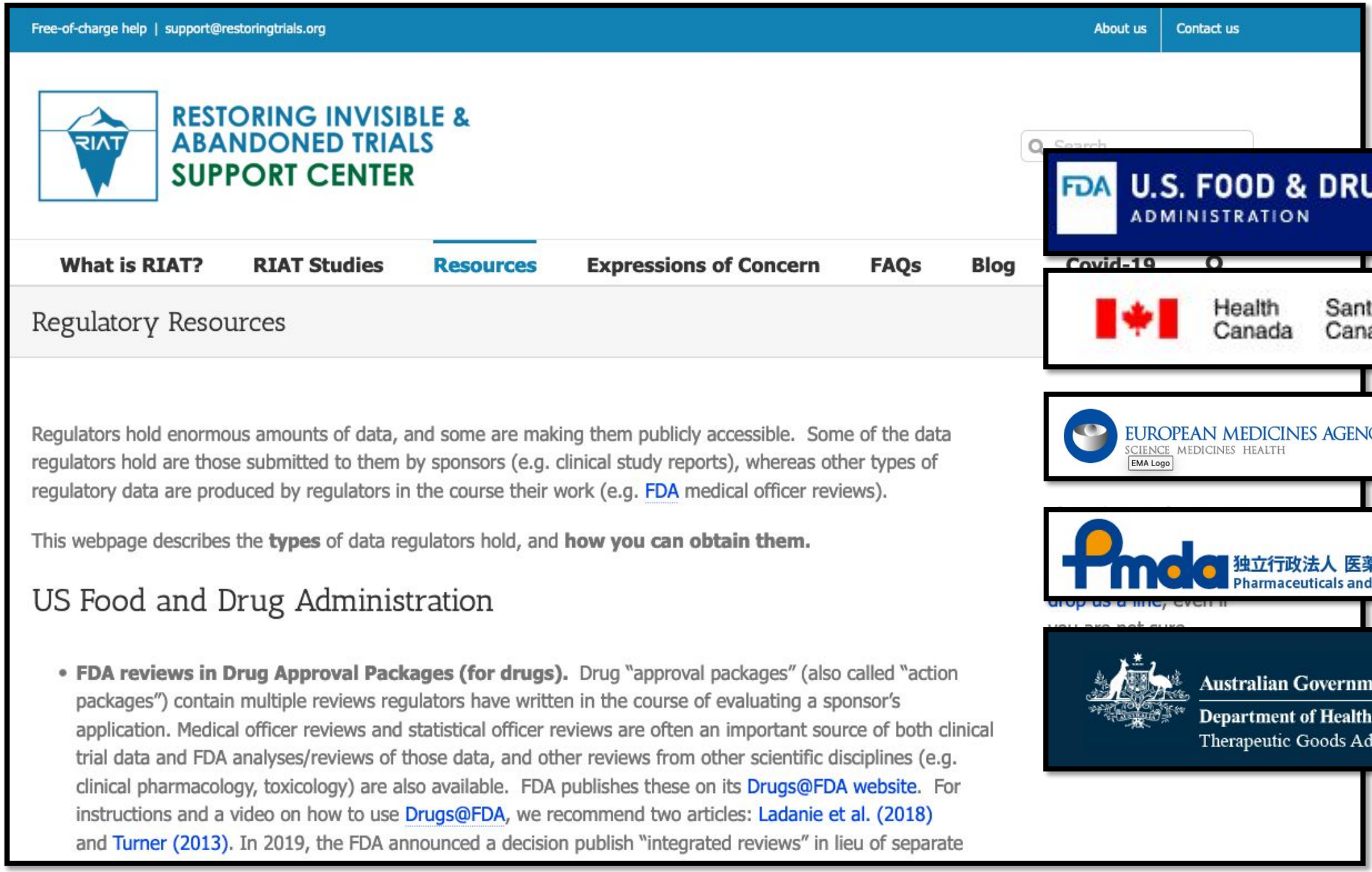
21 October 2020

“None of the trials currently under way are designed to detect a reduction in any serious outcome such as hospital admissions, use of intensive care, or deaths. Nor are the vaccines being studied to determine whether they can interrupt transmission of the virus.”

“Our trial will not demonstrate prevention of transmission,” [Moderna CMO] Zaks said, “because in order to do that you have to swab people twice a week for very long periods, and that becomes operationally untenable.”

