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

Version #2

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1 Introduction

Since December 2019, Coronavirus, Severe Acute Respiratory Syndrome (SARS-COV-2) has spread rapidly across the globe from Wuhan Province, China.

The World Health Organization (WHO) has declared a global pandemic on March 11, 2020.

Many pharmaceutical companies have been racing to find a vaccine since the publication of the SARS-COV-2 genome by China on January 12, 2020, when the complete sequence of the coronavirus genome was detected in samples taken from their first patients. On January 29, 2020, the Pasteur Institute announced the virus' genome sequencing based on material collected from two of the first three confirmed cases in France.

Source : https://www.pasteur.fr/fr/espace-presse/documents-presse/institut-pasteur-sequence-genome-complet-du-coronavirus-sars-cov-2

On March 16, 2020, the U.S. National Institute of Health began a trial of an "experimental" vaccine in collaboration with the biotechnology company Moderna Inc, with the trial involving 45 healthy adults, ages 18-55.

Source : https://fr.euronews.com/2020/06/30/coronavirus-les-dates-cles-de-la-course-au-vaccin

As of April 8, 2020, at least 115 vaccines were already in the pipeline worldwide, with 73 already in the exploratory or preclinical stage, with Inovio, Moderna, CanSino Biologicals, and the Shenzhen Genoimmune Medical Institute leading the way.

Source : https://www.nature.com/articles/d41573-020-00073-5

In May 2020, Operation Warp Speed in the United States, initially a public/private partnership initiated by the U.S. government, was transferred to the White House covid-19 response team in order to promote mass production of several vaccines and new technologies.

This has presented unique practical and ethical challenges for those working in the clinical trials industry.

This report is intended to be an objective analysis of clinical trials practices compared to those used in the COVID-19 trials and specifically in the Pfizer/BioNtech Phase 1-2-3 trial.

It does not argue about the regulatory processes of vaccine manufacturing or preclinical studies, each of which would deserve a full report.

It does not call into question the competence or the involvement of the thousands of people involved in the trials, but rather the **respect of Good Clinical Practices, an essential element in the world of the pharmaceutical industry in order** to obtain honest and reliable statistical results and to be able to evaluate the benefit/risk ratio.

2 Who I am

Training

- Master in Statistics and Economy – University of Toulouse
- Masters in Financial Markets and Intermediaries - University of Toulouse

Experience

- Founder and director of a contract research company, subcontractor of the pharmaceutical industry (CRO - Clinical Research Organization) for 22 years.
- Management of Biometrics activities on behalf of laboratories in the context of clinical trials: Monitoring, Data management and Biostatistics

Skills

- Clinical trial methodology
- Writing of statistical parts of clinical trial protocols,
- Calculating the number of subjects to include in a trial
- Development of randomization lists
- Setting up websites to collect clinical trial data
- Coding of adverse events using the MedDRA dictionary
- Expert statistician for interim analyses (DSMB Data Safety Management Board)
- Programming of statistical analyses in SAS®.
- CRO Quality Assurance: drafting of standard operating procedures according to pharmaceutical industry recommendations, monitoring of quality policy

Customers

- More than 500 clinical trials, observational surveys, Temporary Use Authorization (TUA), Temporary recommendations for use (TRU)
- Various therapeutic areas: oncology, dermatology, central nervous system, gastrointestinal system, autoimmune diseases, osteoarticular system, odontology, pneumology, ophthalmology, nutrition ...

- Various: 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 ...

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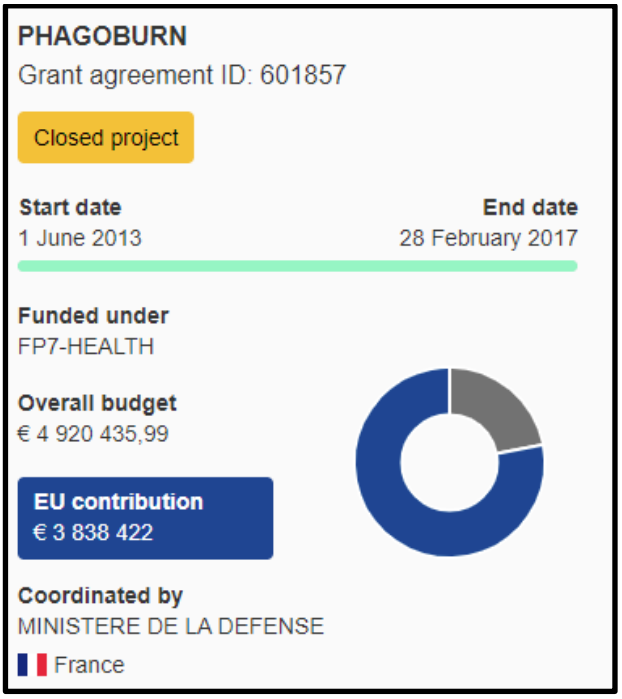
Last study managed

PHAGOBURN, a project conducted from 2013 to 2017 and funded by the European Commission with 4.9 million euros. It is the first study in the world to have rigorously evaluated, compared to a reference treatment, the efficacy of bacteriophages produced according to pharmaceutical standards to treat bacterial infections. The patients were hospitalized in 11 burn centers in France, Belgium and Switzerland and were suffering from burns (due to P. aeruginosa). The Percy BTC alone included 40% of the patients. In the end, bacteriophages have effectively demonstrated their capacity to eliminate target bacteria, with several limitations that are instructive.

Illustration 1 : Phagoburn project financing by Europe



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

Clinical trial registration :
https://clinicaltrials.gov/ct2/show/NCT02116010?term=phagoburn&draw=2&rank=1

Articles about this trial :

https://www.mypharma-editions.com/la-cro-statitec-pilote-les-essais-cliniques-du-projet-europeen-phagoburn

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30482-1/fulltext

https://www.defense.gouv.fr/sante/actualites/phagoburn-des-virus-pour-traiter-des-infections-bacteriennes

Illustration 2 : Example of managed studies

Title of the study
Phase III, multicenter, randomized, European trial - Efficacy, pharmacokinetics and safety of X in infants less than 90 days old with **clinical sepsis**
Phase III, randomized, 3-arm, parallel patient trial of X versus Y efficacy and safety in **osteoporotic postmenopausal women**: a 2-year open-label study
Randomized, multicenter, phase III trial comparing two strategies brain radiotherapy followed by chemotherapy to chemotherapy alone in patients with **non-squamous non-small cell lung cancer** with asymptomatic brain metastases
Phase III, randomized, multicenter, placebo-controlled study evaluating the effect of monthly oral X on in vivo bone micro-architecture parameters, measured by peripheral micro CT scan in **osteopenic postmenopausal women**
Phase III trial, X versus Y as induction therapy prior to Autologous Stem Cell Transplantation in patients with newly diagnosed **multiple myeloma**
Phase III, randomized, open-label, parallel-group trial - Equivalence, efficacy and safety of X versus Y in **seborrheic dermatitis** of the face
Phase III, multicenter, randomized, double-blind, placebo-controlled trial - Efficacy of X in the recovery of **neurological disorders after stroke**
Phase III, randomized, double-blind, equivalence study of X versus placebo for the treatment of **seasonal allergic rhinitis**
Randomized Phase III Trial - The Value of Maintenance Treatment with X after Autologous Stem Cell Transplantation in **Myeloma Patients** Under 65 Years of Age
Phase II, multicenter, open-label trial - Efficacy of Y in patients with progressively relapsed or **refractory multiple myeloma** with a karyotypic abnormality by 17p deletion or translocation (4;14)
Phase II, multicenter, open-label, randomized, parallel-group trial - Efficacy of X versus placebo in the treatment of **anal fissure**
Phase II, randomized, double-blind, controlled, efficacy versus efficacy trial in patients with **Friedreich's ataxia**
Phase II, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial - Efficacy and safety of X for **migraine prophylaxis**
Phase II, single-center, randomized, double-blind, parallel group trial - Efficacy and safety of X versus placebo in patients with active **ophthalmopathy**
Phase II, randomized, double-blind, effect of X versus placebo on cerebral glucose metabolism in elderly patients with memory impairment, **mild Alzheimer's disease**
Randomized, open-label, non-comparative, multicenter phase II trial of sequential X plus Y versus Z alone as second-line therapy in patients with progressing stage IV **non-small cell lung cancer**
Phase I-II, multicenter, randomized, European trial. Safety of X in infants less than 90 days old with **meningitis**
Phase I/II trial – Randomized. Determination of the maximum tolerated dose, safety, pharmacokinetics and antitumor activity of X combined with concurrent chemoradiotherapy in patients with **squamous cell carcinoma of the head and neck**
Effects of X, Y, Z and placebo on driving performance in 16 healthy volunteers, double-blind Latin square

Title of the study
Phase II, multicenter, trial to evaluate the efficacy and safety of X in stabilizing tumor growth in patients with **neuroendocrine tumors**
Phase I, open-label trial to study the influence of repeated doses of X on the pharmacokinetic profile in healthy volunteers
Phase I, randomized, placebo-controlled trial to study the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple oral doses of Y
Phase I trial:Pharmacodynamic effects on alertness of a single oral dose of X (20 mg, 50 mg or 100 mg) versus Y (200 mg) in healthy subjects during **sleep deprivation**
Pharmacodynamic study of the effect of oral alpha2 antagonist X with or without exercise on lipolysis in **obese subjects**". Double-blind, cross-over, randomized, placebo-controlled study
Open-label, non-comparative, multicenter study of the efficacy, safety, and pharmacokinetics of the 22.5 mg formulation of X in patients with **central precocious puberty**
Evaluation of gastric emptying rate during **colonic preparation** with Y®
Open-label, non-controlled, multicenter, long-term follow-up study of insulin therapy in patients with **type 1 diabetes**
Impact of continuous glucose monitoring system on glycemic control in **diabetic hemodialysis patients**
An open-label, non-comparative, multi-center study of the efficacy, safety, and pharmacokinetics of the 22.5 mg formulation of X in patients with **central precocious (gonadotropin-dependent) puberty**
Bioequivalence study of x (30 mg) after single oral administration: comparison of two tablets manufactured by different processes. Single-dose, open-label, randomized, crossover study in healthy young male volunteers
Evaluation of the efficacy of X 10% against natural infestations of Neotrombicula autumnalis in dogs
Effect of X versus placebo on detrusor overactivity in **women with mixed incontinence**. A double-blind randomized controlled trial
Tolerance and efficacy of X in the treatment of moderate to **severe obstructive sleep apnea syndrome** in adults
Treatment of adult patients with **locally advanced or metastatic non-small cell lung cancer** with EGFRm+ and T790M mutations who have progressed during or after treatment with an EGF receptor tyrosine kinase inhibitor
Efficacy and tolerance of X in adult **seborrheic dermatitis**
Open-label, multicenter, randomized clinical trial comparing the efficacy and safety of X in subjects with **type 1 diabetes mellitus**
Medico-economic evaluation of the value of X in treated **multiple myeloma** patients under 65 years of age
Study of the effect of X on the **salivary bacterial load**
Efficacy and safety of X versus Placebo in **telogenous effluvium** - Multicenter, double-blind, randomized study in two parallel groups
Efficacy and safety study of X versus placebo in the local treatment of adult **periodontitis**

Title of the study
Efficacy and safety study of X versus Y in the treatment of **contact dermatitis, psoriasis and lichenification**
Evaluation of the analgesic effect of X- Study on capsaicin-induced **pain model**
Phase IV, open-label, multicenter, non-comparative trial of the efficacy and safety of X in **cervical dystonia**
Phase IV, multicenter, open-label, non-comparative trial to evaluate the efficacy and tolerability of X in the treatment of **dynamic equinus foot deformity** in young children with cerebral palsy
Randomized, parallel-group, open-label study of local tolerance and **behavior** in patients using nicotine chewing gum versus X
Efficacy and tolerance of X on vulvitis observed in cases of **vulvovaginal candidiasis**
Study of intestinal permeability and rectal sensitivity in patients with **irritable bowel syndrome** with visceral hypersensitivity treated by X
Efficacy, local tolerance and acceptability of a moisturizing emollient in patients undergoing maintenance **renal dialysis with xerosis**
…..
Observational study : Clinical, bacteriological and respiratory functional profiles of patients consulting a general practitioner for an exacerbation of **chronic bronchitis**
Observational study: Real-life conditions of use of sodium phosphate tablets for **colon cleansing before colonoscopy**
Observational study in medicine of the priority handicap and behavior of patients suffering from **painful osteoarthritis** of the lower limbs
Observational study of the criteria determining the adaptation of estradiol dosage during the first 9 months of hormone replacement therapy
Observational study: Evaluation of Therapeutic Strategies in **Coronary Patients** and Observation of the Influence of Risk
Observational Study Description of **Recurrent Sinusitis**
Observational study Management of lower limb **osteoarthritis** flare-ups in private practice
Observational Study: Description of prognostic factors for the occurrence of febrile neutropenia during Granulocyte-Cellular Growth Factor (G-CSF) initiation in patients receiving chemotherapy for **Breast Cancer**
Observational study: Description of risk and protective factors at the time of diagnosis of **Alzheimer's disease**
Observational study: Determination of the profile of patients with a **pregnancy** under treatment X®
Observational study: Description of the semiology of **chronic cancer pain** in patients with background opioid treatment and paroxysmal pain attacks
Observational study Management of memory complaints and diagnosis of **Alzheimer's disease**
Observational study: Description of psychotic symptomatology in the elderly
Observational study: Description of depressive symptomatology at the initial diagnosis of **Alzheimer's disease**

