Evaluation of the methodological practices implemented in the Pfizer/BioNtech trials in the development of its COVID-19 RNA-messenger vaccine in relation to Good Clinical Practices

Truth is a science with a future

Christine COTTON

Pierre - OpenVAET

Who am I

Christine Cotton OFFICIEL
@StatChrisCotton

Biostatistician since 1995

Founder and CEO of a CRO

Clinical Research Organization during 22 years ,

subcontractor of pharmaceutical industry for the management of clinical data

In charge of monitoring, data-management, statistics

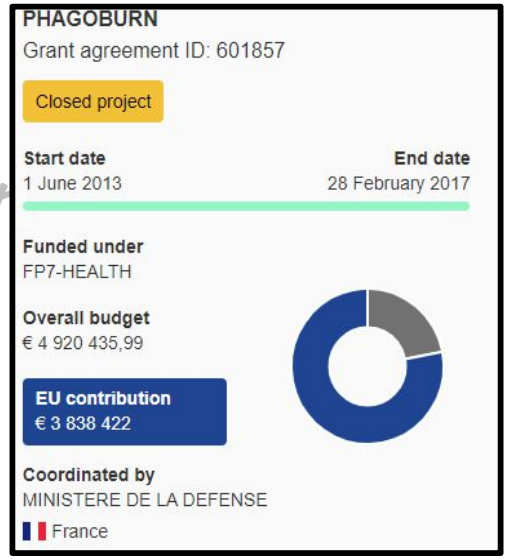
Experience

- **in all study phases and various therapeutic domains:** Allergy, Cardiology, Dermatology, Endocrinology, Gastric domain, Gynecology, Metabolism, Odontology / Dentistry,Onconlogy, ENT, Pneumology, Central Nervous System, Osteo-Muscular system, Rheumatology, Urology, Virology ..
- **Protocol statistical part, methodology, sample size (number of subjects necessary to include in a trial to conclude to efficacy)**
- **Statistical analyses**
- **Tables to be included into the Clinical Study Report**

Clients

AbScience, AstraZeneca, Aventis, Bausch et Lomb, Bayer, Debiopharm, Galderma, Horus, Intergroupe Francophone du Myélome, Institut de recherche Servier, Ipsen, Janssen-Cilag, Medtronic, Menarini, Orfagen, Pfizer, Pherecydes Pharma, Pierre Fabre, Roche, Sanofi, Thea, Takeda, Synthelabo, United Pharmaceutical, Virbac, Yamanouchi,
Various hospitals ...

https://cordis.europa.eu/project/id/601857/reporting



Statistician Expert in IDMC (Independent Data Monitoring Committee)

https://christinecotton.com/cv

Heard by French OPECST (composed by senators and deputies) and ANSM (French Agency) in July 2022

Why a biostatistician is credible when talking about clinical trials

According to the LEEM : Les Entreprises du Médicament's : The Medicine companies
The LEEM's mission is to **represent and defend the pharmaceutical industry**, manage contractual policy with the French government, negotiate with social partners, and promote and defend ethics.

"*The biostatistician contributes to the design and development of biostatistical methodologies used in pre-clinical, clinical or epidemiological studies, and analyzes biological data to extract useful information and interpret it, in order to help the research team make decisions*"

- Participate in the development of **working hypotheses** in collaboration with physicians and the clinical studies team
- Choice of statistical model and definition of biostatistical methodology for pre-clinical, clinical or epidemiological studies
- Determination of the number of subjects to be studied
- Drafting the statistical section
- Participation in protocol drafting and validation
- Design of statistical analysis plan
- Setting up the experimental design of trials: methodology, evaluation criteria, hypothesis testing, randomization plans
- **Validation of evaluation criteria**
- Validation of data consistency in collaboration with data management
- Proposal of the most appropriate statistical model for the clinical problem at hand
- Carrying out and programming analyses
- Write statistical sections of study reports
- Participate in drafting communication materials
- Present statistical results to regulatory agencies
- Answering questions asked by agencies

ACTIVITÉS

Le/La biostatisticien/ne participe à l'encadrement d'un seul projet.

Mise en œuvre des études

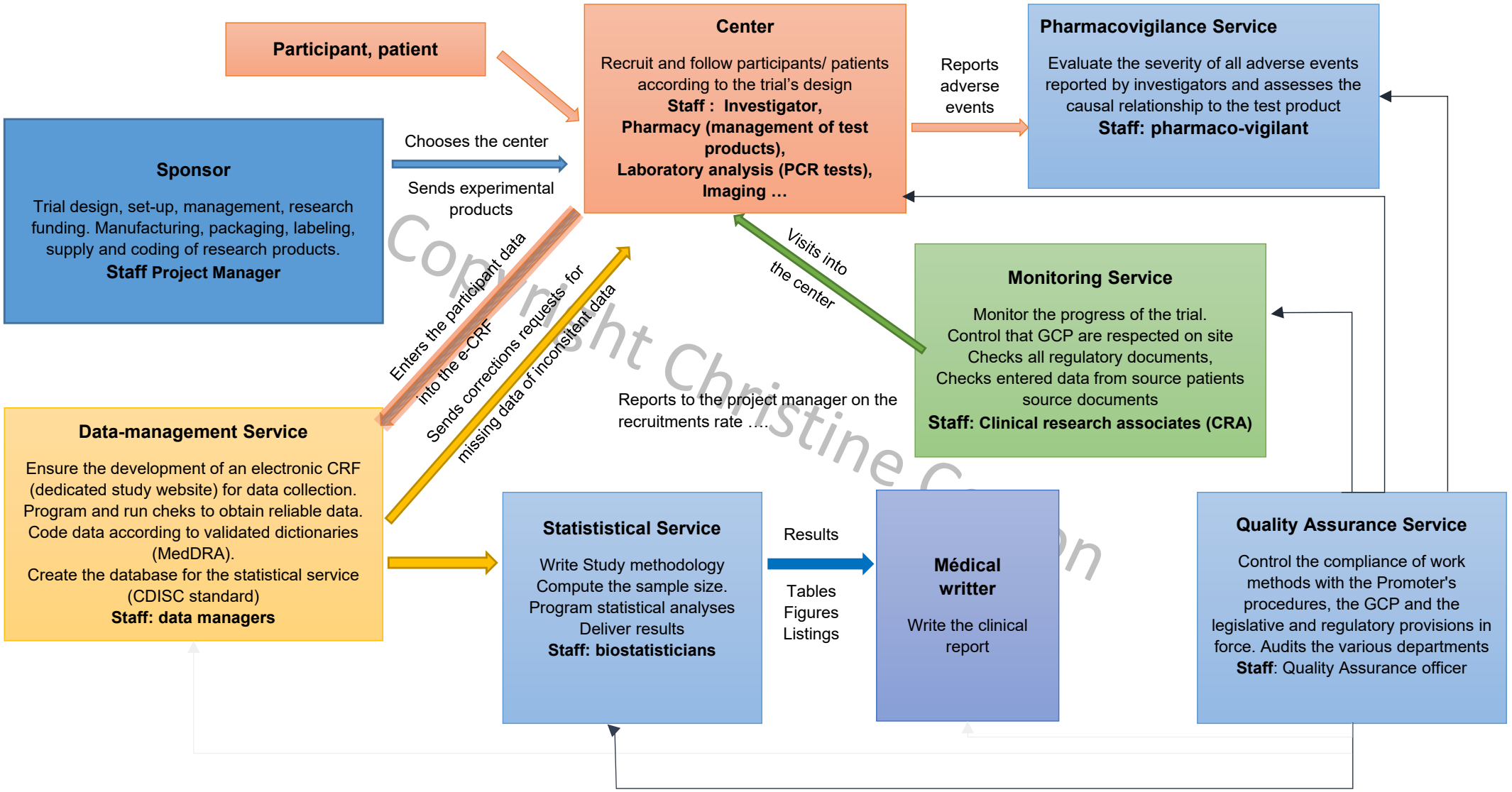
- Participation à la réflexion et aux hypothèses de travail en collaboration avec les médecins et l'équipe d'études cliniques
- Choix d'un modèle statistique et définition de la méthodologie biostatistique des études pré- cliniques, clinique ou épidémiologiques
- Détermination du nombre de sujets étudiés
- Rédaction de la section statistique
- Participation à la rédaction et à la validation du protocole
- Conception du plan d'analyse statistique
- Mise en place du plan expérimental des essais : méthodologie, critères d'évaluation, tests d'hypothèses, plans de randomisation
- Validation des critères d'évaluation
- Validation de la cohérence des données en collaboration avec le data management
- Proposition du modèle statistique le plus en adéquation avec la problématique clinique
- Modélisation informatique des processus biologiques afin de proposer un modèle à des phénomènes biologiques observés
- Observation des conséquences sur le modèle de variations d'un paramètre local

Interprétation et diffusion des résultats

- Production de revues de données
- Réalisation et programmation des analyses
- Rédaction de la partie statistique des rapports d'études
- Participation à la rédaction des supports de communication
- Présentation des résultats statistiques aux agences réglementaires
- Réponse aux questions posées par les agences

https://www.leem.org/referentiels-metiers/biostatisticienne

Clinical research stakeholders INTERACTIONS



A world of norms and regulation

In **every step of a clinical trial**, existence of **guidelines to homogenize practices** all over the world and ensure **the safety of the persons participating in the research as well as the integrity and accuracy of the data**, which are grouped under the name of Good Clinical Practices (GCP).