This was discoverable through a close reading of each trial’s design

Source: Doshi P. Will covid-19 vaccines save lives? Current trials aren't designed to tell us. BMJ. 2020 Oct 21;371:m4037. https://doi.org/10.1136/bmj.m4037 PMID: 33087398.



https://restoringtrials.org/regulatory-resources/

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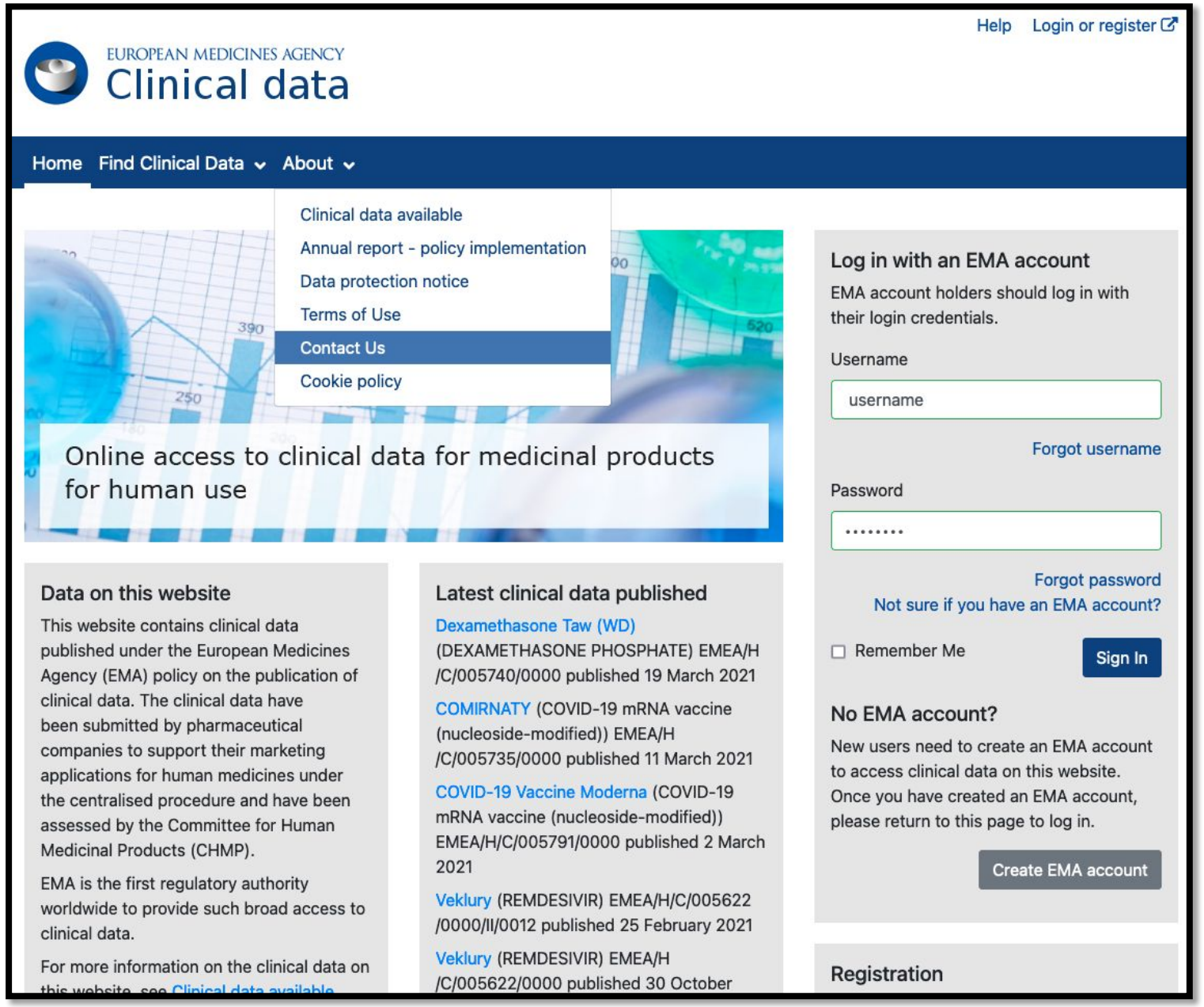

