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

To Maxime Beltra

Christine COTTON

Who am I

Biostatistician, manager of a CRO

- **Master in statistics and economy**
- 23 years for pharmaceutical industries
- Run, during 22 years , my own company : a CRO - **Clinical Research Organization : subcontractor of pharmaceutical industry, in charge of monitoring, data-management, statistics**

Experience

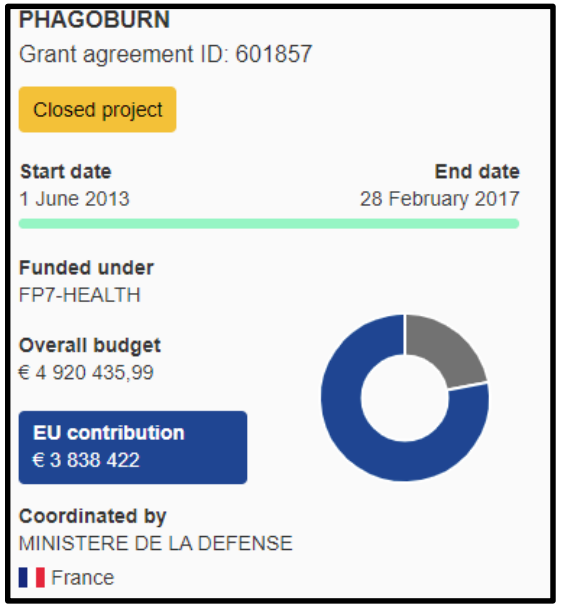
- **in all study phases and various therapeutic domains:** Allergy, Cardiology, Dermatology, Endocrinology, Gastric domain, Gynecology, Metabolism, Odontology / Dentistry,Onconlogy, ENT, Pneumology, Central Nervous System, Osteo-Muscular system, Rheumatology, Urology, Virology ..
- **Protocol statistical part, number of subjects necessary to include in a trial to conclude to efficacy**

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 ...

Statistician Expert in IDMC (Independant Data Monitoring Committee)

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



Documents used for expertise

- **Clinical study protocol:**

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

- **Clinical study reports**
  - 10/12/2021: 92 pages report https://www.fda.gov/media/144246/download
    53 pages report https://www.fda.gov/media/144245/download
  - 09/04/2021: https://www.fda.gov/media/148542/download
  - 26/10/2021: https://www.fda.gov/media/153409/download

- **Analyse cumulative des rapports d'événements indésirables postérieurs à l'autorisation du 28/02/2021**

https://phmpt.org/wp-content/uploads/2021/11/5.3.6-postmarketing-experience.pdf

- **Risk Management Plans – Last examined 26/11/2021 :**
  https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf

- **Pfizer Presentation - CDC - 22/09/2021**
  https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/02-COVID-Gruber-508.pdf

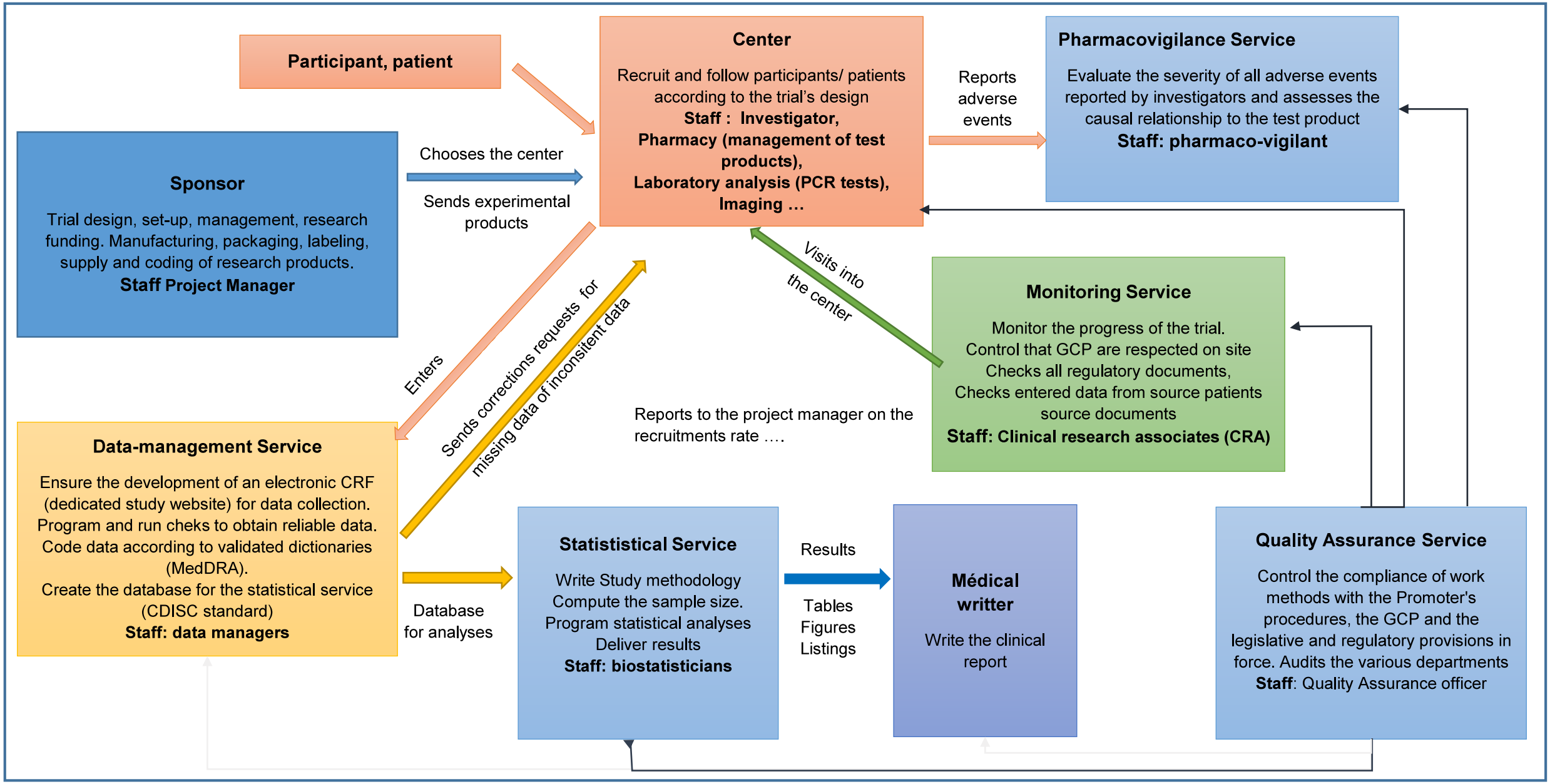
- **FDA Audit** : https://www.fda.gov/vaccines-blood-biologics/comirnaty
- **Ventavia case** : https://www.bmj.com/content/375/bmj.n2635