The **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)**, assumes the role of centralizing practices by having as members health agencies from most of the world, EMA (European Medicines Agency), MHLW/PMDA (Japan), FDA (Food and Drug Administrations), Swissmedic (Switzerland), Health Canada (Canada), ANVISA (Brazil), HSA (Singapore), MFDS (Republic of Korea), NMPA (China), SFDA (Saudi Arabia)….
https://www.ich.org/

- Clinical trial design, choice a control group (placebo, already existent treatment…)
- Guidelines in data-management with the structure of the database *https://www.cdisc.org/standards*
- Guidelines for management of adverse events : for high-risk products, Risk Management Plan
- Guidelines for statistical methods
- Staff working into clinical trials must follow all the guidelines and write relevant documents **to minimize the risk of error** at any level (regular audits to check if the process are respected)

Good Clinical Practices
List of Guidelines

https://www.ich.org/

Example of Guideline on clinical evaluation of new vaccines
18 October 2006
EMEA/CHMP/VWP/164653/2005
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-new-vaccines_en.pdf

ICH guidelines

Share

The European Medicines Agency publishes scientific guidelines on human medicines that are harmonised by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH guidelines are provided for

- Quality
- Safety
- Efficacy
- Multidisciplinary
- Considerations

ICH: efficacy

Share

The European Medicines Agency publishes scientific guidelines on human medicines that are harmonised by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

For a complete list of scientific guidelines currently open for consultation,

- Clinical safety
- Clinical study reports
- Dose-response studies
- Ethnic factors
- Good clinical practice
- Clinical trials
- Clinical evaluation by therapeutic category
- Clinical evaluation

Therefore, recommendations for boosting (or confirmation of provisional recommendations) may have to be based on long-term immunological follow-up (humoral antibody and, where possible cell-mediated immunity) and/or data on vaccine effectiveness that are obtained during the post-authorisation period. Also, more than one booster dose may be needed to provide life-long protection. Therefore, whatever the data available at the time of initial authorisation, plans should be in place for appropriate post-marketing studies for the determination of the need for booster doses and these should be presented in the application dossier.

Clinical trials

- ICH E7 Studies in support of special populations: geriatrics - questions and answers
- ICH E8 General considerations for clinical studies
- ICH E9 statistical principles for clinical trials
- ICH E10 Choice of control group in clinical trials
- ICH E11(R1) step 5 guideline on clinical investigation of medicinal products in the pediatric population
- ICH guideline E17 on general principles for planning and design of multi-regional clinical trials
- ICH E18 Guideline on genomic sampling and management of genomic data

Clinical safety

- ICH E1 Population exposure: the extent of population exposure to assess clinical safety
- ICH E2A Clinical safety data management: definitions and standards for expedited reporting
- ICH E2B (R3) Electronic transmission of individual case safety reports (ICSRs) - data elements and message specification - implementation guide
- ICH E2C (R2) Periodic benefit-risk evaluation report
- ICH E2D Post-approval safety data management
- ICH E2E Pharmacovigilance planning (Pvp)
- ICH E2F Development safety update report
- ICH guideline E19 on optimisation of safety data collection - Step 2b

Clinical study report

- ICH E3 Structure and content of clinical study reports

Dose response studies

- ICH E4 Dose response information to support drug registration

Ethnic factors

- ICH E5 (R1) Ethnic factors in the acceptability of foreign clinical data
- ICH E5(R1) Ethnic factors in the acceptability of foreign clinical data - questions and answers

Understanding the Trial documents

- **Publicly available documents:**
  Protocol, Risk Management Plans, Summary of Product Caracteristics,
  VRBPAC (Vaccines and Related Biological Products Advisory Committee) documents and meetings (FDA Youtube channel),
  Clinical Study Reports…
- **Data leaks** (EMA e-mails)
- **Court ordered documents released**, thanks to the action of the "Public Health and Medical Professionals for Transparency" (PHMPT.org), and Aaron Siri in the US : mainly .PDF files, .XPT files. (SAS ® software database)
- https://phmpt.org/pfizer-16-plus-documents/
- https://vaccines.shinyapps.io/abstractor/
- **FOIA :** Freedom of Information Act: administrative documents released on demand

1. The FDA shall produce the "more than 12,000 pages" articulated in its own proposal, *see* ECF No. 29 at 24, **on or before January 31, 2022.**
2. The FDA shall produce the remaining documents at a rate of **55,000** pages every **30 days**, with the first production being due **on or before March 1, 2022**, until production is complete.
3. To the extent the FDA asserts any privilege, exemption, or exclusion as to any responsive record or portion thereof, FDA shall, concurrent with each production required by this Order, produce a redacted version of the record, redacting only those portions as to which privilege, exemption, or exclusion is asserted.
4. The Parties shall submit a Joint Status Report detailing the progress of the rolling production by **April 1, 2022**, and every **90 days** thereafter.[6]

SO ORDERED on this **6th day** of **January, 2022.**

Mark T. Pittman
UNITED STATES DISTRICT JUDGE

https://phmpt.org/wp-content/uploads/2022/01/ORDER_2022_01_06.pdf

An international team of volunteer researchers

Christine Cotton OFFICIEL
@StatChrisCotton

Biostatistician 23 years experience
in pharmaceutical industry

CEO of my own company,
a CRO Clinical Research Organization
christinecotton.com

Josh Guetzkow
@joshg99

Sociologist | Criminologist |
Human Being Being Human

Geoffrey Norman Pain
@FluoridePoison

Authorized by Dr Geoff Pain
Monbulk Victoria Australia

Jikkyleaks
@Jikkyleaks

Home for @jikkykjj the
whistleblowing lab mouse
#Modernagate
#CTCCTCGGCGGGCACGTAG #3Tablets
Pronouns: mouse/mouseself
Tweets are public interest disclosures

Brook Jackson
@IamBrookJackson

Clinical Research |
Big Pharma Whistleblower

J Kunadhasan
@DrJKunadhasan

Anaesthetist and Perioperative Physician ,
AMPS Treasurer #STOP MEDICAL
CENSORSHIP LET US WORK!Fired over
vaccine mandates: Risk benefit analysis
please...

a_concerned_amyloidosis
@a_nineties

#stoptheshots ||
MFA neurologie/ neurology assistant ||
pre-authorization trial nerd ||
modarnlife.substack.com ||
FOIA count: 19

Canceled Mouse
@canceledmouse

The problem is to find the right cable to eat.

And many more, listed at https://openvaet.substack.com/p/pfizerbiontech-c4591001-trial-april

Levels of proof

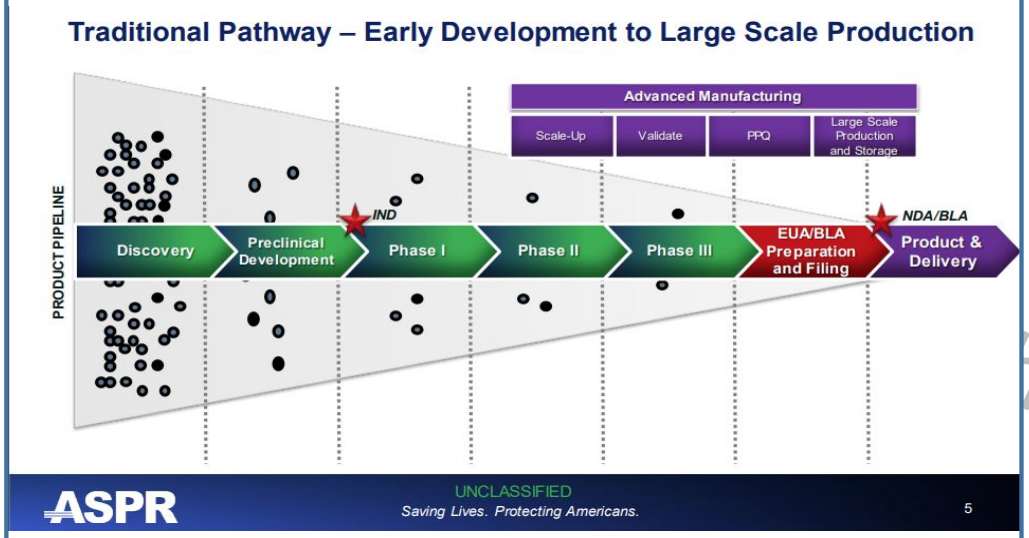
In France, guideline on the Level of evidence and gradation of recommendations

Grade of recommendations	Level of scientific evidence provided by the literature
A **Established scientific proof**	Level 1 - high-power randomized controlled trials ; - meta-analysis of randomized controlled trials; - decision analysis based on well-conducted studies.
B **Scientific presumption**	Level 2 - low-power randomized controlled trials ; - well-conducted non-randomized comparative studies ; - cohort studies.
C **Low level of scientific scientific**	Level 3 - case-control studies Level 4 - comparative studies with important biases ; - retrospective studies ; - case series ; - descriptive epidemiological studies (cross-sectional, longitudinal).