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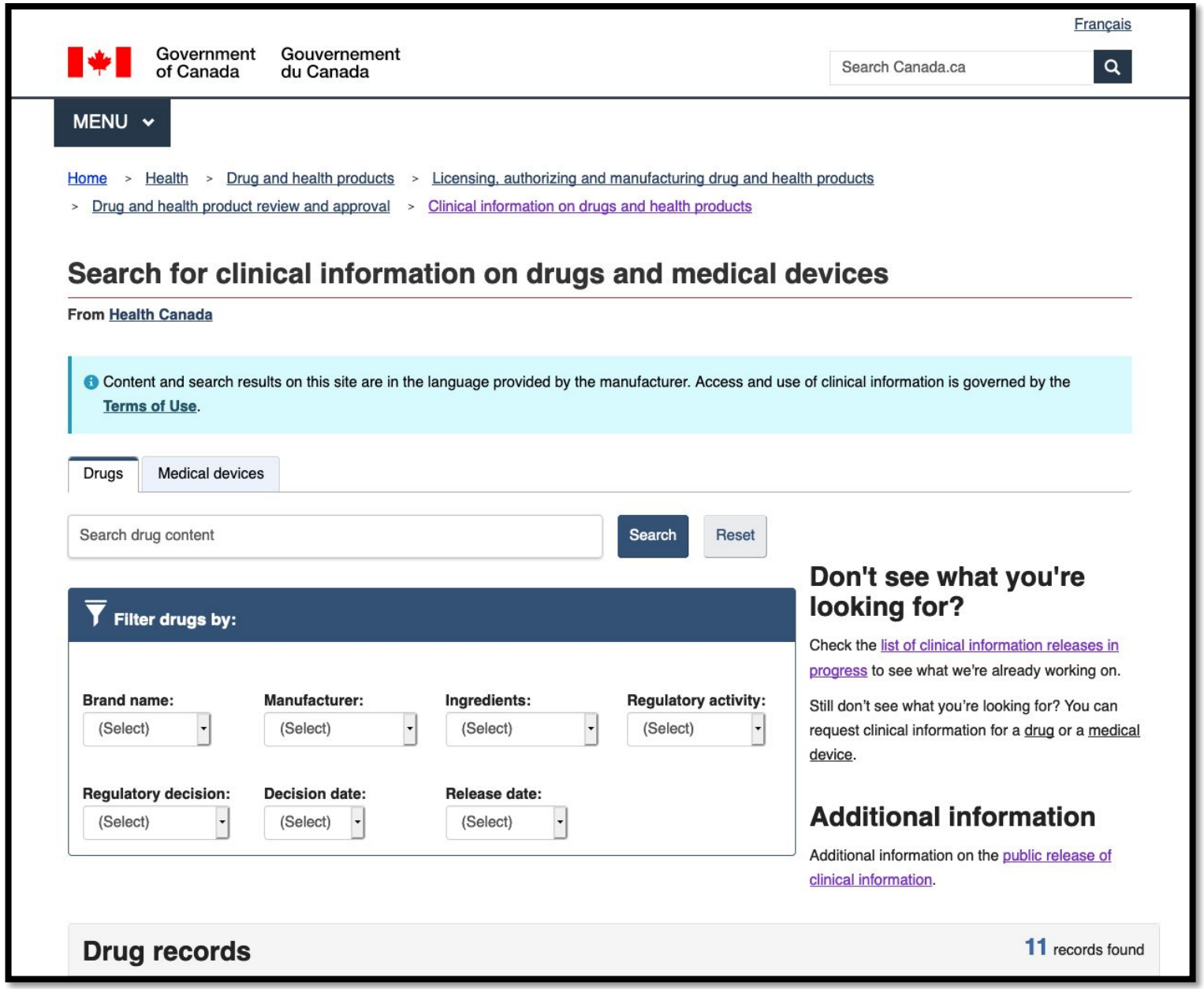

https://clinical-information.canada.ca/

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申請資料

RMP	RMP資材		改訂指示反映履歴および根拠症例	審査報告書／再審査報告書／最適使用推進ガイドライン等
	医療従事者向け	患者向け		
○	適正使用ガイド［コミナティRTU筋注（1価：オミクロン株XBB.1.5），コミナティ筋注5～11歳用（1価：オミクロン株XBB.1.5），コミナティ筋注6ヵ月～4歳用（1価：オミクロン株XBB.1.5）］ 適正使用ガイド［コミナティRTU筋注	新型コロナワクチンコミナティを接種されるお子さまと保護者の方へ［コミナティ筋注5～11歳用（1価：オミクロン株XBB.1.5），コミナティ筋注6ヵ月～4歳用（1価：オミクロン株XBB.1.5）］（6ヵ月～11歳の小児の被接種者） 新型コロナワクチン	2022年10月19日薬生薬審発1019第1号、薬生安発1019第1号 別紙2 2022年06月10日薬生安発0610第1号 別紙1 2022年04月25日薬生薬審発0425第8号、薬生安発0425第4号 別紙1 2022年03月23日薬生薬審発0323第4号、薬生安発0323第1号 別紙1	審査報告書 審査報告書(2021年11月11日) 申請資料概要 審査報告書(2021年02月14日) 申請資料概要