Regulation in clinical trials

Clinical research stakeholders

- **Sponsor** : an individual, a company, an institution, or an organization that takes responsibility for the research: pharmaceutical company …
- **Center** : place where one person is responsible for the conduct of the clinical trial, the investigator. If a trial is conducted by a team of people at one site, the investigator is the leader of the team and may be called the principal investigator.
- **Clinical Research Associates (CRAs):** they ensure the follow-up of the trial through regular visits to the investigating centers in order to verify the documents kept by the investigator and the reporting of the measured parameters in the database. They also ensure that GCP is respected. These tasks are grouped under the name of monitoring.
- **Data-managers** : they are in charge of data management, they develop a secured website in which the centers will enter the measurements made during the trial, they also ensure the control in order to obtain reliable data and the coding of adverse events according to validated dictionaries..
- **Statisticians** : they are involved as soon as the clinical study protocol (document containing all the information about the trial) is written, since they calculate the number of subjects to be included in order to be able to conclude on the efficacy, write the methodology of the analyses that will be carried out, ensure the programming of these analyses and provide all the tables, listings and graphs that will be inserted in the clinical report
- **Medical writer**: generally with a medical background, he/she writes the clinical report of the study often in collaboration with the statistician.
- **Pharmacovigilants** : they assess the **seriousness** of all adverse events reported to them by investigators and the causal link with the study product.
- **Quality Assurance**: they are in charge of writing the working methods to be followed (Standard Operating Procedures). They carry out audits of the various parties involved in order to check that the working methods comply with the laboratory's internal procedures, recommendations and legislative and regulatory provisions in force.

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/

- Guidelines for statistical methods
- Clinical trial design, choice a control group (placebo, already existent treatment…)
- Guidelines in data-management with the structure of the database
- Guidelines for management of adverse events : for high-risk products, Risk Management Plan

https://www.cdisc.org/standards

- 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)