- The **Good Clinical Practices** are set up since 30 years to guarantee that all a clinical trial stakeholders work according to guidelines in order to insure reliable results
- These guidelines are covering every aspect of a trial (protocol writing, recruitment and follow-up of patients, blood samples storage …., choice of statistical methods, reporting …)
- Aim: to avoid bias (element that false the results)
- **Real-life studies have a much lower level of proof than clinical trials, especially studies on retrospective data (more bias)**

The Pfizer's clinical trial
An accelerated development

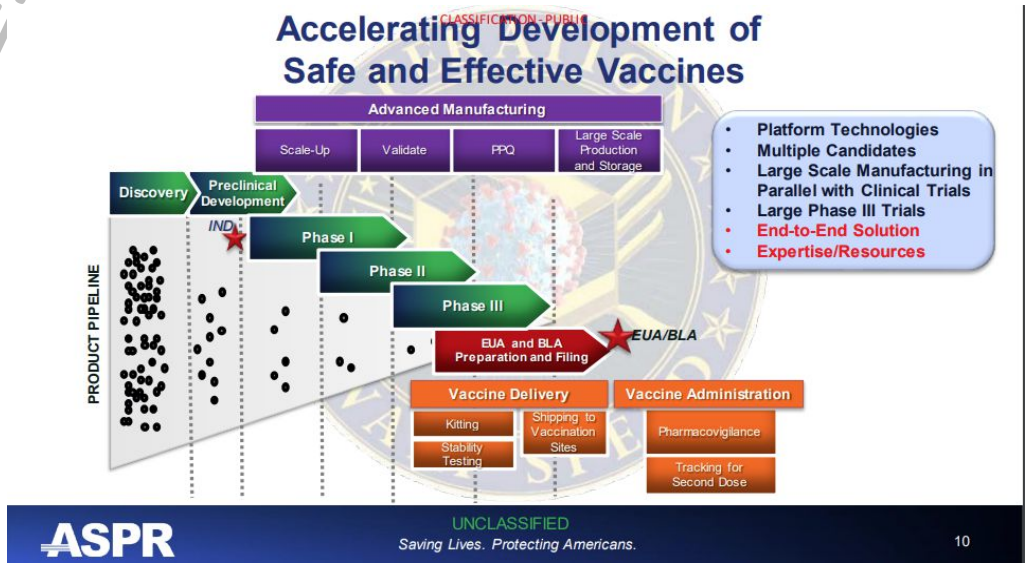
➢ Classic development



https://www.fda.gov/media/143560/download

Date	Number of participants	Number of centers	Number of days	Recruitment rate per day	Recruitment rate per hour
27/07/2020	360				
20/08/2020	11000		25	426	53
06/10/2020	37000	120	48	541,7	67,7
14/11/2020	44000	150	40	175,0	21,9

➢ Accelerated development

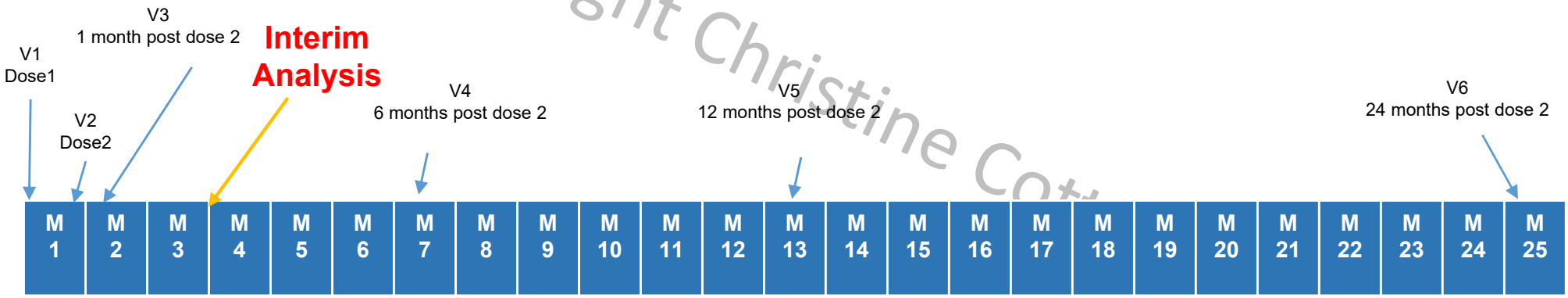


- + rolling reviews
- + fast-track

Characteristics of the Pfizer-BioNtech Phase 1-2-3 trial

Planned visits : flowchart

- Visit 1: 1st dose placebo or vaccine candidate Day 1
- Visit 2: 2nd dose injected between 19 and 23 days after visit 1
- *Visit 3: at 1 week after dose 2 phase 1-2, not planned in phase 3*
- *Visit 4: at 2 weeks after dose 2 phase 1-2, not planned in phase 3*
- Visit 5: at 1 month after dose 2
- Visit 6: at 6 months after dose 2 Visit 7: 12 months after the second dose
- Visit 8: at 24 months after dose 2



Duration of follow-up at interim analyses

Median time follow-up of 2 months after dose 2

Clinical Study Report- December 10, 2020 on the ≥ 16 yo

Table 3. Follow-Up Time After Dose 2 – ~38000 Subjects for Phase 2/3 Analysis – Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=18860) n[b] (%)	Placebo (N[a]=18846) n[b] (%)	Total (N[a]=37706) n[b] (%)
Subjects (%) with length of follow-up of:			
<2 Months	9329 (49.5)	9310 (49.4)	18639 (49.4)
<2 Weeks	363 (1.9)	388 (2.1)	751 (2.0)
≥2 to <4 Weeks	1223 (6.5)	1200 (6.4)	2423 (6.4)
≥4 to <6 Weeks	3239 (17.2)	3235 (17.2)	6474 (17.2)
≥6 to <8 Weeks	4504 (23.9)	4487 (23.8)	8991 (23.8)
≥2 Months	9531 (50.5)	9536 (50.6)	19067 (50.6)
≥8 to <10 Weeks	6296 (33.4)	6329 (33.6)	12625 (33.5)
≥10 to <12 Weeks	2853 (15.1)	2809 (14.9)	5662 (15.0)
≥12 to <14 Weeks	382 (2.0)	398 (2.1)	780 (2.1)

Note: HIV-positive subjects are included in this summary but not included in the analyses of the overall study objectives.
a. N = number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of subjects with the specified characteristic.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (10:49) Source Data: adsl Table Generation: 18NOV2020 (05:34) (Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_IA_P3_2MPD2/adsl_s005_fup_time_d2_saf

https://www.fda.gov/media/144246/download

Clinical Study Report-April 9, 2021 on the 12-15 years old

Table 3. Follow-up Duration After Dose 2, Participants 12 Through 15 Years of Age, Safety Population

	Vaccine Group (as Administered)		
Length of Follow-up[c]	BNT162b2 (30 µg) (N[a]=1131) n[b] (%)	Placebo (N[a]=1129) n[b] (%)	Total (N[a]=2260) n[b] (%)
<1 Month	13 (1.1)	25 (2.2)	38 (1.7)
≥1 Month to <2 months	458 (40.5)	456 (40.4)	914 (40.4)
≥2 Months to <3 months	612 (54.1)	599 (53.1)	1211 (53.6)
≥3 Months	48 (4.2)	49 (4.3)	97 (4.3)

Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 3, page 20.
[a] N=number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n=number of subjects with the specified characteristic.
[c] Length of follow-up is the total exposure from Dose 2 to cutoff date or the date of unblinding, whichever date was earlier.