Title of the study
Observational study: Initiation of appropriate symptomatic treatment in patients with **Alzheimer's disease**
Observational study: Interest of a therapeutic contract in **diabetic patients** treated with Proton Pump Inhibitors "on demand"
Observational study describing the role of the caregiver in the accompaniment of patients with **multiple sclerosis** treated with subcutaneous X from three perspectives: neurologist, patient and caregiver
Observational study: Prevalence of oropharyngeal events according to type of inhaled corticosteroid therapy
Observational study: Assessment of **asthma and COPD** control by use of inhaled rescue bronchodilator therapy by X
Observational study on **mucovisidosis**
Evaluation in real situation of use of the new formula X cream
Observational study - Study of physicians' therapeutic attitudes in **hypertensive patients** who have failed a calcium channel blocker monotherapy
Observational study: Cohort study of patients treated with X combined with a diuretic, for non-controlled **hypertension** in general practice and cardiology
Observational, descriptive, cross-sectional study with real patients conducted among a sample of the population of dermatologists and their patients with predominantly **erythematotelangiectatic rosacea**
Observational study - Risk factors for **bullous pemphigoid**
Large-scale study of DNA copy number variations and gene expression profile of bone marrow plasma cells from monoclonal gammopathies of undetermined significance (MGUS) and indolent myeloma (IMM). Search for correlations with evolutionary risk in order to establish a predictive model of early malignant transformation
Study of the immunological function and phenotype of peripheral Natural Killer cells and other blood subsets from healthy volunteers
Observational study - Management of patients with breast cancer: evaluation of the supported pathway implemented at the Institut du Sein
Observational study on compliance with immunosuppressive therapy after **renal transplantation** in patients with access to a software to manage organ transplants
…..
TUA - Treatment of adult patients with **locally advanced or metastatic non-small cell lung cancer**, carrying EGFRm+ and T790M mutations, who have progressed during or after treatment with an EGF receptor tyrosine kinase inhibitor
TUA - Treatment of **advanced metastatic prostate cancer** (castration-resistant) in adult patients who have received prior X
TUA - Treatment of **chronic hepatitis C** due to HCV genotype 1, in adult patients with compensated liver disease and documented cirrhosis (F4)
TUA - Treatment of **HIV-1** infection in adults
TUA - Treatment of multidrug-resistant pulmonary **tuberculosis** (MDR-TB) in adult patients, when the use of another effective treatment regimen is impossible due to resistance or intolerance

Title of the study
TUA - Treatment of **chronic hepatitis** C due to genotype 1 or 4 virus, in combination with other drugs, in adult patients with advanced disease (with F3/F4 hepatic fibrosis or with extrahepatic manifestations of HCV)
TUA - Treatment of adult patients with relapsed or refractory **mantle cell lymphoma** with chronic lymphocytic leukemia who have received at least one prior therapy, or as first line therapy in case of 17p deletion or TP53 mutation
TUA - Treatment of proliferative childhood **hemangiomas** with life-threatening or functional risks, and ulcerated hemangiomas not responding to simple care, in children not eligible for inclusion in a clinical trial
TUA - Treatment of adult patients with active, moderate to severe **ulcerative colitis or Crohn's disease** who have had an inadequate response or loss of response to conventional therapy and anti-TNFα (tumor necrosis factor-alpha antagonist) or who have been intolerant to these treatments

Note:

TAU: Temporary Use Authorization
French procedure created in 1986 that allows certain categories of patients to use drugs that have not yet been marketed. It was split into early access authorizations and compassionate access authorizations (AAC) in July 2021, is a

TRFU: Temporary recommendations for use
Same mechanism as for TAU for products that have been granted marketing authorization but are not yet covered by the health insurance system

3 From molecule to drug, the obstacle course

3.1 The phases of drug development

Medicines undergo an extremely long and tedious life cycle, passing through several regulated stages to ensure their quality, safety and effectiveness for patients.

3.1.1 Basic research

Out of 10,000 molecules screened during the exploratory research stage, only 10 drug candidates will be patented and one will pass all the stages of testing and clinical trials to become a drug: the path from innovation to patient is thus long, complex and costly.

Basic research is the stage during which thousands of molecules likely to be of therapeutic interest are selected in order to retain only those that could become potential drug candidates. It is during this phase that the galenic development begins, which defines the formulation and manufacturing choices.

This stage can last from 2 to 3 years.

3.1.2 Pre-clinical studies

Preclinical studies are an essential step in the development of drugs or vaccines and are part of a multi-stage testing strategy. This phase evaluates the efficacy and safety of the vaccine in animal and cell models (in vitro) before moving on to human trials.

Preclinical trials consist of the following

- **Toxicity studies** on the potential of the product to cause
    - and possible effects on the lymph nodes,
    - systemic toxicity (effects on different organs) and on the immune system.
- **Pharmacokinetic studies** studying the distribution of the product after injection in the different organs, its metabolism and its elimination**.**

This phase can be completed by studies on development and fertility, as well as studies on genotoxicity and carcinogenicity. Mutagenicity is also considered in the case of new adjuvants or additives.

This preclinical phase is important because it will determine the indicators to be followed in future clinical trials in humans.

These animal models are not perfect and often fail to predict immunogenicity (ability to develop immunity) and efficacy in humans, which will only be assessed in subsequent clinical trials. Furthermore, the absence of detectable toxicity in animal studies does not mean that a drug/vaccine will be safe for humans.

3.1.3 Clinical trials

There are four distinct evaluation phases, each of which results in a different clinical trial.

- **Phase I :**

Phase I clinical trials involve a small number of healthy volunteers and are designed to test the safety of the drug in humans. These are proof-of-concept studies of the mechanism of action. They mainly study the pharmacological effects (dose ranges, Maximum Tolerated Dose) and pharmacokinetic parameters in humans. They can last from several weeks to several months.

- **Phase II :**

Phase II clinical trials take place if the results of Phase I are conclusive and safe for humans. They consist of testing the efficacy of the drug and determining its optimal dosage (several doses tested) in sick patients, the dose chosen being an effective dose with the least possible harmful side effects.

- **Phase III :**

The purpose of Phase III clinical trials is to confirm efficiency by comparing the efficiency of the new drug to the reference treatment (when it exists) and/or to a placebo (when no treatment exists) and to evaluate its tolerance.

This phase involves a large number of patients recruited in several countries, by dozens of different doctors, and may last several years. The aim is to evaluate the benefit/risk ratio of the drug being tested and the precautions to be taken when using it due to its various side effects. During this phase, trials relating to industrial development and the mode of administration and packaging (capsules, tablets, syrup, etc.) are also carried out.

It is at the end of Phase III that the reports are submitted to the health authorities for marketing authorization (MA), the verification process by the regulatory authorities generally last from 12 to 18 months. The marketing of the drug is not authorized until the authorities are satisfied and issue a marketing authorization.

Many countries also require cost-effectiveness studies of the new drug, which will help the government or insurance companies to make recommendations and decide whether the drug should be obtained by prescription, and whether it should be reimbursed by the country's health insurance system.

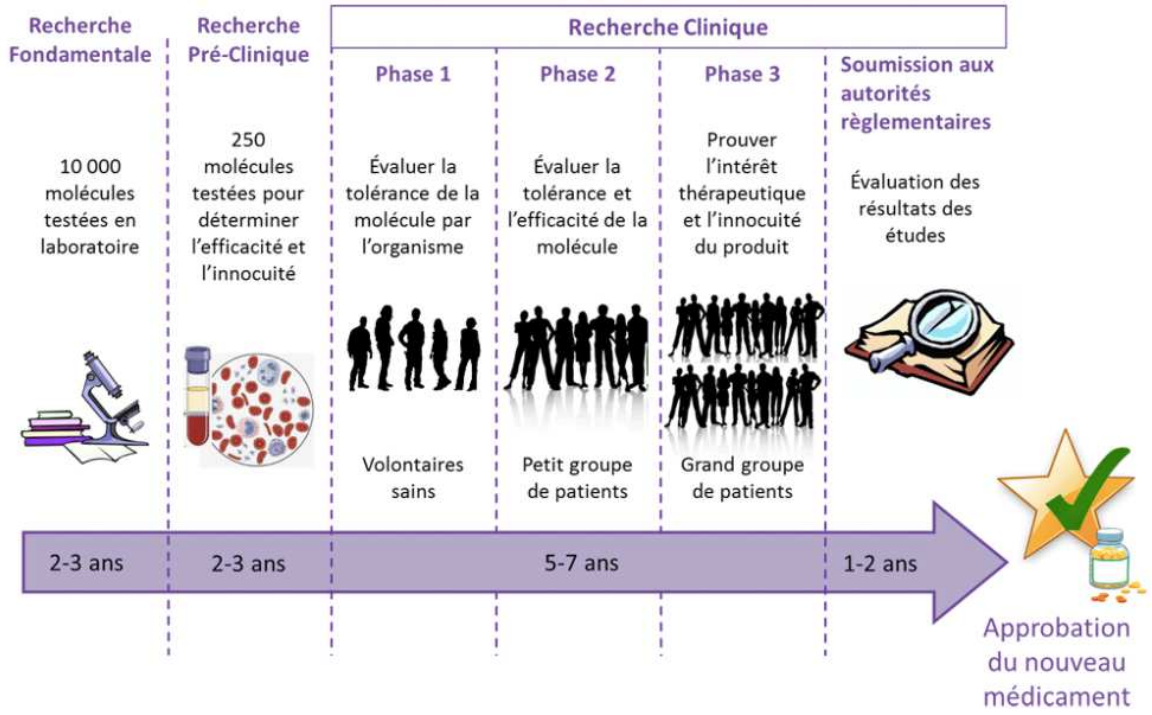
The marketing process also requires the communication of the information collected on the new drug to physicians and other health professionals, so that they are informed of its effects and can prescribe it in the cases they consider appropriate.

- **Phase IV :**

These trials are carried out once the drug is marketed. They allow us to learn more about the drug under real conditions of use and to evaluate its tolerance on a large scale and over the long term in order to detect undesirable effects of the drug that were not detected during the previous phases, and thus to understand **its real benefit/risk ratio**.

Phases I to III generally last 5 to 7 years.

Illustration 3 : The different stages of drug development



Source : https://colcot.mhicc.org/recherche.php?lang=fr

In summary, while there is no fixed development time for a drug to be tested and approved, it is common for all phases of development from research to market to take 10 to 15 years.

The development of vaccines is identical to that of a drug, the patient not being ill, is called a participant.

3.2 Clinical research stakeholders

In order to carry out a clinical trial, there are many 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
- **The 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.

All services can be located **within the laboratory or outsourced to subcontractors** or contract research organizations called CROs (Clinical Research Organizations).

All participants, whether they are internal to the laboratory or external companies, are subject to the same regulations and must follow the working methods, reference documents, guidelines, etc., all of these rules being grouped together under the name of **Good Clinical Practice (GCP)** as well as all the recommendations issued by the health authorities relating to its activity, whether they are global, from the World Health Organization (WHO), European, American or local.

The sponsor retains full responsibility for the trial, and must ensure that it is adequately monitored, depending on the objective, purpose, complexity, whether or not there is randomization, whether or not products are kept "blind", the number of subjects to be included, the trial's evaluation criteria, etc. **On-site monitoring, before, during and after the trial is therefore necessary to ensure the progress of the study, to control and validate the documents and data collected.**

3.3 Regulation in clinical trials

Every clinical trial is governed by a set of principles whose purpose is to 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), originally founded in 1990, became a non-profit legal entity in 2015, and 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/)

Its mission is **to draft and maintain guidelines or recommendations** and technical documents to be followed by clinical research stakeholders in order to homogenize practices at the global level in terms of safety, quality and efficacy, in order to facilitate the work of health agencies when pharmaceutical companies apply for marketing authorization for new products.

The Good Clinical Practice reference document - "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) - Guidance for Industry" is available at

- The ICH website

https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

- Health agency websites

FDA : https://www.fda.gov/media/93884/download

EMA : https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf

Ministry of Health Canada : https://www.cpp-sudmed2.fr/IMG/pdf/e6_f.pdf

This document is THE reference for all those involved in Clinical Research as it is defined as "an international **ethical and scientific quality standard for the design and conduct of trials** involving human subjects and for the recording and reporting of trial data. **Adherence to such a standard assures the public that the rights, safety, and well-being of trial subjects are protected**, consistent with the principles of the Declaration of Helsinki, and that clinical trial data are reliable.

The ICH recommendations concerning efficacy, tolerance, quality ... have been in place for years, the list is in the following tables, the column corresponds to the version, the data being the date of last revision.