List of Guidelines

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

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

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

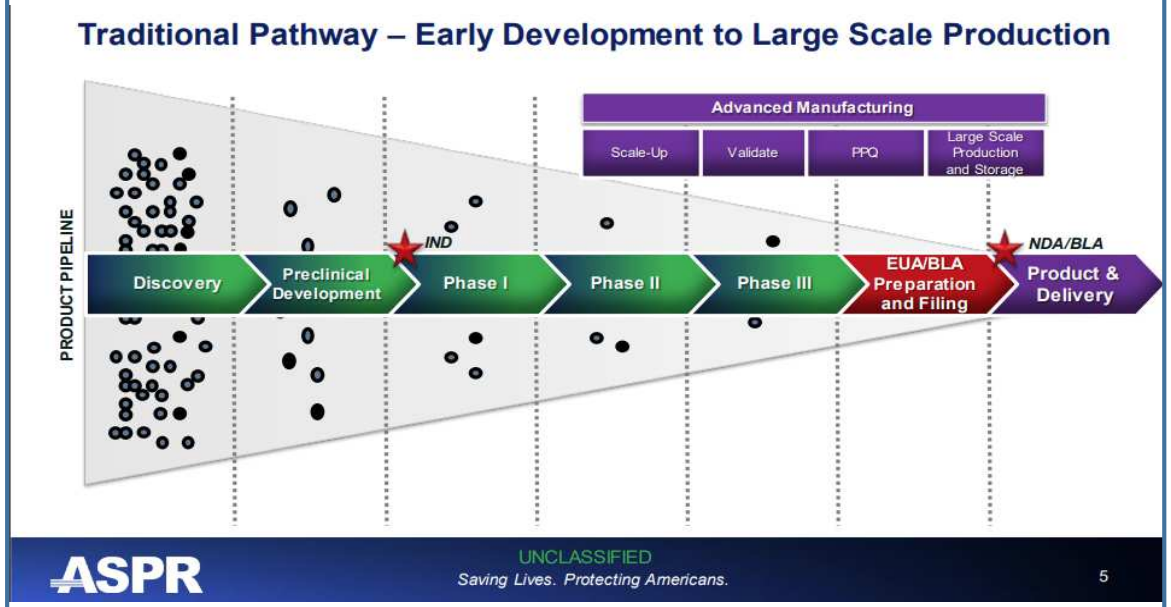
Ethnic factors

- 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

Accelerated Development of the Pfizer's COVID-19 vaccine

Accelerated development

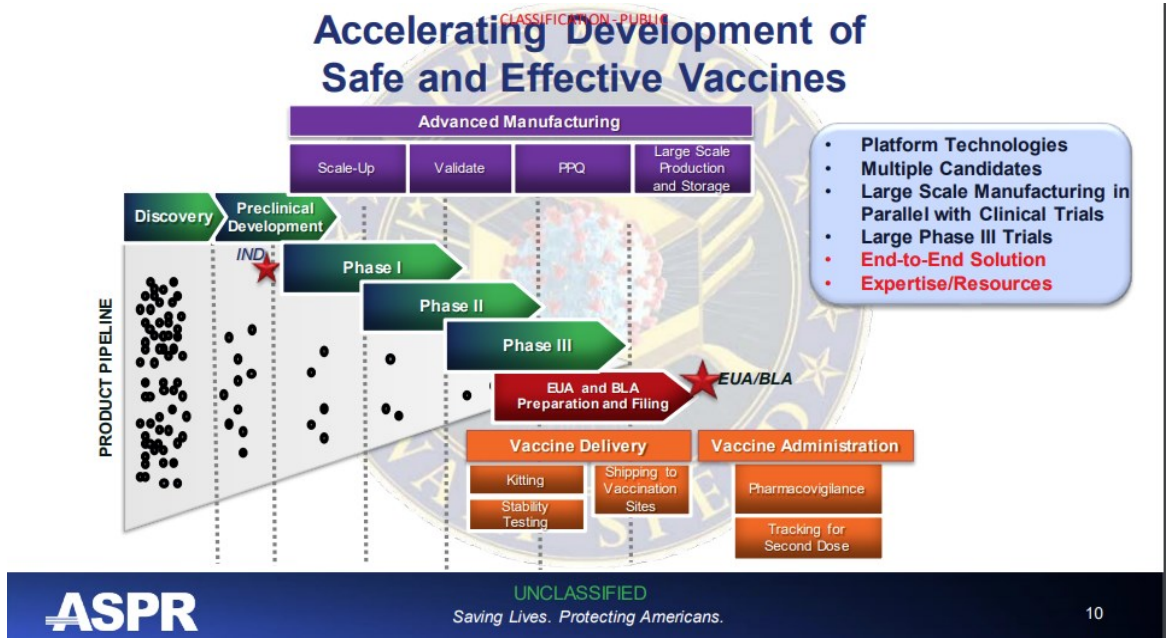
➢ Classic development



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



Pfizer press release-1

Date	Information
March 13, 2020	Five-pronged plan in the fight against COVID-19, calling on biopharmaceutical industry players to begin an unprecedented collaboration alongside Pfizer. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-outlines-five-point-plan-battle-covid-19
April 9, 2020	Pfizer and German biotech company BioNTech joined forces to develop a vaccine. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-further-details-collaboration
On April 22, 2020	**First clinical trial of a COVID-19 vaccine candidate a Phase 1/2 trial**, testing a variety of investigational vaccines in 200 healthy volunteers, ages 18 to 55 with dose escalations ranging from 1 µg to 100 µg https://www.pfizer.com/news/press-release/press-release-detail/biontech_and_pfizer_announce_regulatory_approval_from_german_authority_paul_ehrlich_institut_to_commence_first_clinical_trial_of_covid_19_vaccine_candidates
On April 29, 2020	12 participants in the German study already treated with the BNT162 vaccine candidates for the trial began on April 23, 2020. https://www.pfizer.com/news/press-release/press-release-detail/biontech-and-pfizer-announce-completion-dosing-first-cohort
On May 5, 2020	First phase 1/2 participants had been treated at New York University Grossman School of Medicine and the University of Maryland School of Medicine https://www.pfizer.com/news/press-release/press-release-detail/pfizer_and_biontech_dose_first_participants_in_the_u_s_as_part_of_global_covid_19_mrna_vaccine_development_program
June 2020	U.S. Department of Health and Human Services + FDA+ Center for Biologics Evaluation and Research issued **Recommendations for Vaccine Development**: definition post hoc of the primary efficacy endpoint for a phase 3 trial, Confirmed SARS-COV2 infection with at least one of the following symptoms : Fever, Coughing, Shortness of breath or difficulty breathing, Fatigue, Muscle or body aches, Headache, New Loss of taste or smell, Sore throat, Congestion or runny nose, Nausea or Vomiting, Diarrhea, https://www.fda.gov/media/139638/download
July 13, 2020	Pfizer/BioNtech obtained approval from the FDA to file its application via an accelerated procedure called Fast Track https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-early-positive-data-ongoing