https://www.fda.gov/media/144246/download

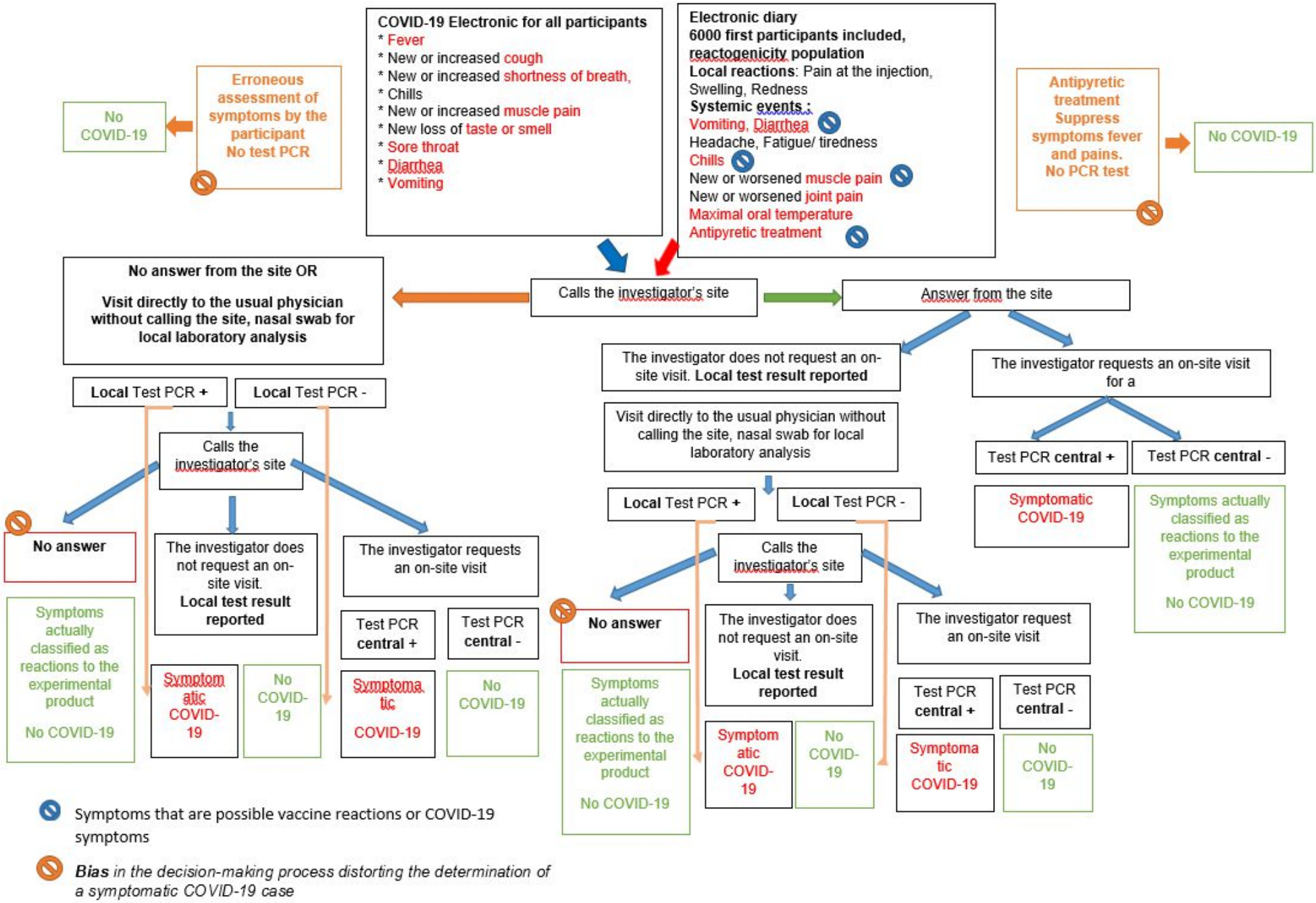
October 26, 2021 Clinical Study Report on 5-11 years old

Table 1. Follow-up Time After Dose 2 - Phase 2/3 - 5 to <12 Years of Age - Safety Population

	Vaccine Group (as Administered)		
	BNT162b2 10 µg (N[a]=1518) n[b] (%)	Placebo (N[a]=750) n[b] (%)	Total (N[a]=2268) n[b] (%)
Time from Dose 2 to cutoff date			
<1 Month	7 (0.5)	4 (0.5)	11 (0.5)
≥1 Month to <2 months	67 (4.4)	32 (4.3)	99 (4.4)
≥2 Months to <3 months	1444 (95.1)	714 (95.2)	2158 (95.1)
≥3 Months	0	0	0
Mean (SD)	2.2 (0.19)	2.2 (0.22)	2.2 (0.20)
Median	2.3	2.3	2.3
Min, max	(0.0, 2.5)	(0.0, 2.5)	(0.0, 2.5)

Christine COTTON – 27/01/2022

Mild or moderate Symptomatic covid cases confirmed by PCR test



Main criterion calculation

Mild or moderate Symptomatic covid cases confirmed by PCR test

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see Section 8.13), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.[9] In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA and Pfizer validated), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in Section 8.13) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2
- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
  - Fever;
  - New or increased cough;
  - New or increased shortness of breath;
  - Chills;
  - New or increased muscle pain;
  - New loss of taste or smell;
  - Sore throat;
  - Diarrhea;
  - Vomiting.

https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see Section 8.14) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

Efficacy

Christine Cotton OFFICIEL
@StatChrisCotton

Main criterion results

Mild or moderate Symptomatic covid cases confirmed by PCR test

44 000 participants included, almost 38 000 analyzed into the first interim analysis in December 2020

Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])		(95% CI[e])	Pr (VE >30% | data)[f]
First COVID-19 occurrence from 7 days after Dose 2	8	2.214 (17411)	162	2.222 (17511)	95.0	(90.3, 97.6)	>0.9999

0,044 %

0,88 %

https://www.fda.gov/media/144246/download

Some symptoms are both possible reactions to the vaccination and symptoms of COVID-19 such as fever, chills, muscle aches, diarrhea, vomiting.

PCR tests ONLY on **people who declared SYMPTOMS**

The diagnostic method chosen; although usual in the clinical trials on vaccines, is very surprising in the context of a pandemic where any person infected with COVID-19 could contaminate those around him or her, transmitting a potentially fatal disease.

- 3.5 times more use of antipyretics which suppress symptoms in the vaccine group compared to the placebo group
- No symptom means No PCR test
- No PCR test means no Covid = success for the vaccine

	18 to 55 Years of Age		>55 Years of Age and Older	
Adverse Event	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)	BNT162b2 Dose 2 N=1660 n (%)	Placebo Dose 2 N=1646 n (%)
Fever				
≥38.0°C	331 (15.8)	10 (0.5)	181 (10.9)	4 (0.2)
>38.0°C to 38.4°C	194 (9.2)	5 (0.2)	131 (7.9)	2 (0.1)
>38.4°C to 38.9°C	110 (5.2)	3 (0.1)	45 (2.7)	1 (0.1)
>38.9°C to 40.0°C	26 (1.2)	2 (0.1)	5 (0.3)	1 (0.1)
>40.0°C	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chills[a]				
Any	737 (35.1)	79 (3.8)	377 (22.7)	46 (2.8)
Mild	359 (17.1)	65 (3.1)	199 (12.0)	35 (2.1)
Moderate	333 (15.9)	14 (0.7)	161 (9.7)	11 (0.7)
Severe	45 (2.1)	0 (0.0)	17 (1.0)	0 (0.0)
New or worsened muscle pain[a]				
Any	783 (37.3)	173 (8.2)	477 (28.7)	87 (5.3)
Mild	326 (15.5)	111 (5.3)	202 (12.2)	57 (3.5)
Moderate	410 (19.5)	59 (2.8)	259 (15.6)	29 (1.8)
Severe	47 (2.2)	3 (0.1)	16 (1.0)	1 (0.1)
Use of antipyretic or pain medication	945 (45.0)	266 (12.6)	625 (37.7)	161 (9.8)

No PCR test for ALL participants

Statistical bias leading to an underestimation of the cases for the vaccine group: very concerning : violation of Helsinki declaration

Efficacy Severe Cases - >12 years old

No efficacy statistically proved on severe cases, on every populations

Clinical Study Report- December 10, 2020 on the ≥ 16 yo

Table 16. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population

	Vaccine Group (as Randomized)						
	BNT162b2 (30 µg) (N[a]=18198)		Placebo (N[a]=18325)				
Efficacy Endpoint	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])	Pr (VE >30% | data)[f]
First severe COVID-19 occurrence from 7 days after Dose 2	1	2.215 (17411)	3	2.232 (17511)	66.4	(-124.8, 96.3)	0.7429

Abbreviations: N-binding = SARS-CoV-2 nucleoprotein–binding; NAAT = nucleic acid amplification test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.
Note: Subjects who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (ie, N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.
a. N = number of subjects in the specified group.
b. n1 = Number of subjects meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all subjects within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Credible interval for VE was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
f. Posterior probability (Pr) was calculated using a beta-binomial model with prior beta (0.700102, 1) adjusted for surveillance time. Refer to the statistical analysis plan, Appendix 2, for more details.
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 17NOV2020 (16:47)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_sev_cov_7pd2_wo_eval

https://www.fda.gov/media/144246/download

Clinical Study Report-April 9, 2021 on the 12-15 years old

Severe COVID-19 cases

There were no reports of severe COVID-19 cases (and no cases of MIS-C) in participants 12-15 years of age.

https://www.fda.gov/media/148542/download

Efficacy Severe Cases - Children

No efficacy statistically proved on all populations on severe cases

October 26, 2021 Clinical Study Report on 5-11 years old

3.6.8.1. Severe COVID-19 and MIS-C Illness – Phase 2/3

As of the data cutoff date (06 September 2021), no severe COVID-19 or MIS-C were reported in pediatric participants 5 to <12 years of age in Study C4591007 in the safety database.

https://www.fda.gov/media/153409/download

Clinical Study Report- June 14 - 15, 2022 on ≥ 6 months-4 yo

Catastrophic results

More severe cases into the BNT162b2 group compared to placebo

Severe COVID-19 and MIS-C

Severe COVID-19 criteria (as described in the protocol, based on FDA definition and modified for children to have very high sensitivity to alert for any potential severe illness) were fulfilled for 7 cases (6 BNT162b2 and 1 placebo [taking into account 2:1 randomization]) among children 2 to <5 years of age. Of these, 5/6 cases in the BNT162b2 group fulfilled a single criterion of increased heart rate or respiratory rate and 1 case in the placebo group fulfilled a single criterion of decreased SpO_2 (88% on room air); all occurred post-Dose 2 (Table 5). Note that in 2 such cases in the BNT162b2 group, the participants reported illness after they were unblinded, which could have introduced potential bias.