Tableau 1 : Efficacy guidelines

Title	Step	Date
E1 - The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions	Step 5	27 October 1994
E10 - Choice of Control Group and Related Issues in Clinical Trials	Step 5	20 July 2000
E11(R1) - Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population	Step 5	18 August 2017
E11A EWG - Paediatric Extrapolation	Step 1	-
E12 - Principles for Clinical Evaluation of New Antihypertensive Drugs	-	-
E14 - The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	Step 5	12 May 2005
E14 Q&As (R3) - Questions & Answers: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	Step 5	10 December 2015
E14/S7B IWG - Questions & Answers: Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential	Step 3	27 August 2020
E15 - Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories	Step 5	1 November 2007
E16 - Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions	Step 5	20 August 2010
E17 - General principles for planning and design of Multi-Regional Clinical Trials	Step 5	16 November 2017
E18 - Genomic Sampling and Management of Genomic Data	Step 5	6 September 2017
E19 EWG - Optimisation of Safety Data Collection	Step 3	4 April 2019
E20 EWG - Adaptive Clinical Trials	Step 1	-
E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting	Step 5	27 October 1994
E2B(R3) - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (ICSRs)	Step 5	1 November 2012
E2B(R3) EWG/IWG - Electronic Transmission of Individual Case Safety Reports (ICSRs)	-	-
E2B(R3) Q&As - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports	Step 5	1 June 2019
E2C(R2) - Periodic Benefit-Risk Evaluation Report	Step 5	17 December 2012
E2C(R2) Q&As - Questions & Answers: Periodic Benefit-Risk Evaluation Report	Step 5	31 March 2014
E2D - Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting	Step 5	12 November 2003

Title	Step	Date
E2D(R1) EWG - Post Approval Safety Data Management: Definition and Standards for Expedited Reporting	Step 1	-
E2E - Pharmacovigilance Planning	Step 5	18 November 2004
E2F - Development Safety Update Report	Step 5	17 August 2010
E3 - Structure and Content of Clinical Study Reports	Step 5	30 November 1995
E3 Q&As (R1) - Questions & Answers: Structure and Content of Clinical Study Reports	Step 5	6 July 2012
E4 - Dose-Response Information to Support Drug Registration	Step 5	10 March 1994
E5 Q&As (R1) - Questions & Answers: Ethnic Factors in the Acceptability of Foreign Clinical Data	Step 5	2 June 2006
E5(R1) - Ethnic Factors in the Acceptability of Foreign Clinical Data	Step 5	5 February 1998
E6(R2) - Good Clinical Practice (GCP)	Step 5	10 November 2016
E6(R3) EWG - Good Clinical Practice (GCP)	Step 1	-
E7 - Studies in Support of Special Populations: Geriatrics	Step 5	24 June 1993
E7 Q&As - Questions & Answers: Studies in Support of Special Populations : Geriatrics	Step 5	16 July 2010
E8 - General Considerations for Clinical Trials	Step 5	17 July 1997
E8(R1) EWG - Revision on General Considerations for Clinical Studies	Step 5	6 October 2021
E9 - Statistical Principles for Clinical Trials	Step 5	5 February 1998
E9(R1) EWG - Addendum: Statistical Principles for Clinical Trials	Step 5	20 November 2019

Tableau 2 : Safety guidelines

Title	Step	Date
S10 - Photosafety Evaluation of Pharmaceuticals	Step 5	13 November 2013
S11 - Nonclinical Safety Testing in Support of Development of Paediatric Medicines	Step 5	14 April 2020
S12 EWG - Non-clinical Biodistribution Considerations for Gene Therapy Products	Step 3	3 June 2021
S1A - Need for Carcinogenicity Studies of Pharmaceuticals	Step 5	29 November 1995
S1B - Testing for Carcinogenicity of Pharmaceuticals	Step 5	16 July 1997
S1B(R1) EWG - Rodent Carcinogenicity Studies for Human Pharmaceuticals	Step 3	10 May 2021
S1C(R2) - Dose Selection for Carcinogenicity Studies of Pharmaceuticals	Step 5	11 March 2008
S10 - Photosafety Evaluation of Pharmaceuticals	Step 5	13 November 2013
S2(R1) - Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use	Step 5	9 November 2011
S3A - Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies	Step 5	27 October 1994

Title	Step	Date
S3A Q&As - Questions and Answers: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure - Focus on Microsampling	Step 5	16 November 2017
S3B - Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies	Step 5	27 October 1994
S4 - Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)	Step 5	2 September 1998
S5(R2) - Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility	Step 5	1 November 2005
S5(R3) - Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals	Step 5	18 February 2020
S5(R4) Maintenance EWG - Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals	-	-
S6(R1) - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals	Step 5	12 June 2011
S7A - Safety Pharmacology Studies for Human Pharmaceuticals	Step 5	8 November 2000
S7B - The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals	Step 5	12 May 2005
S8 - Immunotoxicity Studies for Human Pharmaceuticals	Step 5	15 September 2005
S9 - Nonclinical Evaluation for Anticancer Pharmaceuticals	Step 5	18 November 2009
S9 Q&As - Questions and Answers: Nonclinical Evaluation for Anticancer Pharmaceuticals	Step 5	27 April 2018

3.4 Conduct of a clinical trial

Each clinical trial begins with the writing of a document, the **protocol**, which stipulates the objectives of the research, the type of population (choice of subjects in terms of age, sex, comorbidities, etc.), the follow-up time of the participants (duration of the study), the number of visits, the efficacy criteria, the tolerance criteria, the quality control and assurance procedures, etc. It also details the statistical methodology that will be used to analyze all the criteria collected during the trial.

In agreement with the laboratory and certain health professionals specialized in the field studied, the **biostatistician** writes the **statistical methodology** and calculates the number of subjects to be included in order to be able to conclude on the efficacy based on hypotheses on the expected efficacy of the experimental product, particularly for phase 3 trials.

The writing of such a document requires several months of work depending on the complexity of the trial and a certain amount of back and forth with the health agencies in order to obtain a consensus on the statistical methodology, the choice of the clinical criteria that will be analyzed and in particular the primary efficacy criterion on which the number of subjects is calculated.

The protocol is accompanied by the Case Report Form (CRF) which includes, in the form of checkboxes, free text, tables of values, date fields, times, etc., all the information required in the protocol and which must be reported to the sponsor on each participant in the trial.

It is also a question of recruiting the centers participating in the trial, the final list of which is most often included in the protocol. Out of habit and convenience, the laboratories contact the hospital services with which they are used to working.

Once the trial has been approved by the health authorities and the centers have been identified, the study can be set up in the investigating centers.

The tasks of each stakeholder are explained below.

- **The Sponsor**

Prior to the start of the trial, the Sponsor must prepare and provide the participating centers with the regulatory documents :

  - The investigator's brochure which contains a description of the product and its properties as well as the results of all non-clinical studies on pharmacology;
  - The Case Report Form (CRF) which includes all the information required in the protocol to be reported to the sponsor on each trial participant,
  - The informed consent form for participants to sign,
  - Financial contracts between the center and the laboratory, with the centers being paid for each participant included in the trial
  - The letters of approval of the study by the authorities

  …

It is also a question of **developing the distribution chains for the tested products**, which must be transported under the right conditions of storage, temperature, etc., from the production site to the pharmacies of the sites recruiting the patients, and the pharmacies must ensure proper conservation according to the manufacturer's standards.

During the trial, the project manager in charge of the study must ensure its progress by coordinating the various departments or subcontractors

- **Data-management Service :**

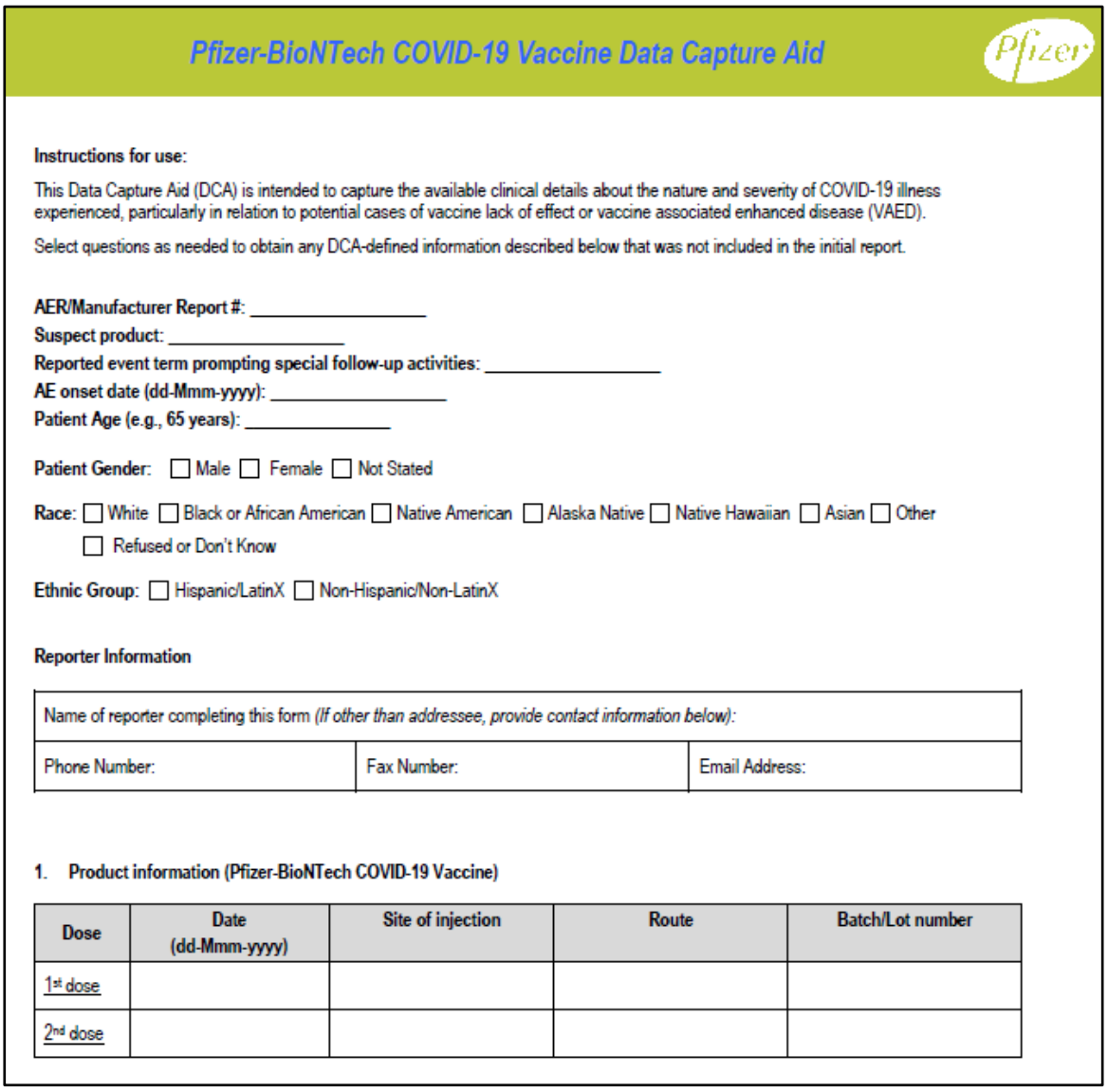
Data management activities are governed by the **Good Data Management Practices** and other technical documents mentioned below.

Prior to the start of the trial the data manager(s) must complete the following documents:

  - The data-management plan, which explains the working methods that will be implemented to manage the test, the software that will be used
  - The Data Validation Plan, which details all the controls that will be implemented during data entry by the centers to detect missing data and data entry errors

They must also ensure the development of the trial-specific website, named e-CRF for electronic CRF, which contains the data entry screens defined in the patient's booklet (Case Report Form).

Illustration 4 : Example of a CRF page



Pfizer-BioNTech COVID-19 Vaccine Data Capture Aid

Instructions for use:

This Data Capture Aid (DCA) is intended to capture the available clinical details about the nature and severity of COVID-19 illness experienced, particularly in relation to potential cases of vaccine lack of effect or vaccine associated enhanced disease (VAED).

Select questions as needed to obtain any DCA-defined information described below that was not included in the initial report.

AER/Manufacturer Report #: _____
Suspect product: _____
Reported event term prompting special follow-up activities: _____
AE onset date (dd-Mmm-yyyy): _____
Patient Age (e.g., 65 years): _____

Patient Gender: ☐ Male ☐ Female ☐ Not Stated

Race: ☐ White ☐ Black or African American ☐ Native American ☐ Alaska Native ☐ Native Hawaiian ☐ Asian ☐ Other ☐ Refused or Don't Know

Ethnic Group: ☐ Hispanic/LatinX ☐ Non-Hispanic/Non-LatinX

Reporter Information

Name of reporter completing this form *(If other than addressee, provide contact information below)*:		
Phone Number:	Fax Number:	Email Address:

1. Product information (Pfizer-BioNTech COVID-19 Vaccine)

Dose	Date (dd-Mmm-yyyy)	Site of injection	Route	Batch/Lot number
1st dose				
2nd dose				

The data-manager(s) have also **to program the correct allocation of treatments** (randomization) to each new participant included. For example, the first participant will receive product A, the second will receive product A, participants 3 and 4 will receive product B, participant 5 will receive B, participant 6 will receive A, participant 7 will receive A, participant 8 will receive B... in order to obtain regularly the same number of participants in each group, in our case, every 4 patients. Randomization avoids that investigators choose themselves the treatment to give to a new patient, this choice being made on subjective criteria, which can distort the results (for example, patients in a more serious state in one of the groups).

The data manager(s) program the order of the fields to be entered in order to guide the investigator to the next relevant field (e.g. if no history for the patient, next page, if at least one history, mandatory filling of the nature of the history).

They also program **consistency checks or tests to detect missing or inconsistent data**. These checks must be clearly defined in a prior document called the Data Validation plan.

Since a certain number of people will have access to the electronic notebook, it is also necessary to create **different access profiles** for which read/write/modify rights have been established: the person(s) in charge of the study in the laboratory (project manager), the investigators, the data-manager(s), the clinical research associates, etc. Each person has a username and password known only to him/her. The user is generally deactivated (access cut off) in case of repeated entries of a wrong password. The system must therefore provide for the possibility of recovering passwords so as not to block the user for too long.