Pfizer press release-2

Date	Information
July 20, 2020	Preliminary results for the BNT162b1 candidate being evaluated in the German Phase 1/2 trial including 60 healthy adults aged 18-55. *https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate*
July 27, 2020	After review of preclinical and clinical data from the Phase 1/2 clinical trials, and in consultation with the FDA's Center for Biologics Evaluation and Research (CBER) and other global regulatory agencies, Pfizer/BioNTech selected its BNT162b2 vaccine candidate in the Phase 2/3 study at a dose of 30 µg in a 2-dose regimen. *https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate*
August 20, 2020	Phase 1 safety and immunogenicity results on BNT162b2 at 30 µg from their ongoing U.S. study. Phase 2/3 trial : more than 11,000 participants had been enrolled. *https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-share-positive-early-data-lead-mrna*
October 6, 2020	Based on preliminary results from preclinical and early clinical studies in adults suggesting antibody production following injection of the BNT162b2 vaccine candidate, Start of discussions with the European Medicines Agency (EMA) for the BNT162b2 vaccine candidate. **Phase 3 study of BNT162b2 included 37,000 participants enrolled at 120 clinical sites** including the U.S., Brazil, South Africa and Argentina, and more than 28,000 participants had received their second dose *https://www.pfizer.com/news/press-release/press-release-detail/biontech-and-pfizer-initiate-rolling-submission-european*
December 2, 2020	The U.K. Medicines and Healthcare products Regulatory Agency (MHRA), based on the results of the interim analysis, granted emergency marketing authorization for the Pfizer/BioNtech vaccine under Regulation 174, with the companies ready to deliver the first doses to the U.K. immediately. *https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-achieve-first-authorization-world*
December 10, 2020	Efficacy results on the selected primary endpoint of COVID-19 infections from 7 days after the second dose (95% vaccine efficacy) as well as safety **results from the interim analysis of BNT162b2 in 43,448 Phase 3 clinical trial participants enrolled from more than 150 clinical trial sites in the U.S., Germany, Turkey, South Africa, Brazil and Argentina**. *https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-publication-results-landmark*

Pfizer Phase 1-2-3 trial

Characteristics of the Pfizer Phase 1-2-3 trial

- **Randomized:** experimental product attributed according to a predefined design or stratification factors
- **Controlled** : versus placebo, 0.9% saline solution
- **Blinded : for the participant, the investigator, the study coordinator and other site personnel as the physical appearance of the experimental vaccine candidates and the placebo could be different. Personnel in charge of storage, distribution, preparation and administration not blinded**
- **Phase 1,2: several doses of vaccines candidates, BNT162b2 vaccine candidate at the 30 µg dose was selected after Phase 2**
- **Multicenter : several clinical sites**
- **Primary objective of Phase 2-3: to evaluate the efficacy of BNT162b2 in preventing the development of symptomatic COVID-19 from 7 days after the second dose of vaccine in participants without pre-vaccination COVID-19 infection.**
- **Population:**
  - Initial protocol: over 18 years of age
  - Amendment 6 on September 8 allows 16-17 year olds to be included
  - Amendment 7 on October 6, 2020 expands the population to 12-15 year olds.
- **8 visits**
  - Visit 1: first dose of the experimental product on Day 1
  - Visit 2: second dose of the experimental product between 19 to 23 days after the D1
  - *Visit 3: 1 week after 2nd dose, suppressed from phase 3*
  - *Visit 4: 2 weeks after 2nd dose, suppressed from phase 3*
  - Visit 5: visit at 1 month after visit 2 (2nd dose)
  - Visit 6: visit at 6 months after 2nd dose
  - Visit 7: visit at 12 months after 2nd dose
  - Visit 8: visit at 24 months after 2nd dose

Contact participant - site

- **Connection with the site via electronic apps on participant's devices**
  - Alert in case of hospitalization of the participant.
  - Visit reminders.
  - Messages of thanks and encouragement from the study team.
  - A platform for recording local reactions and systemic events (electronic reactogenicity diary)

- **All participants: COVID-19 Electronic Illness Diary to report symptoms that could represent potential COVID-19-related illness (see Section 8.13)**

Fever	
New or increased cough	New loss of taste or smell
New or increased shortness of breath	Sore throat
Chills	Vomiting
New or increased muscle pain	Diarrhea

- **The first 6000 participants included in the Phase 3 trial : Reactogenicity Electronic Diary to report reactions to the experimental product (see Section 8.2.2 Electronic Diary) from one day after injection to 7ème days after injection, i.e., for approximately 14 days:**

Local reactions	Systemic events
Pain at the injection	Vomiting
Swelling	Diarrhea
Redness	Headache
	Fatigue/ tiredness
	Chills
	New or worsened muscle pain
	New or worsened joint pain
	Maximal oral temperature

Main Criterion Calculation

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.

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:

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

Lacks and Bias in Efficacy

Bias concerning efficacy assessment-1

- **As no PCR testing means success for the primary efficacy criterion, missing PCR are a bias. They are due to:**
  - Incomplete report of symptoms by the participant himself : errors of judgment since the participant does not have the clinical competence to assess his/her health status
  - Erroneous evaluation by the site via a telehealth consultation or a phone call for symptom which are also COVID-19 symptoms or possible reactions to the vaccine (diarrhea, vomiting, muscular pain, fever)
  - Use of antipyretics which suppress symptoms : imbalance between the groups for the intake of these treatments (≈ 3 to 4 times higher in the vaccine group).
  - No answer from the site : see the Ventavia affair

- **2 reports on December 10, 2020, one with 92 pages, one with 53 pages which contains a section on suspected COVID-19 cases but not confirmed. Why ?**

409 cases for the BNT162b2 and 287 cases for placebo

Note: With less than 50% efficacy, the vaccine would not have been suitable for emergency use as the "Development and Licensure of Vaccines to Prevent COVID-19" document specified that a vaccine efficacy greater than 50% is necessary to obtain an emergency use. This makes the suspected but unconfirmed cases of covid-19 even more suspect.