Table 5. Characterization of Cases Assigned as Severe That Met FDA Criteria: Children 2 to <5 Years of Age

Group	Age	Timing*	Severity Criteria Met	Severity Range	Meets CDC Criteria	Coinfection
BNT162b2	4 years	32 days	HR=132	>131	No	
BNT162b2	4 years	62 days	RR=32	>29	No	
BNT162b2	3 years	183 days	RR=32	>29	No	
BNT162b2	3 years	208 days	RR-32	>29	No	
BNT162b2	2 years	44 days	HR=150	>142	No	
BNT162b2	2 years	100 days	HR=150 RR=40 SpO2=91% Hospitalization	>142 >38 ≤92%	Yes (Hospitalization)	Parainfluenza virus type 3
Placebo	2 years	162 days	SpO2=88%	≤92%	No	

* All cases occurred post-Dose 2

Highlighted row (gray) presents case information for the only participant who fulfilled >1 severity criterion per protocol pediatric-modified FDA definition and including CDC criterion of hospitalization. This participant had coinfection with parainfluenza virus type 3, and clinical assessment included reported wheezing and salbutamol administration.

HR=heart rate, RR=respiratory rate, SpO_2=oxygen saturation

https://www.fda.gov/media/159193/download

Safety data at 6 months - Deaths

Mortality due to COVID-19

- 1 Covid-19 death in vaccine group (BNT162b2) versus 2 in the placebo group

No vaccine efficacy statistically proven for the deaths due to covid-19

No vaccine efficacy for the overall mortality.

Reported Cause of Death[a]	BNT162b2 (N=21,926) n	Placebo (N=21,921) n
Deaths	15	14
Acute respiratory failure	0	1
Aortic rupture	0	1
Arteriosclerosis	2	0
Biliary cancer metastatic	0	1
COVID-19	0	2
COVID-19 pneumonia	1	0
Cardiac arrest	4	1
Cardiac failure congestive	1	0
Cardiorespiratory arrest	1	1
Chronic obstructive pulmonary disease	1	0
Death	0	1
Dementia	0	1
Emphysematous cholecystitis	1	0
Hemorrhagic stroke	0	1
Hypertensive heart disease	1	0
Lung cancer metastatic	1	0
Metastases to liver	0	1
Missing	0	1
Multiple organ dysfunction syndrome	0	2
Myocardial infarction	0	2
Overdose	0	1
Pneumonia	0	2
Sepsis	1	0
Septic shock	1	0
Shigella sepsis	1	0
Unevaluable event	1	0

Table S4 | Causes of Death from Dose 1 to Unblinding (Safety Population, ≥16 Years Old). a. Multiple causes of death could be reported for each participant. There were no deaths among 12–15-year-old participants.

Source: New England Journal of Medecine -15/09/2021

https://pubmed.ncbi.nlm.nih.gov/34525277/

Reanalyzing Deaths during the trial – Released documents
Collaboration with Pierre from OPENVAET

Christine Cotton OFFICIEL
@StatChrisCotton

Canceled Mouse
@canceledmouse

		BNT162b2	Placebo	Placebo-BNT162b2	Total
DEATH	N	19	17	2	38

38 deaths on more than 46 000 subjects – at the same cut-off date (March 13, 2021)

19 deaths for BNT162b2, 17 for placebo, 2 former members of the Placebo arm who had received BNT162b2 after un-blinding

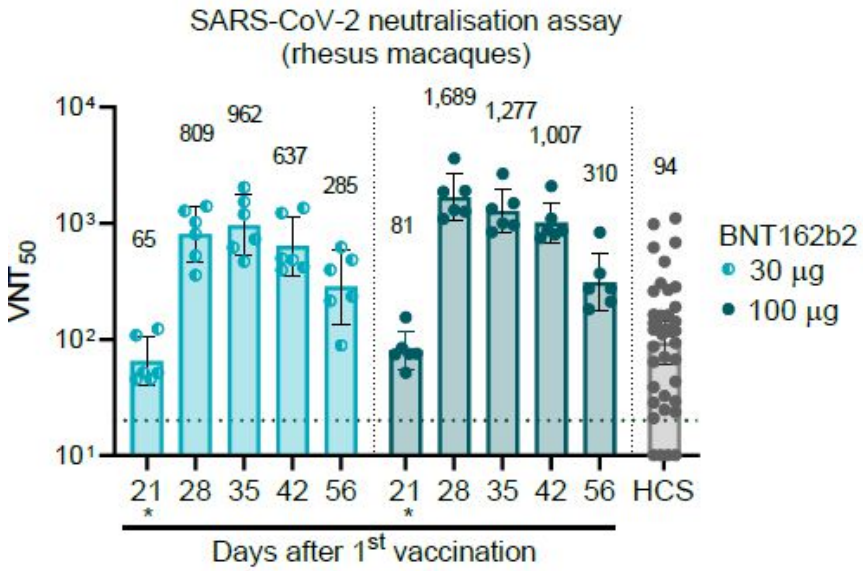
Time of occurrence calculated from onset date of AE and date of doses

https://openvaet.substack.com/p/pfizerbiontech-c4591001-trial-deaths

Immunogenicity

Immunogenicity

Results on macaques



Importantly, BNT162b2 induced potent SARS-CoV-2 neutralizing antibodies in vaccinated-macaques, and viral antigen-specific CD4+ and CD8+ T cells. Rhesus macaques (2-4-year-old males) were immunized by intramuscular (IM) immunization with 30 µg or 100 µg of BNT162b2 or saline control on Days 0 and 21 (2 doses). After two immunizations, neutralization titers were detectable in rhesus macaques sera with geometric mean titers of 962 (on Day 35 for the 30 µg group) or 1,689 (on Day 28 for the 100 µg group). Neutralizing antibody titers persisted to at least day 56, with higher geometric mean titers (GMTs) than those in a panel of human convalescent sera. BNT162b2 vaccination elicited a high frequency of CD4+ T cells that produced IFN-γ, IL-2, and TNF-α, and almost no IL-4 producing CD4+ cells were detectable, indicating a TH1-biased response, which is an immune profile thought to promote vaccine safety. BNT162b2 also elicited spike-specific IFN-γ producing CD8+ T cell responses, which is thought to promote an anti-viral effect.

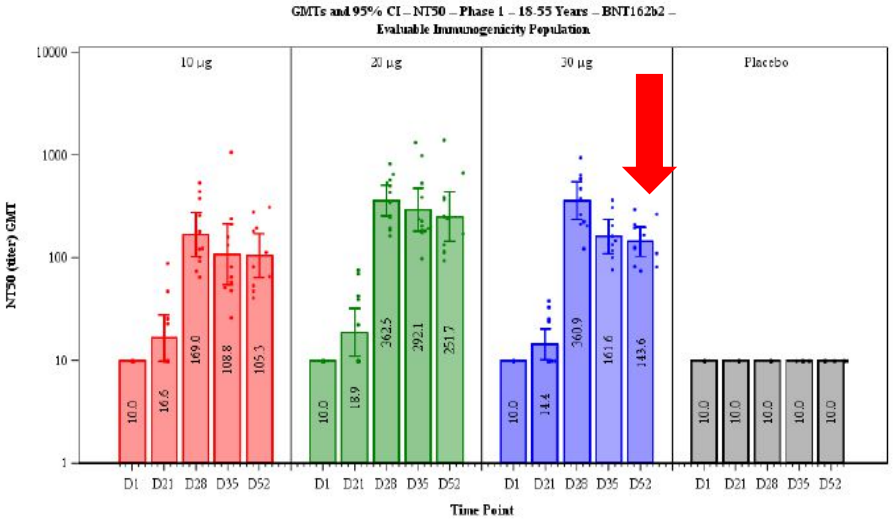
Source: preprint https://www.biorxiv.org/content/10.1101/2020.09.08.280818v1.full.pdf
Source: final https://www.nature.com/articles/s41586-021-03275-y
Ce graphique se trouve *Uniquement dans l'article preprint mais pas dans le final*

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-data-preclinical-studies-mrna

Clinical Study Report - December 10, 2020- Phase 1-2 results

Neutralizing antibodies already showed a decline in immunity at D35 after dose 2, these measurements at D28, D35 were not planned into the phase 3

Figure 6. Geometric Mean Titers and 95% CI: SARS-CoV-2 Neutralization Assay - NT50 – Phase 1, 2 Doses, 21 Days Apart – 18-55 Years of Age – BNT162b2 – Evaluable Immunogenicity Population