Staff at the centers who will be working on the trial must be trained in the completion of the electronic patient record before the study begins.

The tools used for data management are regulated by the FDA 21 CFR part 11 standard. The data entry of a clinical trial is not done in a Microsoft Excel® type spreadsheet

Source : Guidance for Industry Part 11, Electronic Records; -Electronic Signatures — Scope and Application - https://www.fda.gov/media/75414/download

In summary, this standard requires, among other things,

- that the systems used in the development of an e-CRF have been validated in the user's work environment.
- **full traceability of the data entered**, name of the user who entered the data, date/time of recording, user who modified the data, date/time of modification, source of the modification (data entry error, request for corrections from the data manager, from the ARC ....). The set of records for all the fields in the electronic notebook for all the patients is called an **audit trail.**

The audit-trail review can detect any undocumented data corrections and therefore any change from of an investigator, a data manager, a CRA ....

The data manager(s) check that the website setup has been correctly parameterized by creating "false patients" called "test patients". The aim is to create enough patients to ensure that the randomization assigns treatments correctly, and **to validate that all the programmed tests detect all the possible problems** (missing data, wrong date, biological value not compatible with the standard entered, start date of an event later than the end date, time between visits compatible with the protocol ....). It is common practice to enter all the data required for at least 50 patients in order to cover all the possibilities. The test patients should be kept as well as all the results of the tests performed in order to prove the proper functioning of the website in case of an audit.

The e-CRF can only be made available to centers (from test mode to production mode) once it has been fully tested and validated.

This step can take up to 3 months in the case of a complex CRF, numerous visits, multiple examinations including laboratory data (blood tests), imaging examinations...

As the investigating centers recruit participants and ensure data entry into the electronic case report form (e-CRF), the data manager(s) runs the programmed checks in **order to send correction requests to the centers so that they can complete the missing data and correct the inconsistent data** from the patient documents available on the site (demographic data, concomitant medications, adverse events, biological check-ups, PCR test results, etc.)

According to ICH recommendations, all participant medical histories, adverse events, previous and concomitant medications should be coded to facilitate analysis.

As with any activity that is part of drug development, the coding of adverse reactions is regulated. To help pharmacovigilance services as well as health authorities to evaluate the adverse events of a product, **a medical dictionary for regulatory activities (MedDRA)** was developed in the late 1990s by the ICH.

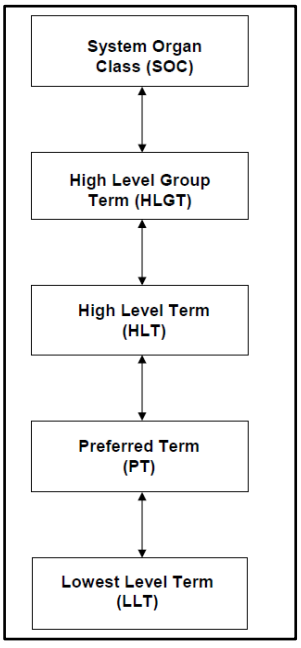
The MedDRA coding system uses keywords representing the medical condition(s) described in the reported case and converts them into standardized codes. In order to be used worldwide, it includes multilingual databases to avoid translation.

Coding of adverse events is performed by the data manager(s) when they are reported in clinical trials.

MedDRA has a hierarchical structure, from the most specific to the most general.

The lowest level term (LLT) provides maximum specificity. High Level Terms (HLT) and High Level Group Terms (HLGT) facilitate data retrieval and presentation by providing a grouping of clinically relevant terms. Preferred terms (PT) should be unambiguous, as specific and self-descriptive as possible in the context of international requirements. The System Organ Class (SOC) is the highest level of the hierarchy that provides the broadest concept for data retrieval.

Illustration 5 : MedDRA hierarchical structure



The validation of the coding must be carried out by the Pharmacovigilance department. The two departments therefore go back and forth until the coding is fully validated.

The data manager is also responsible for i**mplementing the extraction of the data entered into the e-CRF into a database** that can be used by the statistician. This database consists in several files, with the parameters measured during the trial put in columns and the individuals in rows. Since it would be unreadable and therefore unusable to create a single file containing all the data of all the participants in a trial, the data are arranged by type in different files.

Here again, **the database format must follow specifications** in terms of file names, variable names, data organization, etc. The Clinical Data Interchange Standards Consortium (CDISC), a worldwide non-profit organization, develops data standardization systems. Their reference documents constitute the standards to be implemented to define the format of the files or tables to be parameterized.

Special recommendations have been written for the COVID-19 databases.

https://www.cdisc.org/standards/therapeutic-areas/covid-19

Source : https://www.cdisc.org/system/files/members/standard/ta/TAUG-COVID-19_v1.0_0.pdf

It goes without saying that the data export process must be validated in order to put all the fields of the e-CRF in the right place.

At the end of the study, the data must have been 100% checked and cleaned by the data manager(s). When the database is documented as error-free, it can be "frozen", i.e. it cannot be modified afterwards. Any "unlock" of the database is an indicator of poor quality of the work of the data manager(s), since it means that errors have not been corrected despite the checks made.

The data manager export the data at the end of the process to create the files that will be sent to the statistician.

- **The monitoring service**

Monitoring activities are governed by the **Good Monitoring Practices** and other technical documents mentioned below.

Prior to the start of the trial the clinical research officer(s) must complete the following document the monitoring plan which contains the key data to be checked, the schedule of visits …

CRAs should ensure that the investigator site has received the trial and investigational product management documents, and that site personnel who will be working on the study have been trained in the protocol and its required practices.

During the study, like the data manager(s) with whom they work closely, the clinical research associates (CRAs) also perform **some checks on the data and visit the sites** that have included participants in order to verify that the data reported in the e-CRF are indeed those of the local examinations (source data) to which the data manager does not have access.

They check that the patients included in the study respect the inclusion criteria in terms of age, associated pathologies .... that the consent has been signed by the patients... They must also verify that the centers respect the storage conditions of the study products as foreseen by the Sponsor, that all the entries, exits, returns of the products are traced, that the patients have been correctly followed ....

Like the data manager(s), they can issue requests for corrections to the centers, which must respond to them. **They also verify that adverse events have been identified and reported to the pharmacovigilance department.**

In recent years, in order **to limit the costs and duration of trials**, it has become increasingly common, particularly in the context of **fast-track** process, for CRAs to carry out part of their

checks remotely, in what is known as **remote monitoring**. The CRA schedules telephone or video conferences with the center's staff, who transmit the source medical documents to the CRA via a secure area so that the CRA can compare the source data with the data entered in the e-CRF. Although this practice is accepted at the regulatory level, it is still less effective than on-site visits, which is why it is common to keep face-to-face visits in order to compare the quality of the audit with on-site monitoring.

It is therefore often also necessary to have a document exchange platform for remote monitoring but also for any type of confidential document exchange, including statistical results, as the secure platform prevents confidential documents from being sent by e-mail.

At the end of the study, the source documents must be 100% verified.

- **The pharmacovigilance service :**

Pharmacovigilance activities are governed by **Good Pharmacovigilance Practice**s.

Prior to the start of the trial, the pharmacovigilance department should prepare the Pharmacovigilance Plan.

As adverse events are reported by the investigating sites, the pharmacovigilance staff assess the severity of the events and the causal link with the tested product. They are the ones who establish the responsibility of the product in the occurrence of adverse events (imputability).

- **The statistical service :**

Prior to the start of the trial the statistician(s) shall:

  - Develop the randomization list, which should be developed by a laboratory statistician and kept secret until the end of the trial
  - Write the statistical analysis plan according to the protocol methodology.

The statistician **will program the statistical analyses** based on all the data exported from the electronic patient case form in a format compatible with the chosen statistical analysis software (SAS® type or other).

When **intermediate** analyses are planned, since the laboratory staff should not know which products have been given to the participants (due to the blind design), the analyses are sent to experts outside the laboratory, the so-called IRC (Independent Review Committee).

As with any stakeholder, the working methods and documents to be provided by IRCs are regulated.

The statistical analyses are carried out by the Committee's expert biostatistician, who programs the planned analyses using one or more **software programs validated in clinical research** (SAS® or other) and provides the results, which will be examined by the other members of the Committee, generally physicians or professors working in the field of research.

Within the framework of his activities, the **biostatistician must follow very strict regulations** and must respect a very large number of reference documents concerning the statistical analysis methods to be used according to the type of study (parallel groups, crossover studies, equivalence studies, non-inferiority studies, etc.) and the parameters to be analysed (quantitative and qualitative parameters) .... One of the reference documents is the ICH E9 "Statistical Principles for Clinical Trials".

Source : https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

A second statistician must validate all programs for critical data including the calculation of the primary endpoint on which the efficacy conclusion of a phase 3 study is based. The programs are executed and the records of the execution of the programs (log) are kept as evidence in case of audit, a file containing the list of programs, the name of the programmer, the day of the programming, the name of the "validator", the date of validation, the date of execution ...

Once the database frozen by the data manager and the regulatory certificates issued, it is possible to obtain the decoding of the experimental products since the knowledge of the treatment actually given to each patient is necessary to provide the results.

The decoding of the products is therefore transmitted to the biostatistician so that he can execute his programs.

As with the interim analyses, the “logs” are recorded as evidence in the event of an audit. Any changes from what was planned in the protocol must be documented. Tables, graphs and listings are integrated into the clinical report, which will be commented on by a medical writer.

During the study, the various participants must maintain and keep all the evidence of their actions on the study by filling in all the documents drawn up beforehand. All these documents and records constitute a file to be kept, either at the investigator site, or at the Sponsor's, or at both, depending on the type of data concerned. The complete file is called **Trial Master File** (TMF).

This paper or dematerialized file allows the operational staff as well as the auditors and inspectors to evaluate the respect of the protocol, the good progress of the test and the quality of the obtained data.

The documents to be included in the TMF are referenced in the "**Guideline on the content, management and archiving of the clinical trial master file**".

Sources : Guideline on the content, management and archiving of the clinical trial master file- 06 December 2018 - Good Clinical Practice Inspectors Working Group (GCP IWG)
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

https://www.ijclinicaltrials.com/index.php/ijct/article/view/442

In summary, in any center, the personnel involved in the trial must be trained to the study practices before starting the study. Each person, investigator, nurse, staff in charge of the management of the trial products, staff in charge of the laboratory analyses... must sign the **sign-in sheet** to prove that the training has been carried out.

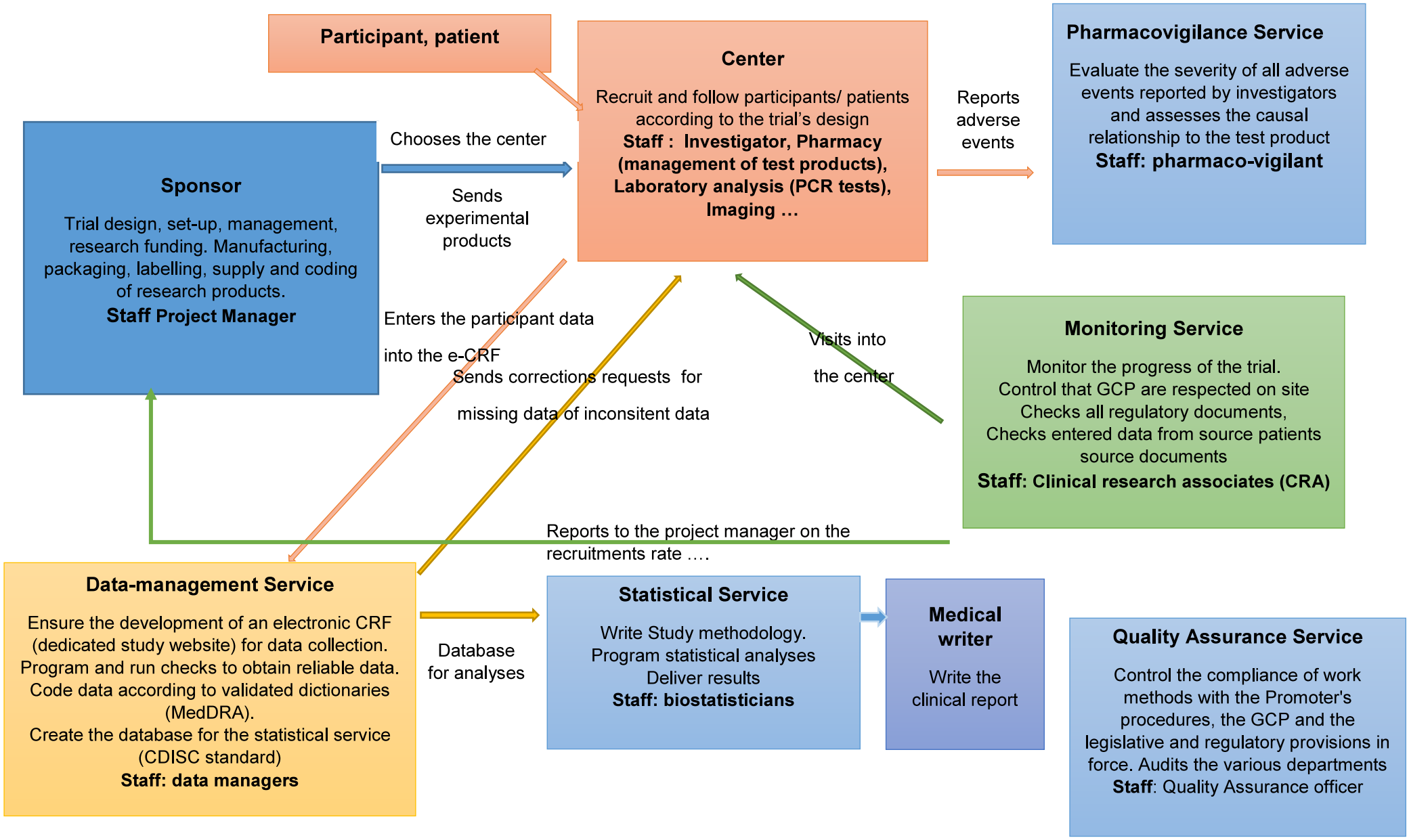
All workers must be trained in Good Clinical Practices and be familiar with all documents regulating their activities.