Pfizer-BioNTech COVID-19 Vaccine
VRBPAC Briefing Document

Suspected COVID-19 Cases

As specified in the protocol, suspected cases of symptomatic COVID-19 that were not PCR-confirmed were not recorded as adverse events unless they met regulatory criteria for seriousness. Two serious cases of suspected but unconfirmed COVID-19 were reported, both in the vaccine group, and narratives were reviewed. In one case, a 36-year-old male with no medical comorbidities experienced fever, malaise, nausea, headache and myalgias beginning on the day of Dose 2 and was hospitalized 3 days later for further evaluation of apparent infiltrates on chest radiograph and treatment of dehydration. A nasopharyngeal PCR test for SARS-CoV-2 was negative on the day of admission, and a chest CT was reported as normal. The participant was discharged from the hospital 2 days after admission. With chest imaging findings that are difficult to reconcile, it is possible that this event represented reactogenicity following the second vaccination, a COVID-19 case with false negative test that occurred less than 7 days after completion of the vaccination series, or an unrelated infectious process. In the other case, a 66-year-old male with no medical comorbidities experienced fever, myalgias, and shortness of breath beginning 28 days post-Dose 2 and was hospitalized one day later with abnormal chest CT showing a small left-sided consolidation. He was discharged from the hospital 2 days later, and multiple nasopharyngeal PCR tests collected over a 10-day period beginning 2 days after symptom onset were negative. It is possible, though highly unlikely, that this event represents a COVID-19 case with multiple false negative tests that occurred more than 7 days after completion of the vaccination regimen, and more likely that it represents an unrelated infectious process.

Among 3410 total cases of suspected but unconfirmed COVID-19 in the overall study population, 1594 occurred in the vaccine group vs. 1816 in the placebo group. Suspected COVID-19 cases that occurred within 7 days after any vaccination were 409 in the vaccine group vs. 287 in the placebo group. It is possible that the imbalance in suspected COVID-19 cases occurring in the 7 days postvaccination represents vaccine reactogenicity with symptoms that overlap with those of COVID-19. Overall though, these data do not raise a concern that protocol-specified reporting of suspected, but unconfirmed COVID-19 cases could have masked clinically significant adverse events that would not have otherwise been detected.

https://phmpt.org/wp-content/uploads/2021/11/5.3.6-postmarketing-experience.pdf

Bias concerning efficacy assessment-2

« 5.3.6 Cumulative Analysis of Post-authorization Adverse Event Reports » provides an analysis of cumulative U.S. and international post-authorization safety data and a cumulative analysis of identified significant risks, significant potential risks, and Missing Information from **December 01, 2020 to February 28, 2021**.

It appeared as early as February 2021 that it would be relevant to question the **real protection of the vaccine since the post-vaccination infection rate in the adverse events reported was of 4.6% (vaccine failure), hence more than 100 times equal to the infection rate of the clinical trial which was 0.044%.**

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])	VE (%)	(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

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

Table 2. Events Reported in ≥2% Cases

MedDRA SOC	MedDRA PT	Cumulatively Through 28 February 2021 AEs (AERP%) N = 42086
	Pain	3691 (8.8%)
	Malaise	2897 (6.9%)
	Asthenia	2285 (5.4%)
	Drug ineffective	2201 (5.2%)
	Vaccination site erythema	930 (2.2%)
	Vaccination site swelling	913 (2.2%)
	Influenza like illness	835 (2%)
Infections and infestations		
	COVID-19	1927 (4.6%)
Injury, poisoning and procedural complications		
	Off label use	880 (2.1%)
	Product use issue	828 (2.0%)
Musculoskeletal and connective tissue disorders		
	Myalgia	4915 (11.7%)
	Pain in extremity	3959 (9.4%)
	Arthralgia	3525 (8.4%)
Nervous system disorders		
	Headache	10131 (24.1%)
	Dizziness	3720 (8.8%)
	Paraesthesia	1500 (3.6%)
	Hypoaesthesia	999 (2.4%)
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	2057 (4.9%)
	Cough	1146 (2.7%)
	Oropharyngeal pain	948 (2.3%)
Skin and subcutaneous tissue disorders		
	Pruritus	1447 (3.4%)
	Rash	1404 (3.3%)
	Erythema	1044 (2.5%)
	Hyperhidrosis	900 (2.1%)
	Urticaria	862 (2.1%)
Total number of events		**93473**