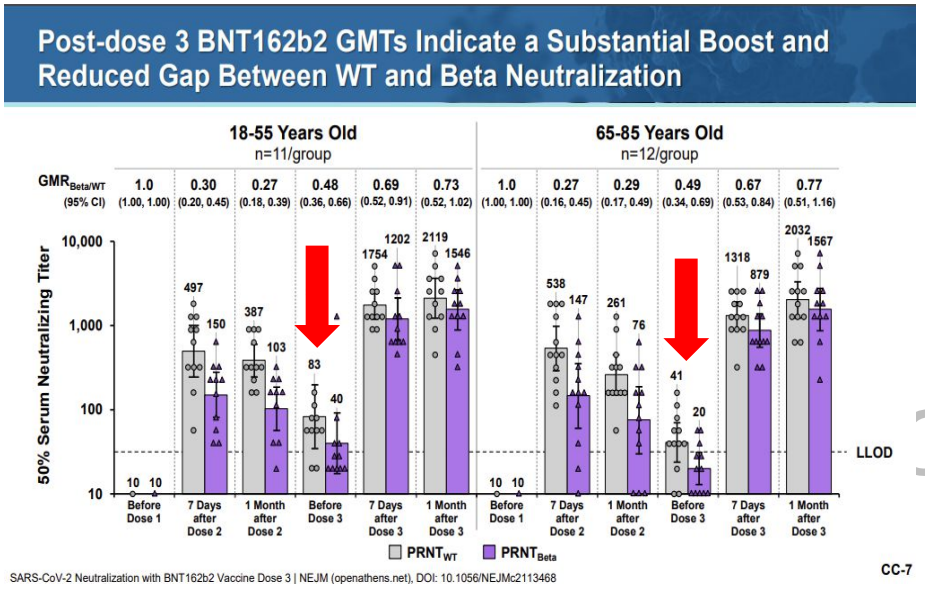


Abbreviations: GMT = geometric mean titer; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001 [A P1 Serology/adva f002 sars 50 18 b2 p1

https://www.fda.gov/media/144246/download

Immunogenicity

Pfizer presentation - CDC 22/09/2021



In the preclinical study on the macaques, the graph presented for the dosage clearly indicates a decrease in the neutralizing antibody level at 2 months after dose 2.

This decrease was also visible into the phase 1-2 in human.

On September 22, 2021, Pfizer acknowledged to the CDC that "data from Israel and the United States suggest that vaccine protection against COVID-19 declines approximately 6 to 8 months after the second dose".

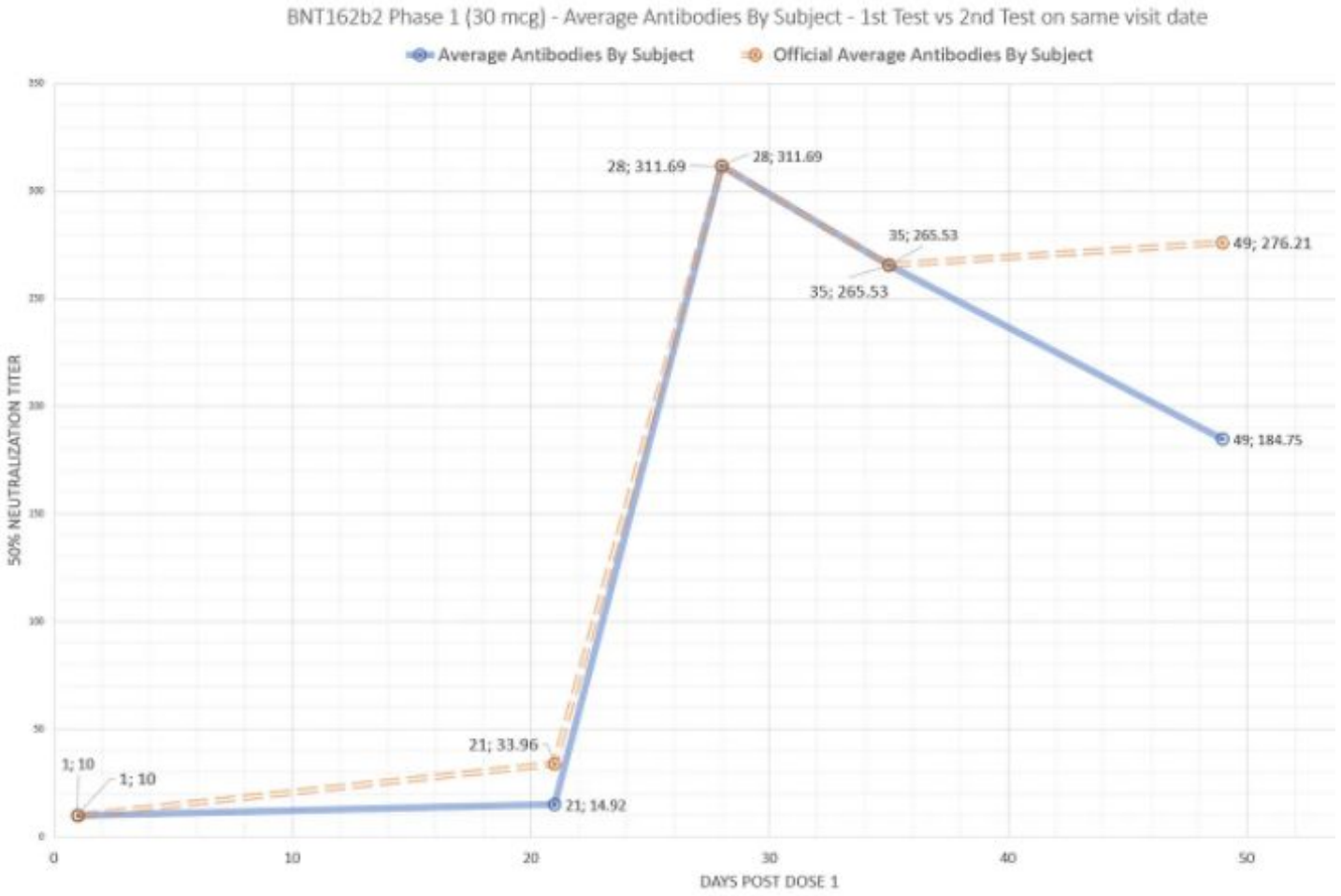
A booster dose was therefore authorized to compensate for the drop in protection of the vaccine as well as the following doses.

If the antibody assay had been performed at 3 months post-dose 2 and the drop was observable as early as December 2020, would the authorities have given an authorization?
Very difficult to communicate « 2 doses and you are done » schedule

Phase 1 neutralizing antibodies analysis
Collaboration with Pierre from OPENVAET

- In Phase 1, several dosages : 10 mcg, 20 mcg, 30 mcg, **100/10 mcg** and Placebo
- Analysis on Placebo and 30 mcg : for several subjects, 2 tests on the same day", the most favourable were kept

Canceled Mouse
@canceledmouse



Known Risks

Risks and missing information : populations not included into the clinical trial

- **Missing information in the December 2020 Risk Management Plan**
  - Use in **pregnancy** and while breast feeding
  - Use in **immunocompromised** patients
  - Use in **frail** patients with co-morbidities (e.g. chronic obstructive Pulmonary disease [COPD], diabetes, chronic neurological disease, Cardiovascular disorders)
  - Use in **patients with autoimmune** or inflammatory disorders
  - **Interaction with other vaccines**
  - Long term safety data
- **Significant health risks to patients are anaphylaxis, myocarditis and pericarditis, and vaccine-associated enhanced disease (VAED).**

The Risk Management Plan clearly demonstrate, due to the huge amount of missing information, that the risk assessment presented in the clinical trial is totally incomplete

BNT162b2
Risk Management Plan 20 December 2020

Table 31. List of Important Risks and Missing Information

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

On page 38 of the CSR on the 12-15 yo

5.2 Unknown Benefits/Data Gaps

The unknown benefits and data gaps associated with the Pfizer-BioNTech COVID-19 vaccine when used in adolescents 12-15 years of age are the same as those detailed in the memorandum authorizing the vaccine for emergency use in for the individuals 16 years of age and older.[1] They relate to:

- Duration of protection
- Effectiveness in certain populations at high risk of severe COVID-19
- Effectiveness in individuals previously infected with SARS-CoV-2
- Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections
- Vaccine effectiveness against asymptomatic infection
- Vaccine effectiveness against long-term effects of COVID-19 disease
- Vaccine effectiveness against mortality
- Vaccine effectiveness against transmission of SARS-CoV-2

This EUA Amendment provides additional insight for the following unknown benefit/data gap that was previously considered:

Effectiveness in pediatric populations

The study enrollment is limited to participants 12 years of age and older. No data are available at this time to evaluate the vaccine effectiveness in children under 12 years of age.

https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

Risks and missing information : populations not included into the clinical trial

Table 77. List of Important Risks and Missing Information

Important identified risks	Myocarditis and Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

Anaphylaxis removed ?