The sponsor is responsible for the coordination of its trial and for ensuring that the working procedures comply with GCP and applicable laws and regulations.

The Quality Assurance department oversees audits of the various departments and subcontractors in order to evaluate the quality of work.

The interactions between the different participants in a trial are shown in the following figure.

Illustration 6 : Interactions between the different stakeholders in a clinical trial



3.5 Risks and bias

All the guidelines have only one goal, to minimize the risk of error in the evaluation of the benefit-risk in order to avoid any risk of using a potentially ineffective or even dangerous product in real life.

It is therefore necessary to identify the elements that may cause the results to deviate from their true value, these elements are called biases.

Some biases come from, among other things,

- Non-randomization, e.g., treatment assignment such that low-risk subjects are systematically assigned to a treatment.
- From **unequal distribution** of subjects per treatment at each center, trials with large differences in the number of subjects between centers or with very few participants may induce heterogeneity in treatment effect across centers.
- The calculation of the criteria themselves
- The definition of analysis populations. For example, protocol violations and exclusion of subjects from the analysis based on knowledge of the subject's outcome are possible sources of bias that may affect the accurate assessment of the treatment effect.
- Poor quality of participant follow-up within the centers reducing the quality of reported data

Therefore, it is necessary to take precautions to reduce bias and ensure the ability of the trial to conclude correctly.

In summary, the world of clinical trials is full of guidelines that have been put in place to **supervise, homogenize and regulate the practices** of all those involved in the trial, regardless of their role in the trial, all over the world.

The complexity of the trial, in its design, the number of parameters collected, the type of parameters (clinical examination, laboratory data, imaging results, PCR tests...), the number of participants/patients, the duration of the follow-up... requires many staff and therefore a constant coordination.

Throughout the trial, the interveners must write and maintain documents to document all the actions performed according to the models pre-established in the guidelines, the audits of these documents allow evaluating, at any time, the quality of the work performed.

The greater the number of patients, the heavier the workload of the project managers, data managers and CRAs, who must keep up with the pace of data filling in order to meet the deadlines imposed by the trial schedule, particularly when intermediate analyses are planned. **It is indeed unthinkable to obtain analysis results on computer databases containing potentially erroneous data.**

Failure to comply with all these technical and methodological recommendations aimed at minimizing bias, grouped together under the name of **Good Clinical Practice**, by any of the participants in the chain, both at the

- centers recruiting the patients themselves, investigator, nurse, center pharmacy, analysis laboratory,
- or stakeholders in charge of managing the trial, clinical research associates, data managers, pharmaco-vigilants, biostatisticians

can lead to erroneous data and therefore unreliable results in terms of efficacy, immunogenicity and tolerance, which represents a risk of concluding that the benefit/risk ratio is inaccurate, thus putting an ineffective and potentially life-threatening product on the market.

4 COVID-19 Clinical Trial Development Milestones - The Pfizer/BioNtech Case

4.1 Timeline of the trials that led to the selection and marketing of the BNT162b2 vaccine candidate

Pfizer's own press releases and their timeline show key dates in the development of the product.

On March 13, 2020, Pfizer announced a five-pronged plan in the fight against COVID-19, calling on biopharmaceutical industry players to begin an unprecedented collaboration alongside Pfizer. Pfizer outlined five commitments to enable researchers to accelerate the development of solutions and vaccines

1. Sharing tools and knowledge
2. Mobilization of employees
3. Application of our expertise in drug development
4. Adaptation of our manufacturing capacities
5. Improved emergency response

Source: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-outlines-five-point-plan-battle-covid-19

On April 9, 2020, Pfizer and German biotech company BioNTech joined forces to develop a vaccine.
"BioNTech will contribute multiple mRNA vaccine candidates as part of its BNT162 COVID-19 vaccine program, which are expected to enter human testing in April 2020
fizer will contribute its leading global vaccine clinical research and development, regulatory, manufacturing and distribution infrastructure and capabilities."

Source: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-further-details-collaboration

On April 22, 2020, the Paul-Ehrlich Institute, Germany's vaccine certification authority, gave BioNTech and Pfizer the green light to **begin the 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 with the goal of determining the optimal dose for further studies as well as assessing the safety and immunogenicity of the vaccine.
They also announced that they had completed preclinical studies in Germany.

Source: 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, twelve participants in the German study had already been treated with the BNT162 vaccine candidates **since the trial began on April 23, 2020.** Pfizer and BioNTech then planned to initiate trials for BNT162 in the U.S. after regulatory approval, which is expected soon.

Source : https://www.pfizer.com/news/press-release/press-release-detail/biontech-and-pfizer-announce-completion-dosing-first-cohort

According to the regulations, all clinical trials must be registered prior to the start of the trial on the public Internet registry referenced by the World Health Organization (WHO), the U.S. site www.clinicaltrials.gov or the European site www.clinicaltrialsregister.eu set up by the European Medicines Agency (EMA) or another national or WHO-approved registry, in accordance with the applicable regulations and no later than 21 days after the recruitment of the first person.

Also on April 29, 2020, Pfizer registered its Phase 1-2-3 trial at www.clinicaltrias.gov,

https://clinicaltrials.gov/ct2/show/NCT04368728?term=pfizer&cond=Covid19&draw=2

under the title "*Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals*"

On May 5, 2020, Pfizer/BioNtech announced that the first phase 1/2 participants had been treated at New York University Grossman School of Medicine and the University of Maryland School of Medicine.

Source : 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

In June 2020, after the trials had begun, the U.S. Department of Health and Human Services, the Food and Drug Administration (FDA) with the Center for Biologics Evaluation and Research issued Recommendations for Vaccine Development.

Page 13 therefore **defined post hoc how to determine the primary efficacy endpoint for a phase 3 trial**, which was to have a 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,

Illustration 7 : FDA Recommendations for Vaccine Development - Definition of Primary Efficacy Endpoint

- Standardization of efficacy endpoints across clinical trials may facilitate comparative evaluation of vaccines for deployment programs, provided that such comparisons are not confounded by differences in trial design or study populations. To this end, FDA recommends that either the primary endpoint or a secondary endpoint (with or without formal hypothesis testing) be defined as virologically confirmed SARS-CoV-2 infection with one or more of the following symptoms:
  - Fever or chills
  - Cough
  - 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

Source: Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry (fda.gov) - U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research June 2020 - https://www.fda.gov/media/139638/download

On page 6 of the same document, the FDA stated that

Illustration 8 : FDA Recommendations for Vaccine Development - Theoretical risk of respiratory disease

- Data from studies in animal models administered certain vaccine constructs against other coronaviruses (SARS-CoV and MERS-CoV) have raised concerns of a theoretical risk for COVID-19 vaccine-associated enhanced respiratory disease (ERD). In these studies, animal models were administered vaccine constructs

To monitor this risk, page 12 stated that follow-up of participants in the COVID-19 trials, particularly for severe cases, **should be at least 1 to 2 years to assess the duration of protection and to evaluate potential acute respiratory illnesses associated with the vaccine as immune responses wane**.

Illustration 9 : FDA Recommendations for Vaccine Development – Follow-up

- Follow-up of study participants for COVID-19 outcomes (in particular, for severe COVID-19 disease manifestations) should continue as long as feasible, ideally at least one to two years, to assess duration of protection and potential for vaccine-associated ERD as immune responses to the vaccine wane.

Source : Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry (fda.gov) - U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research June 2020 - https://www.fda.gov/media/139638/download

On July 1, 2020, Pfizer/BioNtech announced encouraging results for its Phase 1/2 versus placebo vaccine candidate BNT162b1 in the United States.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-early-positive-data-ongoing

On July 13, 2020, Pfizer/BioNtech obtained approval from the FDA to file its application via an accelerated procedure called Fast Track.
Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-granted-fda-fast-track-designation-two

On July 20, 2020, Pfizer/BioNtech announced its preliminary results for the **BNT162b1** candidate being evaluated in the German Phase 1/2 trial including 60 healthy adults aged 18-55. Of the 60 participants, 48 had received 2 doses of BNT162b1 on days 1 and 22, with 12 subjects receiving a 1 µg dose, 12 a 10 µg dose, 12 a 30 µg dose, and 12 a 50 µg dose; 12 participants received a single 60 µg injection.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate

On 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**.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-choose-lead-mrna-vaccine-candidate

On August 20, 2020, Pfizer/BioNTech announced additional Phase 1 safety and immunogenicity results on BNT162b2 at 30 µg from their ongoing U.S. study. They also announced that, with respect to the Phase 2/3 trial that began in July 2020, more than 11,000 participants had been enrolled.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-share-positive-early-data-lead-mrna

On 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, Pfizer/BioNtech announced the start of discussions with the European Medicines Agency (EMA) for the **BNT162b2** vaccine candidate.

It was also reported that the global 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.

Source : https://www.pfizer.com/news/press-release/press-release-detail/biontech-and-pfizer-initiate-rolling-submission-european

On November 20, 2020, Pfizer/BioNtech submitted its application to the FDA, and announced that it had already begun submitting applications around the world, including Australia, Canada, Europe, Japan and the United Kingdom.
Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-submit-emergency-use-authorization

On 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.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-achieve-first-authorization-world

On December 10, 2020, Pfizer/BioNtech announced **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.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-publication-results-landmark

On the same day, the results were presented to the FDA's Vaccine and Related Biologics Advisory Committee (VRBPAC), which voted 17-4 in favor of granting **an emergency use authorization** (EUA) for the BNT162b2 vaccine.

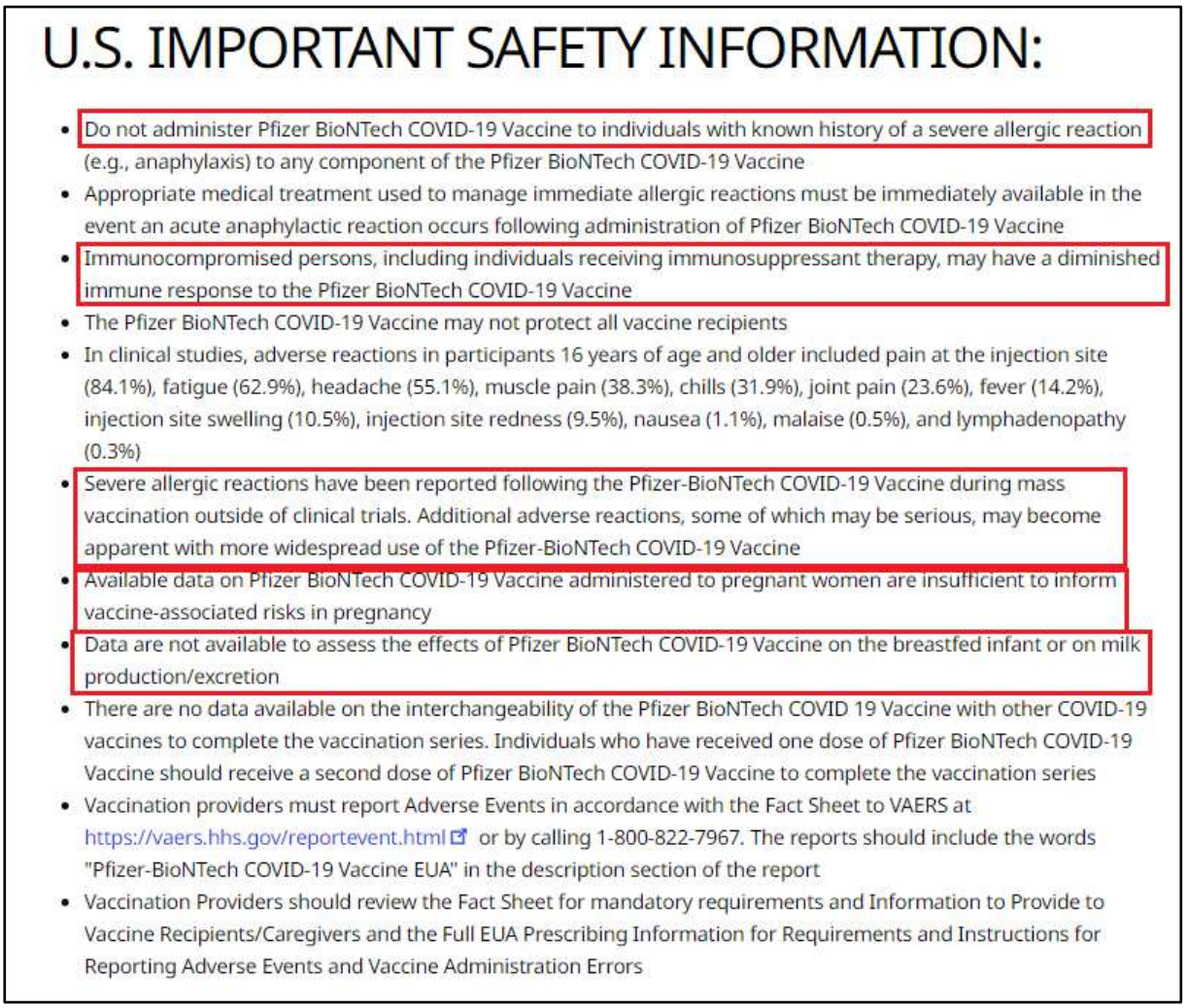
Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-fda-advisory-committee-vote

On December 14, 2020, Pfizer presented the results of the ongoing German Phase 1/2 study, "Analysis of the 37 participants immunized with BNT162b2 showed a broad immune response with SARS-CoV-2 specific neutralizing antibodies, TH1-like CD4+ T cells and a strong expansion of CD8+ T cells of the early effector memory phenotype. The data confirmed previous results from the U.S. trial demonstrating a good safety profile and robust induction of antibody responses **with a longer follow-up period of 85 days**."