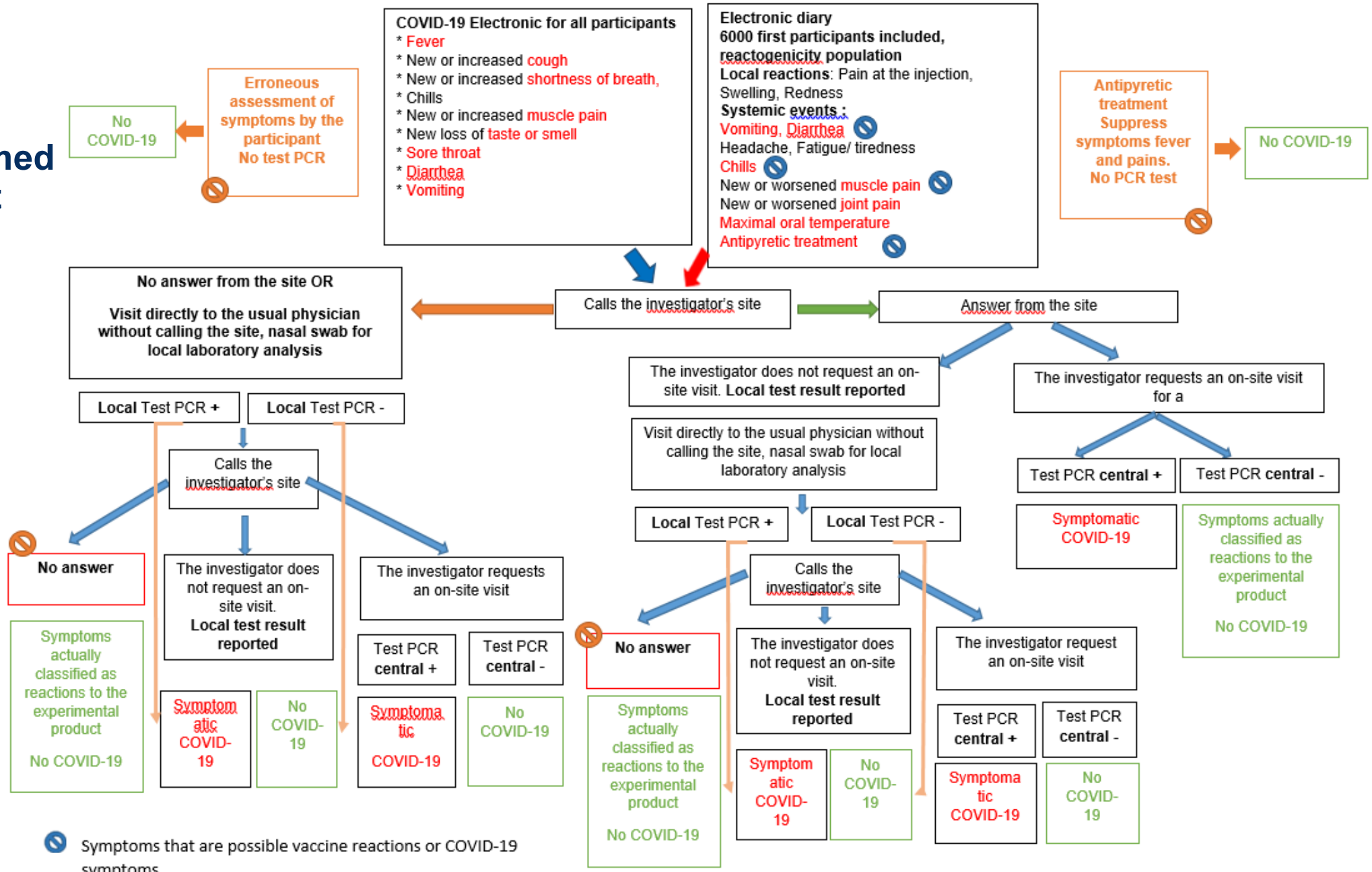
https://phmpt.org/wp-content/uploads/2021/11/5.3.6-postmarketing-experience.pdf

Bias concerning efficacy assessment-3

- The method used to identify symptomatic COVID-19 cases inevitably leads to **a questionable estimate of the actual number of symptomatic COVID-19 cases, making the conclusions of the demonstrated vaccine efficacy unreliable**
- To deal with these multiple biases in counting the number of symptomatic COVID-19 cases, it would have been much more appropriate **to perform PCR testing not only for participants reporting symptoms, but for the entire population included** in the clinical trial.
  This would also have allowed the detection of asymptomatic COVID-19s that are also vectors of the disease.
- This way of managing the participants in their clinical trial is therefore very surprising since any person with COVID-19, even if asymptomatic, **could infect those around him/her, transmitting a potentially fatal disease, which obviously did not worry the laboratory much,**
- Furthermore, any efficacy demonstrated on the primary endpoint chosen refers only to symptomatic cases and not to all COVID-19 cases, as asymptomatic cases are excluded from the efficacy criteria presented, so **such an endpoint cannot claim to demonstrate that the vaccine prevents transmission of COVID-19**

- **Any communication to promote vaccination on the basis of such an argument is therefore not supported by any scientific evidence.**

Process to assess a + Covid-19 Case confimed by PCR test



Christine COTTON – 23/02/2022 ©

Lacks and Bias in Safety

Bias concerning SAFETY assessment-1

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/148542/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)

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

Bias concerning SAFETY assessment-2

Incomplete detection of adverse events into the clinical trials and serious adverse events not reported in the 12-15 yo clinical study report

- **Maddie de Garay, 12 years old at the time of her voluntary participation in the Phase 3 trial**
  - Multiple adverse events after receiving the second dose of vaccine (severe abdominal and chest pain, gastroparesis, nausea, vomiting, erratic blood pressure, heart rate, and loss of memory);
  - Today, still in severe condition, as she is tube-fed and cannot walk intermittently.
  - This serious effect was never reported in the clinical report on the 12-15 year old population. *https://www.foxnews.com/media/ohio-woman-daughter-covid-vaccine-reaction-wheelchair*

- **Sample size of the young population (5 to 11) "is too small to detect potential risks of myocarditis associated with vaccination."** (see page 11 of the report).