Module SVIII. Summary of the Safety Concerns

Table 65. Summary of Safety Concerns

Important Identified Risks	Myocarditis and Pericarditis
Important Potential Risks	None
Missing Information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	Use in frail patients with co-morbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders)
	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

June 2023

VAED removed ?

https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf

Possible AE outcomes, listed in October 2020

The 22 October 2020, a document presented by the FDA itself mentioned an **impressive list of adverse events outcomes** to follow those that have been appearing in real life since the use of the Comirnaty vaccine,

The Risk Management Plan mentioned only a very small part of these.

WHY ?

FDA Safety Surveillance of COVID-19 Vaccines :

DRAFT Working list of possible adverse event outcomes

Subject to change

- Guillain-Barré syndrome
- Acute disseminated encephalomyelitis
- Transverse myelitis
- Encephalitis/myelitis/encephalomyelitis/ meningoencephalitis/meningitis/ encepholapathy
- Convulsions/seizures
- Stroke
- Narcolepsy and cataplexy
- Anaphylaxis
- Acute myocardial infarction
- Myocarditis/pericarditis
- Autoimmune disease
- Deaths
- Pregnancy and birth outcomes
- Other acute demyelinating diseases
- Non-anaphylactic allergic reactions
- Thrombocytopenia
- Disseminated intravascular coagulation
- Venous thromboembolism
- Arthritis and arthralgia/joint pain
- Kawasaki disease
- Multisystem Inflammatory Syndrome in Children
- Vaccine enhanced disease

https://www.fda.gov/media/143557/download

An illusion of double-blind

Anomalies in the Double-blind from the Protocol perspective

Josh Guetzkow
@joshg99

Sociologist | Criminologist | Human Being Being Human

throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).

Normal

- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.

No blind review meeting, the decisions to assess major protocol deviations Completely Abnormal (easier to exclude inconvenient participants) = MAJOR BIAS

- An unblinded team supporting interactions with, and analyses for, the DMC (see Section 9.6). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see Section 8.2.3).

Normal for the Data Monitoring Committee, they need the products administered to assess the safety results

- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

Normal, they only have access to unblinded results

https://jackanapes.substack.com/p/the-pfizer-vaccine-trial-was-not

Anomalies in the Double-blind from the Protocol perspective

INTERNAL REVIEW COMMITTEE CHARTER

Appendix 2. Plan to Control Dissemination of Results

This is an observer-blinded study as the physical appearance of the BNT162 vaccine candidates and placebo differ.

At the study site: The participant, investigator, study coordinator, and other site staff will be blinded. The dispenser(s)/administrator(s) and those study site team members who are involved in ensuring that protocol requirements for investigational product handling, allocation, and administration are fulfilled at the site (e.g. study manager, clinical research associates) will be unblinded for the duration of the study.

Breaking the blind by the Investigator: Blinding codes should be broken by the investigator only when knowledge of the actual treatment code is absolutely essential for further management of the participant. The method will be an electronic process via Impala.

Pfizer: For Stage 1 (dose-finding) and Stage 2 (expanded cohort): Pfizer study team members are unblinded to the vaccine assigned/received by all participants.

Pfizer: Laboratory personnel performing the immunologic assays will remain blinded to vaccine assigned/received throughout the study.

Unblinded Pfizer personnel: Randomization codes will be released to reporting team (unblinded reporting statistician and unblinded programmer) who need access to the codes to generate the summaries and participant data listings for the review by the unblinded committee members during Stages 1 and 2 the study. Randomization codes will be available to the committee via the reporting team.

Release of the randomization codes to designated personnel will only be performed upon completion of the Randomization Code Release Request Form in GRAABS. Randomization codes and unblinded data will be maintained in a secure location.

The data itself shows that the blinding was faulty – even for the subjects themselves

Percentage of deviations to unblinding by treatment group

	Placebo	Treatment	N
Potential COVID illness visit not done when required	46%	54%	1494
Nasal swab collected at visit where not required	67%	33%	57
Nasal swab not collected for visit where required	54%	46%	1186
Visit outside of protocol specified window	52%	48%	7571
Receipt of other coronavirus vaccine	78%	22%	546
Receipt of flu vaccine >14 days before/after	56%	44%	221
Revised informed consent not signed	39%	61%	639
Urine pregnancy test not performed	57%	43%	1309

Josh Guetzkow
@joshg99

Participants were managed and behaved differently depending of the product received =SUSPICION ON THE RESPECT of the blind in the site

https://jackanapes.substack.com/p/the-pfizer-vaccine-trial-was-not

More details about the XPT deviations.
https://openvaet.substack.com/p/pfizerbiontech-c4591001-trial-making

Safety

Jackanapes Junction

Is Subject #12312982 the Key to Proving Pfizer Vaccine Trial Fraud?

The Story of Augusto Roux

Josh Guetzkow
May 22

271 68

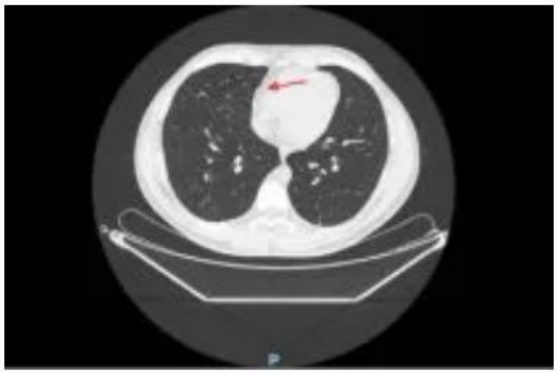
Josh Guetzkow
@joshg99

Sociologist | Criminologist | Human Being Being Human

Dr. Augusto Germán Roux
@RouxAugusto

Serious AEs non-registered or requalified

On the way home after his second dose on Sept. 9, 2020, he began feeling unwell, developed a high fever and felt terribly ill until he fainted on Sept. 11 and finally went to the hospital on Sept. 12 (not the one where the trial was being run). They did a thorough work-up, including a CAT scan of his chest that showed an abnormal collection of fluid around the outside of the heart. Basically he had pericarditis.



On October 7, the clinical trial notes that "at the request of the sponsor" (AKA BioNTech), the adverse event code was update to suspected COVID-19 disease. And that's how Pfizer/BioNTech made cases of myocarditis and pericarditis disappear, by sweeping them under the rug of suspected COVID-19. Moreover, the diagnosis of suspected COVID-19 would not count against the efficacy calculations, since those required a positive PCR test to confirm diagnosis.

A day before the hearing (and a day after the change in AE status), Polack wrote in Augusto's clinical trial records that he had had an attack of severe anxiety starting on September 23, not caused by the vaccine, and wrote that Augusto suspected a conspiracy between the two hospitals, described his anxiety as constitutional, and noted that it was ongoing.

Adverse events changed to transform SAE in covid suspected case

https://jackanapes.substack.com/p/is-subject-12312982-the-key-to-proving

Subjects missing from the Database

39633	1231	12312774	Placebo	21/08/2020 13:00	Present
39634	1231	12312775	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present
39635	1231	12312776			Missing
39636	1231	12312777			Missing
39637	1231	12312778	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present
39638	1231	12312779	Placebo	21/08/2020 13:00	Present
39639	1231	12312780			Missing
39640	1231	12312781			Missing
39641	1231	12312782			Missing
39642	1231	12312783			Missing
39643	1231	12312784			Missing
39644	1231	12312785	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present
39645	1231	12312786			Missing
39646	1231	12312787	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present
39647	1231	12312788			Missing
39648	1231	12312789			Missing
39649	1231	12312790	Placebo	21/08/2020 13:00	Present
39650	1231	12312791			Missing
39651	1231	12312792			Missing
39652	1231	12312793			Missing
39653	1231	12312794			Missing
39654	1231	12312795			Missing
39655	1231	12312796	Placebo	21/08/2020 13:00	Present
39656	1231	12312797	Placebo	21/08/2020 13:00	Present
39657	1231	12312798	Placebo	21/08/2020 13:00	Present
39658	1231	12312799	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present
39659	1231	12312800	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present
39660	1231	12312801			Missing
39661	1231	12312802	Placebo	21/08/2020 13:00	Present
39662	1231	12312803	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present
39663	1231	12312804	Placebo	21/08/2020 13:00	Present
39664	1231	12312805	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present
39665	1231	12312806	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present
39666	1231	12312807	Placebo	21/08/2020 13:00	Present
39667	1231	12312808	Placebo	21/08/2020 13:00	Present
39668	1231	12312809			Missing
39669	1231	12312810	Placebo	21/08/2020 13:00	Present
39670	1231	12312811	BNT162b2 Phase 2/3 (30 mcg)	21/08/2020 13:00	Present

Canceled Mouse 🐭
@canceledmouse

Josh Guetzkow
@joshg99

Sociologist | Criminologist | Human Being Being Human

Totally impossible in an IWRS (Interactive Web Response System) compliant with the 21CFR part 11 guideline

Participants identification numbers are automatically incremented when the participant is created by a center

Larger number in Argentina

The same day Augusto Roux was recruited in Argentina (center 1231 military hospital), 17 participants number are missing ??

WHY ?