In the same press release, Pfizer/BioNtech expressed a number of reservations and precautions for real-life use (see Illustration 10 : Pfizer - Press releases – December 14, 2020.).

- Do not administer Pfizer BioNTech COVID-19 vaccine to persons with a known history of severe allergic reaction (e.g., anaphylaxis) to any component of Pfizer BioNTech COVID-19 vaccine.
- Immunocompromised individuals, including those on immunosuppressive therapy, may have a decreased immune response to Pfizer BioNTech COVID-19 vaccine.
- Pfizer BioNTech COVID-19 vaccine may not protect all vaccine recipients
- There are no data available to assess the effects of Pfizer BioNTech COVID-19 vaccine on breastfeeding infants or on milk production/excretion.
- There are no data available on the interchangeability of Pfizer BioNTech COVID-19 vaccine with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Pfizer BioNTech COVID-19 vaccine should receive a second dose of Pfizer BioNTech COVID-19 vaccine to complete the vaccination series.

Illustration 10 : Pfizer - Press releases – December 14, 2020



U.S. IMPORTANT SAFETY INFORMATION:

- Do not administer Pfizer BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer BioNTech COVID-19 Vaccine
- Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer BioNTech COVID-19 Vaccine
- Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer BioNTech COVID-19 Vaccine
- The Pfizer BioNTech COVID-19 Vaccine may not protect all vaccine recipients
- In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%)
- Severe allergic reactions have been reported following the Pfizer-BioNTech COVID-19 Vaccine during mass vaccination outside of clinical trials. Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine
- Available data on Pfizer BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy
- Data are not available to assess the effects of Pfizer BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion
- There are no data available on the interchangeability of the Pfizer BioNTech COVID 19 Vaccine with other COVID-19 vaccines to complete the vaccination series. Individuals who have received one dose of Pfizer BioNTech COVID-19 Vaccine should receive a second dose of Pfizer BioNTech COVID-19 Vaccine to complete the vaccination series
- Vaccination providers must report Adverse Events in accordance with the Fact Sheet to VAERS at https://vaers.hhs.gov/reportevent.html or by calling 1-800-822-7967. The reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report
- Vaccination Providers should review the Fact Sheet for mandatory requirements and Information to Provide to Vaccine Recipients/Caregivers and the Full EUA Prescribing Information for Requirements and Instructions for Reporting Adverse Events and Vaccine Administration Errors

Source: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-data-german-phase-12-study

On December 21, the European Commission (EC) granted conditional marketing authorization (CMA) to Pfizer and BioNTech for its vaccine, now called Comirnaty®.

Source : https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-receive-authorization-european-union

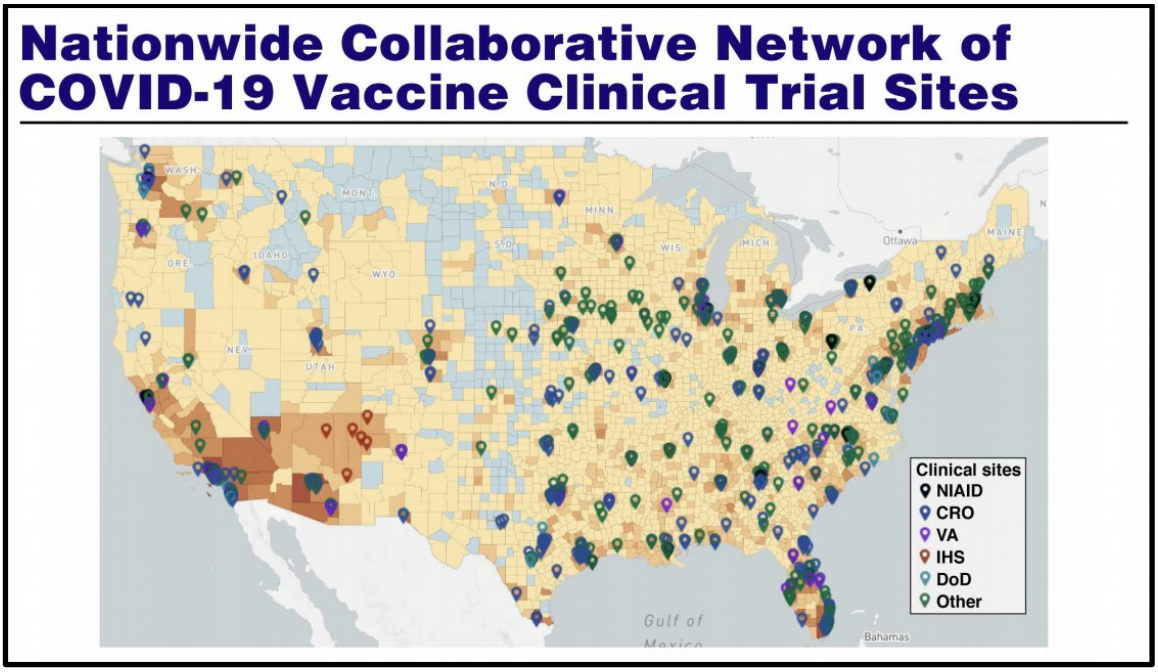
A simple calculation, based on the enrolment figures cited in the press releases, can be used to reconstruct the progress of enrolment in the Phase 2/3 clinical trial that concluded the proof of efficacy of the **BNT162b2** vaccine candidate.

Illustration 11 : Calculated rate of recruitment of participants in the Phase 3 trial

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

The map below shows stakeholders throughout the United States involved in COVID-19 testing.

Illustration 12 : U.S. National Collaborative Network of Clinical Investigation Sites



Source: NIH activities in the development of vaccines against COVID-19 - Hilary Marston, M.D., M.P.H. / Medical Officer and Policy Advisor for Pandemic Preparedness / National Institute of Allergies and Infectious Diseases - https://www.fda.gov/media/143559/download

On the October 22, 2020, the presentation by Robert Johnson at the Vaccines and Related Biologics Advisory Committee Meeting available on the FDA website clearly summarizes the strategy being taken to accelerate development.

Illustration 13 : Normal development of a trial

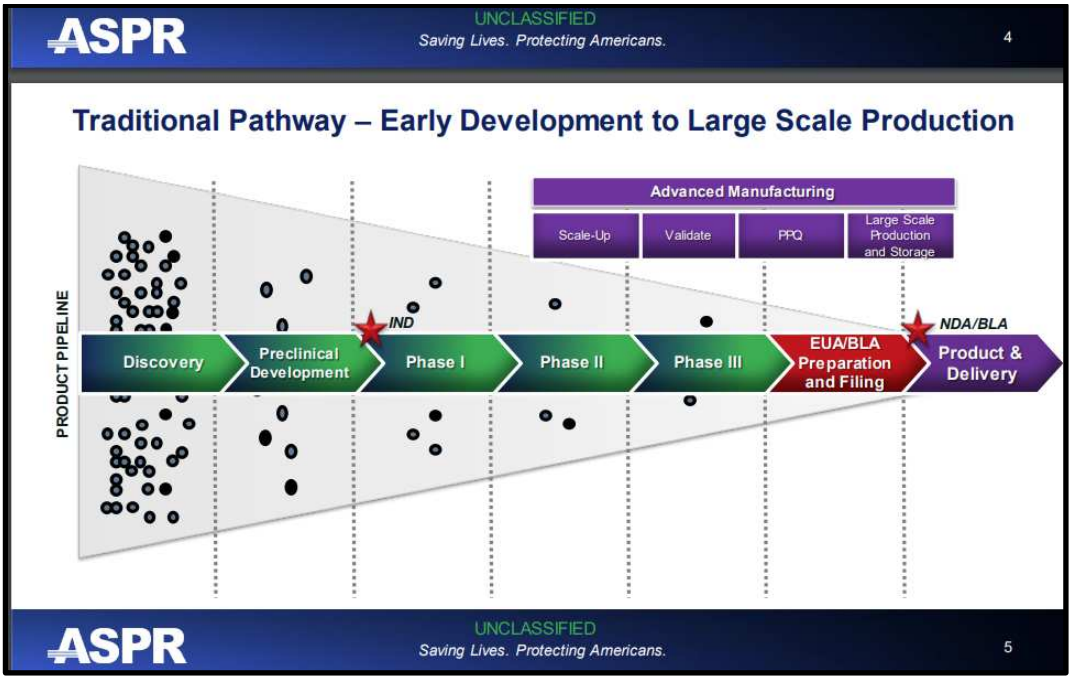
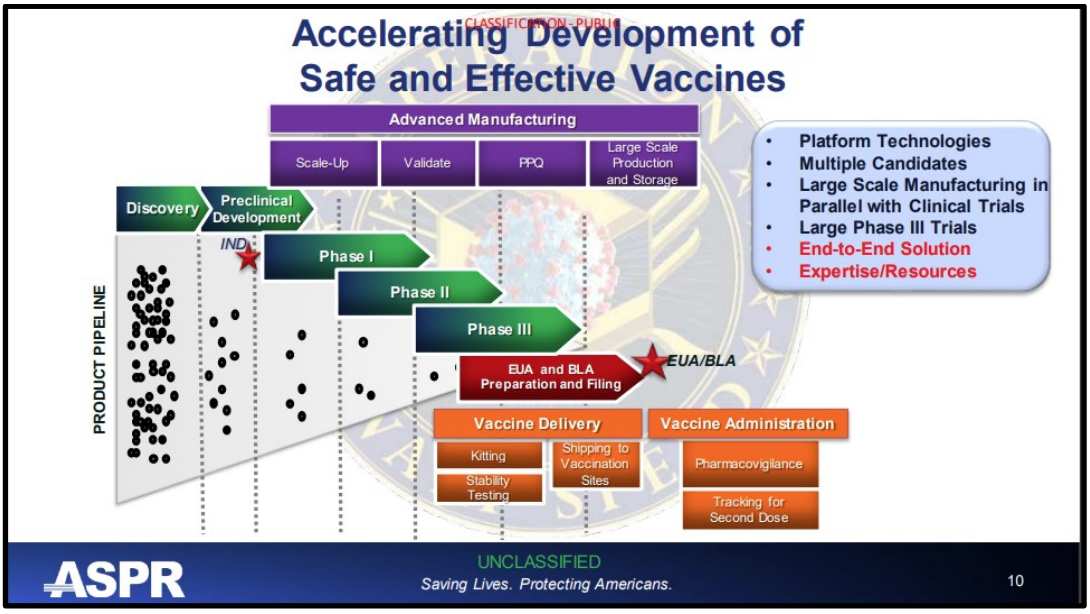


Illustration 14 : Accelerated development of COVID-19 trial



Source: Vaccines and Related Biological Products Advisory Committee, COVID-19 Vaccine Development Portfolio, - Robert Johnson, PhD Director, Division of Influenza and Emerging Infectious Diseases BARDA/ASPR/HHS - https://www.fda.gov/media/143560/download

In summary, between January 12, 2020, the publication of the genome by China, and the beginning of April 2020, BioNtech has therefore developed RNA vaccine candidates, a period of two and a half months.

The first human trial was approved by German authorities 11 days later, and by April 29, 12 patients had already received the vaccine candidates.

In this very short time, the laboratory had to ensure the manufacture of the products according to the regulations in force and to set up the distribution channels, which already appears to be a feat that we will not discuss in this report but which would require some clarification.

On July 27, 2020, phase 1/2 results, led to the selection of the BNT162b2 vaccine candidate for the phase 2/3 study, at a dose of 30 µg in a 2-dose regimen.

As of August 20, 2020, less than a month into the **BNT162b2** trial, 11,000 participants had already been recruited, with the number of participating centers not provided in the release, a rate of approximately **440 participants recruited per day, or 55 per hour.**

As of October 6, 2020, the Phase 2/3 study of BNT162b2 included 37,000 participants enrolled at 120 clinical sites including the United States, Brazil, South Africa and Argentina, and more than 28,000 participants had already received their second dose. Between October 6 and August 20, 26,000 participants were enrolled over a 48-day period, **at a rate of 542 per day, or nearly 68 per hour**.

As of November 14, 2020, the database provided for the interim analysis to the Independent Expert Panel contained nearly 44,000 participants recruited from 150 clinical trial sites across the United States, Germany, Turkey, South Africa, Brazil, and Argentina. This means that **13,000 participants were enrolled over a 40-day period, at a rate of 175 per day, or nearly 22 per hour**.