BNT162b2
VRBPAC Briefing Document

Overall Risk-Benefit Conclusions

COVID-19 continues to be a serious and potentially fatal or life-threatening infection for children and there is a significant unmet medical need in the 5 to <12 years of age population.

Two primary doses of the 10 µg BNT162b2 vaccine given 3 weeks apart in 5 to <12 years of age have shown a favorable safety and tolerability profile, robust immune responses against all variants of concern and high VE against symptomatic COVID-19 in a period where the delta variant was predominant.

The number of participants in the current clinical development program is too small to detect any potential risks of myocarditis associated with vaccination. Long-term safety of COVID-19 vaccine in participants 5 to <12 years of age will be studied in 5 post-authorization safety studies, including a 5-year follow-up study to evaluate long term sequelae of post-vaccination myocarditis/pericarditis.

Israeli safety surveillance databases suggest that incidence rates of rare post-vaccination myocarditis peaks in individuals 16 to 19 years of age males and declines in adolescents 12 to 15 years of age. In addition, the dose for children 5 to <12 years of age is 1/3 of the dose given to older vaccinees (10 µg vs. 30 µg). Based on this information, it is reasonable to predict that post-vaccine myocarditis rates are likely to be even lower in 5 to <12 years of age than those observed in adolescents 12 to 15 years of age.

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

Bias concerning SAFETY assessment-3

- **Short duration of observation of the participants does not allow for the evaluation of long-term safety, which is mentioned in**
  - **The Clinical Study Report-April 9, 2021 –** Unknown benefits and data gaps
  - **the "Comirnaty Risk Management Plan"** for months in chapter SVII.3.2 "Presentation of the Missing Information

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.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Comirnaty is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Comirnaty are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Comirnaty. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 64. List of Important Risks and Missing Information

Important identified risks	Anaphylaxis 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

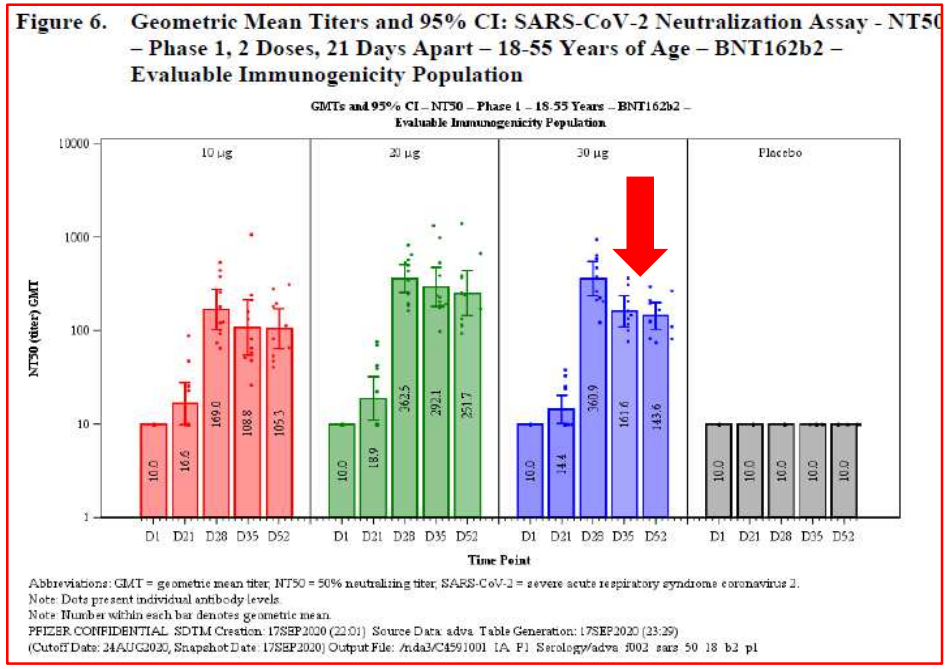
Lacks and Bias in Immunogenecity

Bias concerning IMMUNOGENICITY assessment

The design of the trial ***contributed to masking the drop in antibodies*, which was however predictable from the first report in December 2020**

The short duration of participant observation presented in the various clinical reports and the results of the assays **did not support a duration of protection greater than 3 months**