Ruikar V. Interactive Voice/Web Response System in clinical research. Perspect Clin Res. 2016 Jan-Mar;7(1):15-20. doi: 10.4103/2229-3485.173781. PMID: 26952178; PMCID: PMC4763512. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4763512/

https://openvaet.substack.com/p/pfizerbiontech-c4591001-trial-the

The guinea pigs

Change in the manufacturing process

The Pfizer vaccines administered **in real life are not those used in the clinical trial**. We know from the study protocol available in the appendices of the NEJM publication on the famous 95% efficacy in December 2020 that a new manufacturing process was used, process 2.

250 participants were to receive vaccines from process 2, and immunogenicity and tolerance were to be compared with a sample of 250 randomly selected vaccinated with process 1. These results were never made public.
https://www.nejm.org/doi/full/10.1056/NEJMoa2034577
https://www.nejm.org/doi/suppl/10.1056/NEJMoa2034577/suppl_file/nejmoa2034577_protocol.pdf

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001
Protocol Amendment 9, 29 October 2020

Document History

Document	Version Date	Summary and Rationale for Changes
		• Made various editorial changes.
Protocol amendment 7	06 October 2020	• Reduced the lower age range to include adolescents 12 to 15 years of age and added corresponding objectives. • Removed reference to COVID-19 antibody testing in Section 2.3.2. • Clarified with efficacy estimands and endpoints that last dose refers to second dose. • Added an additional exploratory objective to describe safety and immunogenicity in participants 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2." • Clarified exclusion criterion 5. • Added Section 6.1.1 to describe manufacturing "Process 1" and "Process 2."

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply ("Process 2") will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process "Process 1," and with material from lots generated using the manufacturing process supporting increased supply, "Process 2," will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

Change in the manufacturing process

The mRNA integrity level of process 2 was significantly lower than the one measured with process 1, which led to major objections from the EMA.

The European deputy Michèle Rivasi has raised the issue in the European Parliament.

https://ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf

Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured and controlled by either Wyeth BioPharma Division, Andover, United States or by BioNTech Manufacturing GmbH, Mainz, Germany, and Rentschler Biopharma SE, Laupheim, Germany.

During the procedure, a number of issues were highlighted relating to the GMP status of the manufacture of the active substance and of the testing sites of the finished product for the purpose of batch release. These issues were classified as a Major Objection (MO). After further information was obtained from the sites and inspectors, the MO was considered resolved.

EU GMP certificates for the manufacturing and testing sites were subsequently obtained. In conclusion, appropriate manufacturing authorisations and GMP certificates are in place for all active substance and finished product manufacturing sites.

Recently, the problem has resurfaced with a publication from Josh Gueztkow and Retsef Levi, this point was presented by Andrew Bridgen to the UK Parliament.

We had no efficacy results on this process 2 in December 2020, for the first time in pharmaceutical industry history, people were treated as Guinea Pigs.

Process 1 vs Process 2 – Increased risk on safety

Covid-19: Researchers face wait for patient level data from Pfizer and Moderna vaccine trials

BMJ 2022 ; 378 doi: https://doi.org/10.1136/bmj.o1731 (Published 12 July 2022)
Cite this as: *BMJ* 2022;378:o1731

Rapid Response:

Effect of mRNA Vaccine Manufacturing Processes on Efficacy and Safety Still an Open Question

Dear Editor,

Recent calls for more transparency in COVID-19 vaccine clinical trials is particularly relevant for data on the manufacturing process, which is an integral part of the regulatory approval process to ensure consistent safety and efficacy outcomes.[1,2]

13 May 2023
Josh A Guetzkow
Senior Lecturer
Retsef Levi, Professor, MIT
Hebrew University
Mt. Scopus, Jerusalem
@joshg99, @RetsefL

Conclusions

Conclusions

- **Populations excluded from the trial or with no result**
  - **Pregnant or breastfeeding women**
  - **Immunocompromised patients**
  - **Patients with co-morbidities or autoimmune diseases**
- **Interaction with other vaccines including influenza vaccine not studied**
- **Transmission not studied**
- **Interim analyses on 3-months follow-up on all the studied populations, I> 16 years old, 12-15 yo, 5-11 yo, 6 months-4 yo**
- **Primary endpoint evaluation biased**
- **No statistically proven efficacy on severe covid post-dose 2 (lack of cases) in december 2020 and all other populations**
- **No statistically proven efficacy in 75+ years in December 2020**
- **Neutralising antibodies not measured after 2 months post dose 2 to hide the drop. In December 2020, boost already planned**
- **Follow-up median time = 2 months post dose 2, shorter than the 6 months FU recommanded into the previous guidelines on vaccines. Mean term safety and long term safety unknown**
- **Serious Adverse Events not reported into the database and then missing in the Clinical Study Reports for the interim analyses**

Conclusions

- inappropriate management of participants, inappropriate choice of criteria and inappropriate choice of ways to manage participants (no PCR for all), despite patient protection laws (Declaration of Helsinki)

- Violation to GCP in the centers managed by the CRO Ventavia

No analysis without these centers despite doubtful data integrity
Protocol deviations assessed during non blind meetings for each population analysis, totally ABNORMAL
Less nasal swabs or visits for potential covid into the vaccine group = major statistical bias

- Data integrity not checked during the audits performed by the authorities

- Change in the manufacturing process introduced in october 2020 (protocol) Violation to GOOD MANUFACTURING PROCESS

- mRNA never used in any medication nor vaccine (see Albert Bourla interview)

- Emergency Use Authorization 9 months after the mRNA due to accelerated développement, rolling reviews and fast-track, NO RESULT on the second manufacturing process!

Reliability and integrity of the results doubtful according to Good Clinical Practices

Results of the Analysis at 6 months

- No statistically proven efficacy on Covid mortality
- No statistically proven efficacy on overall mortality

Results on publicly released data

- Umbalance between centres in the number of patients recruited, over 10,000 participants out of 40,000 recruited by 5 centres
  But no analysis by centre performed

- Efficacy calculated on the nucleocapsid serology assay (participants with Covid during the trial and not only

	Balance B: Benefits				R: Risks		
	Efficacy			Immunogenicity	Safety		
Criteria measured	Main criterion : first occurrence of symptomatic COVID-19 from 7 days after dose 2 *The participant had to report his/her symptoms to the site* *No PCR test planned*			Antibodies Dosage / Protection Duration	Adverse events Populations not included in the clinical trial		
Lack / Bias / Fraud in centers ⇒ Quality Indicators are all RED	No PCR test for everyone Incorrect report of symptoms No test done ⇒ No COVID Confirmation Ventavia case: participants with symptoms never called back Confirmation into ADVV SAS® dataset	Use of antipyretics to suppress symptoms that may lead to a diagnosis COVID No test done ⇒ No COVID Confirmation because of imbalance between the groups for the intake of these treatments in CSR.	Anti-nucleocapside serology results (ADVA SAS® dataset) ⇒ Efficacy calculated on the seroconversion around 55 % ⇒ Surestimation of efficacy using the choosen main criterion. + Efficacy assessed only on patients without previous SARS-COV2 (far from real life)	No data after 2 months after dose 2 in interim analyses ⇒ No possibility to conclude to a duration of protection > 3 months	No dosage between 2 months after dose 2 and 6 months after dose 2 planned into the study flowchart ⇒ Large gap between visits may have masked the drop in neutralizing antibodies confirmed a few months later	Median follow-up time of 2 months ⇒ Too short to assess mean term and long term safety	SAE not reported in the CSR Augusto Roux in the >16 yo report Maddie de Garay : not reported in the 11-15 yo report	Many unknowns cited in the Risk Management Plan Populations not studied in trial * Pregnant women ... * Immuno-comromised * Frail patients …

Violations of Good Clinical Practices (Ventavia centers, SAE not reported, missing patients, unblinded study reviews to assess deviations)

+ Main criterion not « representative » of the disease in real life

⇓

Questionnable Results = Erroneous B/R ratio

Duration of protection = 4 months

~~Helsinki declaration~~

~~95%~~

~~No safety issue~~

Bias: elements that may cause the results to deviate from their true value

Conclusions

- Authorisations given on the basis of biased results distorting the assessment of the benefit/risk ratio

- **Given the number of major biases arising from the design of the trial itself**

The results provided in the different Pfizer clinical reports, having been examined in a hurry by the different health authorities, both in terms of efficacy (symptomatic cases, severe cases...), immunogenicity, and safety **cannot be considered as honest and reliable from the point of view of Good Clinical Practices, thus biasing the evaluation of the supposedly favorable benefit/risk ratio of the Comirnaty vaccine.**

- Given the **risks identified and the information still missing**
- Given **the change in manufacturing process**
- Given **the absence of data on the process 2**

The use of Comirnaty vaccine in real life poses a **significant risk to the lives of individuals**.

- **It is therefore necessary to urgently suspend all vaccination by Comirnaty, not only for the populations on which we have no information to date, but also for the entire population while waiting for explanations from Pfizer regarding the choice of its trial design, its evaluation methods, the algorithm for calculating the efficacy criteria...**