The results of the interim analysis were presented on December 10 and the FDA voted the same day for emergency use of Pfizer's vaccine candidate, BNT162b2 versus placebo

This tremendous rate of recruitment of participants (44,000) spread over 150 centers throughout the United States as well as in Germany, Turkey, South Africa, Brazil and Argentina already raises the question of compatibility with

* proper training of investigating centers,

* a homogeneous practice of the centers

* adequate follow-up of participants

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

This is a randomized, controlled Phase 1-2-3 study testing several doses of vaccines candidates; the BNT162b2 vaccine candidate at the 30 µg dose selected in Phase 2 versus placebo, 0.9% saline. The trial is multicenter, meaning that it is taking place at several clinical sites.

Source : Protocole de la phase 1- 2-3

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

The study is composed of 2 parts.

- Phase 1: to determine the best vaccine candidate (choice of dose and dosage)
- Phase 2/3: Expanded cohort and an efficacy portion.

The primary objective of Phase 2-3 is 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.

The second objective is identical to the first one but in participants with or without infection before vaccination.

It is also a question of studying tolerance in terms of local reactions to the injections as well as so-called systemic events (fever, fatigue, chills, vomiting, diarrhea, etc.) and any other serious or non-serious events.

As an exploratory measure, the immune response and its persistence will also be evaluated.

The participant initially had to be over 18 years of age to be included in the trial; Amendment 6 on September 8 allows 16-17 year olds to be included and Amendment 7 on October 6, 2020 expands the population to 12-15 year olds.

As for all clinical trials, pregnant or lactating women are excluded, as they are part of a protected population under patient protection laws.

8 visits were foreseen by the protocol,

- Visit 1: first dose of the experimental product on Day 1
- Visit 2: second dose of the experimental product which was to take place between days 19 and 23 after the first visit
- *Visit 3: 1 week after dose 2 –only phase 1-2*
- *Visit 4: 2 weeks after dose 2 – only phase 1-2*
- Visit 5: visit at 1 month, between 28 and 35 days after visit 2 (2nd dose),
- Visit 6: visit at 6 months, between 175 and 189 days after 2nd dose
- Visit 7: visit at 12 months, between 350 and 378 days after 2nd dose
- Visit 8: visit at 24 months, between 714 to 742 days after 2nd dose

The total duration of the trial was therefore 24 months.

The list of parameters collected during each visit can be seen on the following 3 diagrams.

Illustration 15 : Phase 1-2-3 Pfizer Clinical Study Protocol - Detailed Visit Schedule - - 1

1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit[a]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1[b]	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	

Illustration 16: Phase 1-2-3 Pfizer Clinical Study Protocol - Detailed Visit Schedule -2

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

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit[a]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1[b]	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period)[e]	◄—►	◄—►						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates[e]		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X[f]	X[f]	X[f]	X	X[f]
Collect e-diary or assist the participant to delete application						X		

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

Illustration 17 : Phase 1-2-3 Pfizer Clinical Study Protocol - Detailed Visit Schedule - 3

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

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit[a]	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1[b]	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
c. Including, if indicated, a physical examination.
d. 20 mL is to be collected from participants ≥16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
e. Reactogenicity subset participants only.
f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see Section 8.3.1).

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

In order not to introduce **bias** into the investigator's selection of participants, the study was **blinded**, as the physical appearance of the experimental vaccine candidates and the placebo could be different. The participant was not aware of the product he or she was receiving, nor were the investigator, study coordinator, or other site personnel.

At the investigator site, only the personnel in charge of storage, distribution, preparation and administration of the experimental products were not "blinded" and knew the contents of the vials handled.

Antibody samples (line "Collect Blood sample for immunogenicity" in Illustration 13 were to be taken on Day 1, the day on which the participant received his/her first dose of the experimental product, at Visit 3 (1 month after the second dose), at Visit 4 (6 months after the second dose), at Visit 5 (12 months after the second dose), at Visit 6 (at 24 months after the second dose).

No follow-up visits to participants were planned between 1 and 6 months after injection of the second dose, either to measure antibodies, or to collect tolerance data or COVID-19 infections.

Vaccine efficacy was to be assessed **based on the major clinical endpoint of interest, the so-called primary endpoint, by counting the number of confirmed symptomatic COVID-19 cases**.

In order to classify the participant as symptomatic COVID-19, the diagnosis had to take place as specified in the trial protocol, in its sections "*8.1. Efficacy and/or Immunogenicity Assessments*" and "*8.13. COVID-19 Monitoring*".

Illustration 18 : Phase 1-2-3 Pfizer Clinical Study Protocol (April 15th, 2020) – Determination of COVID-19 cases

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, a 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), 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. Four definitions of potential SARS-CoV-2–related cases will be considered:

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

Illustration 19 : Phase 1-2-3 Pfizer Clinical Study Protocol (April 15th, 2020) - COVID-19 Surveillance

8.13. COVID-19 Disease Surveillance (All Participants)

If a participant experiences any of the following, he or she is instructed to contact the site immediately, and if confirmed, participate in a telehealth visit as soon as possible, optimally within 3 days of symptom onset. 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;
- New or increased sore throat;
- New or increased wheezing;
- New or increased sputum production;
- New or increased nasal congestion;
- New or increased nasal discharge;
- Loss of taste/smell.

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

According to 8.1, efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19.
If the participant experienced at least one of the symptom in the Illustration 19, he should contact the site to plan an in-person visit or a telehealth in order to have a nasal swab, which will be tested at a central laboratory to detect SARS-CoV-2.
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.

It is important to note that, as planned in most trials, in addition to the test result provided by the local laboratory (laboratory in the participant's locality), the nasal swab had to be sent to a central laboratory to confirm or not the initial result and to avoid having heterogeneous diagnostic methods.

In the fourth Amendment of the protocol (30 June 2021), the symptoms for diagnosing COVID-19 were modified to approximate the June 2020 FDA "Development and Licensure of Vaccines to Prevent COVID-19" recommendations as shown in the amendment history page 134 of the pdf document (Illustration 20).

Illustration 20 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Summary of changes

Document	Version Date	Summary and Rationale for Changes
Protocol amendment 4	30 June 2020	Given the rapidly evolving pandemic situation, and the need to demonstrate VE as soon as possible, the protocol has been amended to be powered to meet new efficacy objectives. These new efficacy objectives and corresponding endpoints have been added to Section 3. Further nonclinical data are available to support the study of the BNT162b3 candidate in humans, and the candidate has been added to the protocol. The 6-month safety follow-up telephone contact has been changed to an in-person visit for Stage 3 participants, to allow collection of an immunogenicity blood sample. The COVID-19 illness visit has now added flexibility to permit a remote or in-person visit. The COVID-19 illness symptoms have been updated to align with the FDA-accepted definitions; this change is also reflected in the criteria for temporary delay of enrollment.

Source :
https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf
(page 134 of the pdf document)

This amendment changes the 6-month visit initially planned by simple telephone contact (teleconsultation) into a face-to-face visit allowing a blood sample to be taken for antibody testing.

The amendment also allows that the surveillance visit for COVID-19 was conducted via teleconsultation and no in person at the investigator site.

At the time of the start of the Phase 2/3 trial on July 27, 2020, it was therefore the second definition of symptoms that was underway to determine the occurrence of a COVID-19 as explained in sections 8.1 (Illustration 21), 8.14 (Illustration 27) and 8.13 (Illustration 26) of the protocol.

Illustration 21 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Determination of COVID-19 cases

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.

Source :
https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf
(page 201 of the pdf document)

According to this new definition, by confirmed symptomatic COVID-19, it should therefore be understood:

- **Presence of at least one of the following symptoms**
    - 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.

and

- **Test PCR positif** during or within the 4 days before or after the symptomatic. The nasal should be sent to a central laboratory in order to get homogenous results for all participants.

  If no central result was available, the result of a local laboratory should be used to confirm a COVID-19 case.

The severe cases were defined into the protocol as follows :

- **Confirmed COVID-19**

  and

- **Presence of at least 1 of the following :**
    - Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2 ≤93% on room air at sea level, or PaO2/FiO2 <300 mm Hg);
    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
    - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
    - Significant acute renal, hepatic, or neurologic dysfunction*;
    - Admission to an ICU;
    - Death.

In order to monitor reactions to the injection of the investigational products (reactogenicity) remotely, some participants had access to the study website, as explained in section "**8.2.2 Electronic Diary**" of the protocol. The participant himself/herself or his/her legal representatives could report certain information regarding his/her health status after injection of the investigational vaccine tested during the trial via an application installed on their personal devices.

The participant was trained in the use of this tool on the day of his first injection, cf line "Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required (Illustration 16).

The following items were to be assessed and reported by the first 6000 participants included in the Phase 3 trial (reactogenicity population) from one day after injection to 7ème days after injection, i.e., for approximately 14 days:

- ***Local reactions:***
  - Pain at the injection
  - Swelling
  - Redness

- ***Systemic events :***
  - **Vomiting**
  - **Diarrhea**
  - Headache
  - Fatigue/ tiredness
  - **Chills**
  - **New or worsened muscle pain**
  - New or worsened joint pain
- **Maximal oral temperature**

These possible reactions to vaccine are called “Solicited Eventss”.

The patient was required to alert their investigator in case of:

- **Grade 3** on the local reaction grading scale or grade 3 systemic event (cf Illustration 22 and Illustration 23), the event had to be reported to the investigator in order to plan a possible visit to the center. Grade 4 could only be determined by the investigator who had to inform the Sponsor and remove the patient from the trial
- **Fever ≥ 39 degres**. In case of the fever exceeded 40 degrees, it was imperative that the investigator inform the Sponsor and remove the patient from the trial.

The investigator remained responsible for detecting other serious or non-serious events by interviewing participants during their visit to the center.

Illustration 22 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Local reaction grading scale

Table 2. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	2.5 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

Source :
https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf
(page 207 du document pdf)

Illustration 23 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) - Systemic event grading scale

Table 3. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

Source :
https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf
(page 207 du document pdf)

The participant was also asked to defer the use of antipyretic medication.

Illustration 24 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) - Antipyretic medication

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the e-diary daily during the reporting period (Day 1 to Day 7).

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

The clinical trial will end on May 15, 2023 as indicated on the clinical trial registration site.

Illustration 25 : Pfizer - Trial registration

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	43998 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose:	Prevention
Official Title:	A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, HEALTHY INDIVIDUALS
Actual Study Start Date :	April 29, 2020
Estimated Primary Completion Date :	May 15, 2023
Estimated Study Completion Date :	May 15, 2023

Source : https://clinicaltrials.gov/ct2/show/NCT04368728?term=pfizer&cond=Covid19&draw=2

In reading these elements, we note a number of **inaccuracies** and even **problems in the method of evaluating the primary efficacy criterion**, namely, the number of confirmed symptomatic COVID-19 cases.

In order to calculate this criterion, it was necessary to identify, for each subject, if he had symptoms, if he was a confirmed case, yes or no, if yes, at what date, in particular from 7 days after the 2nd injection for the main analysis and this only during the period of observation before extraction from the database.

To record symptoms suggestive of a potential case of COVID-19, the participant could use an electronic diary as described in Illustration 26.

It should be noted that this method of collecting information is more suited to a young population used to using computer tools than to an elderly population.

Illustration 26 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Determination of COVID-19 cases

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.

Source :
https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf
(pages 241-242 du document pdf)

In order to correctly report his symptoms, the participant had the following means at his disposal (Illustration 27)

- Contact with the investigator, including the opportunity for the participant or the participant's parents/legal guardians, as appropriate, ***to report whether or not the participant has experienced symptoms that could represent potential COVID-19-related illness*** *(COVID-19 Electronic Illness Diary; see Section 8.13).*

- *An 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)*

Illustration 27 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) – Communication between the participant and the investigator site

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:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see Section 8.13).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

Source :
https://www.nejm.org/doi/suppl/10.1056/NEJMoa2107456/suppl_file/nejmoa2107456_protocol.pdf
(page 244 du document pdf)

The participant **was asked to contact the site immediately** but was also encouraged to consult his/her physician if he/she experienced any of the following symptoms: fever, onset or increase of cough, onset or increase of shortness of breath, chills, onset or increase of muscle aches, loss of taste or smell, sore throat, diarrhea, vomiting.

If the participant contacted his/her primary care physician, the physician would obviously proceed to the nasal swab for analysis by a local laboratory.
Did the physician have to take two swabs so that one could be sent to the central laboratory? This is not specified in the protocol.
Once the test result was obtained, the participant had to contact the investigator site to have the result recorded in the database.

If the participant chose to contact the site directly and not to make an appointment with his usual doctor, it is specified in the protocol (see Illustration 18) that symptoms that could be possible **reactions** to the experimental product (fever, chills, muscle aches ...) should not trigger a visit for a potential COVID-19 disease, **unless**

- *If, in the opinion of the investigator, such a visit was necessary.*
- *If, in the opinion of the investigator, the clinical picture was more indicative of possible COVID-19-related disease than vaccine reactogenicity.*
- *If, in the opinion of the investigator, the symptoms were more likely to be vaccine reactogenicity, **a local test for SARS-CoV-2** could be performed.*

This method of diagnosis also implies that the participant has correctly assessed **all** his/her symptoms.
It should be noted that participants completing the electronic diary to assess reactogenicity were also asked to complete the COVID-19 electronic symptom diary, thus he/she had to report identical symptoms (fever, chills, muscle aches, diarrhea, vomiting).

This also meant that center staff responded very quickly to calls from participants reporting symptoms so that PCR testing could be performed as quickly as possible. Given the number of participants recruited per clinical investigation center (on average 293) in record time, in the midst of the COVID-19 pandemic and travel restrictions, did the investigative sites have the capacity to respond to all participant calls?