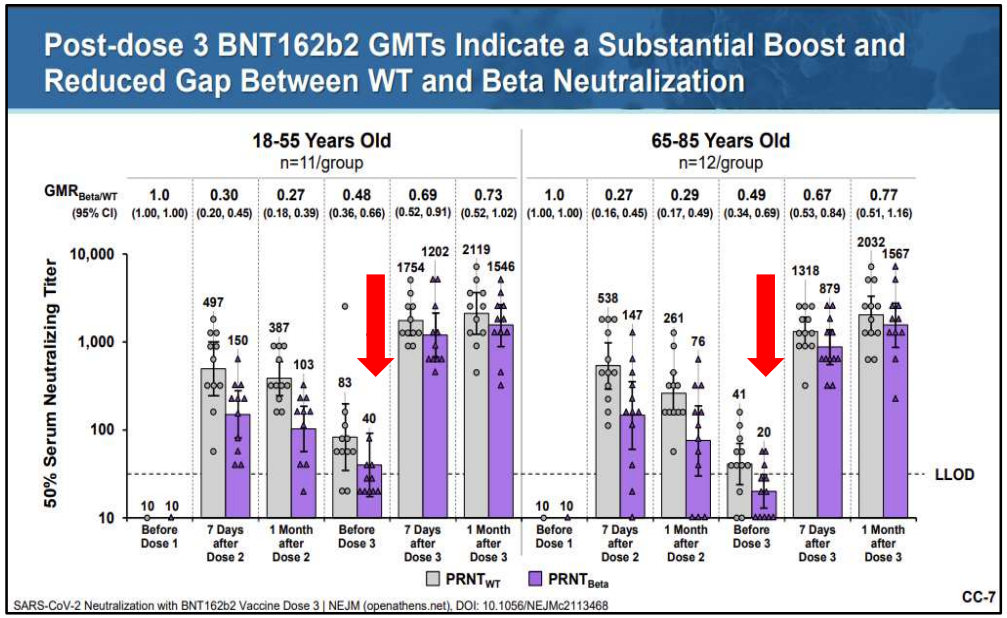
- The neutralizing antibody graphic presented in the December 10, 2020 report, **already indicated a decrease in immunity at less than 2 months after the second dose**.
- Intermediate dosages have deasapeared from other reports



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*" (see page 20).

Booster dose to compensate the wane of protection

Boost already planned in December 2020 (mentionned in HAS)



https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-09-22/02-COVID-Gruber-508.pdf

Risks and missing information

No impact on transmission

- Pfizer recognizes here, the **impotence of its vaccine to act against asymptomatic infections and thus to slow down the transmission of the virus**, the main criterion chosen not being able to claim any effectiveness in this matter.

Mentionned in the HAS letter in December 2020

No impact on transmission

Also see EMA

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

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

Risks and missing information

- **Missing information in the November 2021 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 — November 2021

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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	Use in patients with autoimmune or inflammatory disorders
	Interaction with other vaccines
	Long term safety data

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

Summary of Bias and Quality Issues

Doubts about data quality Of Data

- According to an article in the British Medical Journal, Ms. Brook Jackson, a regional director with 20 years of experience in coordinating and managing clinical trials, hired by CRO Ventavia Research Group (https://www.ventaviaresearch.com/) on September 7, 2020 to oversee operations, recruitment and quality assurance of the company's clinics, has reported **serious breaches of Good Clinical Practices and other reprehensible practices**
  - storage of products at the wrong temperature,
  - lack of respect for anonymization,
  - errors in handling samples,
  - chaotic follow-up of serious adverse events .....
  - **not having performed PCR tests for all participants with COVID-19 symptoms to validate or not the presence of the case.**

    ➡ **confirmation of bias in main criterion results**

- The former research director, although experienced, was **fired by her employer the day she filed her official complaint with the FDA,** on September 25, 2020, reporting to the authorities all the serious failures and problems encountered within Ventavia Research Group.

The Ventavia case only concerns **3 centers having included 1000 participants but, if the facts are proven, this highlights uncertainties** about the laboratory's training, supervision and monitoring of the centers, as well as uncertainties about the quality of the centers' follow-up of participants, leading to an under-estimation of the number COVID-19 symptomatic cases, the main criterion of the study.

This also throws suspicion on the management of all the other centers.

https://www.bmj.com/content/375/bmj.n2635

Christine COTTON

23/02/2022 ©

Balance B Benefit

Efficacy

Immunogenicity

R Risk

Safety

Criteria measured	Main criterion : first occurrence of symptomatic COVID-19 from 7 days after dose 2 *The participant to report his/her symptoms to the site*	Antibodies Dosage / Protection Duration	Adverse events
Lack or Bias → Quality Indicators are all RED	Incorrect report of symptoms No test done → No COVID Confirmation because of imbalance between groups for symptoms. Non confirmed by PCR test	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.	No answer from the site → No test done → No COVID Confirmation Ventavia, participants no called back
	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 → Large gap between visits may have masked antibody drop	
	Median observation time of 2 months → Too short to assesse mean term and long term safety	Sample size too small to highlight severe cases, especially on 12-15 year olds and Maddie de Garay : serious adverse event (invalidity) not reported 5-11 year olds (≈ 2300)	Many unknowns cited in the RMP Because pop not studied in trial Pregnant women ...

Questionnable Results → Erroneous B/R

~~95~~ %

Duration of protection 4 months

No safety issue

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

Conclusion

Conclusion

- **Given the number of major biases arising from the design of the trial itself**
  - timing of planned visits, method of reporting symptoms suggestive of respiratory infection, method of reporting adverse events, no antibody test between 2 and 6 months after dose 2 …),
  - the methods of analysis (intermediate analyses over a shortened follow-up time), and
  - the **major deviations from Good Clinical Practice that are more than likely to occur in the investigating centers**, given the multitude of recommendations

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**

Continued 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...**
- **In addition, the achievement of vaccine herd immunity is statistically not proven and not demonstrable on the basis of this trial.**