It is was also planned that "if a participant or the participant's parents/legal guardians, as appropriate, did not actively complete the electronic reactogenicity log or the COVID-19 electronic disease log, the investigator or designee was to contact the participant or the participant's parents/legal guardians, as appropriate, to determine the reason for this and to obtain details of the missed events."

The Pfizer laboratory was thus well aware of the importance of the postponement of symptoms since section 8.14 of the protocol insists on this point (see Illustration 27)
"**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.**"

Clearly, any incomplete or erroneous reporting of symptoms could therefore lead to an erroneous assessment by the investigator, especially if the participant is behind a screen in a teleconsultation setting.

It is also important to note that any use of antipyretics suppresses fever and reduces or even eliminates pain, symptoms that are among the first signals that may suggest COVID-19 and that should trigger the test to confirm the presence of the virus or not.
It is therefore already clear that **the use of antipyretics introduces a bias by eliminating symptoms and therefore potential COVID-19 cases.**

Moreover, it is well known that some symptoms are both possible reactions to the vaccination and symptoms of COVID-19 such as fever, chills, muscle aches, diarrhea, vomiting.

How could an investigator differentiate between reactions due to the injection of the experimental product and COVID-19 symptoms during teleconsultations, without examining the participant, on the basis of some data reported by the participant himself?

Any participant with any of the symptoms of interest should logically have had a PCR test done immediately to classify the symptom as an adverse event or COVID-19, **without giving the investigator any option to decide otherwise**.

This approach induces a major bias in the evaluation of the occurrence of COVID-19 because it is well understood that no PCR test means no symptomatic COVID-19, so any symptomatic participant without PCR test is de facto classified as a therapeutic success.

Even worse, any symptomatic participant who has a PCR+ test result via their local laboratory but is unable to reach the investigator site is also classified as a therapeutic success.

In order to overcome this major bias, it would have been much more appropriate to perform PCR tests not only for participants reporting symptoms, but for **all** participants, this would also have allowed the detection of asymptomatic COVID-19 who are also vectors of the disease.

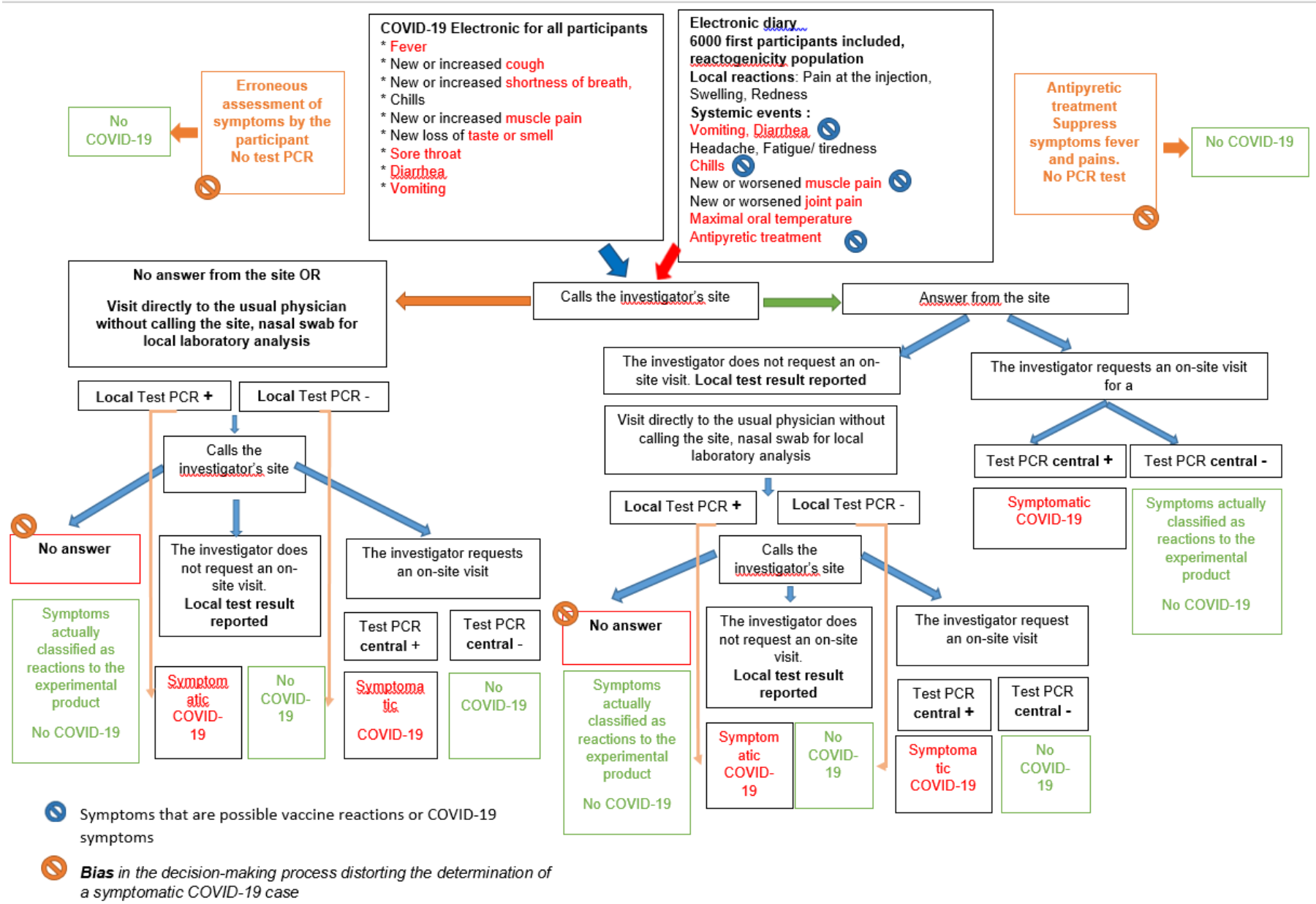
Considering the choice of the primary endpoint itself, we can already conclude that the Pfizer vaccine cannot claim to prevent transmission of COVID-19 since the efficacy is only evaluated on symptomatic cases and not all COVID-19 cases.

The diagnostic method chosen (summarized in the diagram on the following page), 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.

This obviously did not worry the laboratory much, which left the participants on their own without offering them systematic and regular tests as one might have expected.

From the protocol, it is already clear that the method used to determine the occurrence of a symptomatic COVID-19 case confirmed by PCR test, the main criterion of the trial, presents multiple biases that can seriously compromise the results obtained.

Illustration 28 : Main criterion diagnosis, symptomatic COVID-19 confirmed by PCR test



In order to conclude efficacy without waiting for the end of the trial, the protocol planned several interim analyses of the primary endpoint discussed above upon the occurrence of 62 evaluable symptomatic COVID-19 cases, then 92 cases, and finally 120 COVID-19.

Final analysis of all efficacy endpoints (primary and secondary) was to be performed after inclusion of at least 164 evaluable symptomatic COVID-19 cases.

Finally, the December 01, 2020 protocol amendment 10 allows participants who received placebo to receive BNT162b2 (see Illustration 29 page 129 of the pdf document).

This amendment therefore removes any possibility of comparing the BNT162b2 and placebo groups for both efficacy and safety.

Illustration 29 : Phase 1-2-3 Pfizer Clinical Study Protocol (January 4th, 2021) –Summary of changes

Protocol amendment 10	01 December 2020	• Added the possibility of administering BNT162b2 to participants who originally received placebo, following any local or national recommendations

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

4.3 Clinical trial results

4.3.1 December 10, 2020 Clinical Study Report on the > 16 Year Old population

As of November 14, 2020, 43,548 participants had been randomized from the 44,820 selected, 21,220 participants received the vaccine and 21,728 received the placebo.

At the time of the interim analysis reviewed with the health authorities, **the data included are those for the period July 72, 2020, through November 14, 2020**, the date of the interim database freeze, referred to as Cuttoff as indicated under the report's results tables.

At that date, 37,706 participants were analysed in the safety population (18,860 BNT162b2 and 18,846 placebo), half of whom had been followed for more than 2 months after the second dose of vaccine (50.6% exactly), 91.6% had been followed for more than 1 month after the first injection.

Details of participant follow-up times are presented in Table 3 of the clinical report (page 30).

Illustration 30 : Pfizer Clinical Study Report-- December 10th, 2020 – Participants follow-up

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

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

Of the 37,706 participants, **only 780 were followed for more than 3 months at the time of the interim analysis, or 2.1%** of the population analyzed.

The 2010 World Health Organization (WHO) recommendations, in section "*2.13 Follow-up in clinical trials*", called for a **follow-up period of one year for efficacy and 6 months for safety**.

Illustration 31 : 2010 WHO Recommandations

2.13 Follow-up in clinical trials

It is expected that there will be a follow-up of at least 6-months in clinical trials after the last dose of the vaccine, for safety assessment. This should be active and not reliant on spontaneous reports.

For efficacy and immunogenicity assessment longer follow-up, of at least one year, may be expected depending on the clinical endpoint requirements. Applicants are directed to guidance documents on specific vaccines for further information.

Immunogenicity assessment before and after the booster dose will be required for vaccines given as a booster dose.

Source :
https://www.who.int/immunization_standards/vaccine_quality/clinical_considerations_oct10.pdf?ua=1

In October 2020, the FDA wrote special recommandations for COVID-19 vaccines in a document called, "*Emergency Use Authorization for Vaccines to Prevent COVID-19*."

Source : https://www.fda.gov/media/142749/download

The preface indicates in the Public Comment section that this document was implemented **without public review as is customary**.

This document reduces the minimum duration of participant follow-up time to a median of 2 months, i.e., 50% may be followed for less than 2 months to establish efficacy and tolerability as clearly stated in paragraph c. on page 11

Illustration 32 : FDA Emergency Use Authorization for Vaccines to Prevent COVID-19 - Section C-3.c. Information Tolerance and efficacy

c. Data from Phase 3 studies should include a median follow-up duration of at least two months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile, including: adverse events; cases of severe COVID-19 disease among study subjects; and cases of COVID-19 occurring during the timeframe when adaptive (rather than innate) and memory immune responses to the vaccine would be responsible for a protective effect.

Source : https://www.fda.gov/media/142749/download

These new recommendations issued in a hurry are therefore not consistent with all previous recommendations, even the FDA's own recommendations written in June 2020 which were defined to provide valid and reliable results.

The results on page 55 of the clinical report (see Illustration 33) focus on the first appearance of COVID-19 from 7 days after dose 2 in participants without infection before 7 days after dose 2. They indicate that of the 18,198 participants who received BNT162b2, 8 were diagnosed with symptomatic COVID-19 by the definition and diagnostic method used, or 0.0439%, versus 162 in the placebo group, or 0.884%.

The efficacy was calculated as follows

$$\text{Relative risk (RR)} = \frac{8 / 18\,198}{162 / 18\,328} = \frac{0.0439}{0.8840} = 0.0497$$

Vaccine Efficacy = 1- RR = 1-0.497=95 %

The 95% credible interval for VE was 90.3% to 97.6% (95% confidence interval shown in the table below), indicating that the true VE is at least 90.3% with a probability of 97.5% (2.5% error threshold to conclude efficacy) given the observed data.

Illustration 33 : Pfizer Clinical Study Report-- December 10th, 2020 –Efficacy results – Main criterion – Symptomatic COVID-19 – 92 pages Report

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

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 (16:46)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_7pd2_wo_eval

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

A second report was presented by the laboratory during the "*Vaccines and Related Biological Products Advisory Committee*" of December 10, 2020, this one comprising only 53 pages instead of the 92 of the other report.

Source https://www.fda.gov/media/144245/download

The non-numbered page 24 shows exactly the same results as the first report but including results by age strata, confirming that these are the same results over the same observation periods.

Illustration 34 : Pfizer Clinical Study Report-- December 10th, 2020 – Efficacy results – Main criterion – Symptomatic COVID-19 – 53 pages report

5.2.5. Vaccine Efficacy

Primary Efficacy Analyses

Efficacy Results – Primary Endpoint (Evaluable Efficacy Population)

For the first primary efficacy endpoint, vaccine efficacy (VE) for BNT162b2 against confirmed COVID-19 was evaluated in participants without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. For the second primary efficacy endpoint, VE for BNT162b2 against confirmed COVID-19 was evaluated in participants with and without evidence of prior SARS-CoV-2 infection prior to 7 days after Dose 2. Cases were counted from 7 days after Dose 2 for both endpoints. The criterion for success was met if the posterior probability that true vaccine efficacy >30% conditioning on the available data was >99.5% at the final analysis.

For participants without evidence of SARS-CoV-2 infection prior to 7 days after Dose 2, VE against confirmed COVID-19 occurring at least 7 days after Dose 2 was 95.0%. The case split was 8 COVID-19 cases in the BNT162b2 group compared to 162 COVID-19 cases in the placebo group (Table 6). The 95% credible interval for the vaccine efficacy was 90.3% to 97.6%, indicating that the true VE is at least 90.3% with a 97.5% probability, which met the pre-specified success criterion.

Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

*Success criterion: the posterior probability that true vaccine efficacy > 30% conditioning on the available data is >99.5% at the final analysis

[a] N = number of participants in the specified group.

[b] n1 = Number of participants meeting the endpoint definition.

[c] Total surveillance time in 1000 person-years for the given endpoint across all participants 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 participants 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.

[f] Confidence interval (CI) for VE is derived based on the Clopper and Pearson method adjusted to the surveillance time.

Source : https://www.fda.gov/media/144245/download

This document mentions (page 42) **suspected cases of COVID but not confirmed by PCR test**, this part of the report has disappeared from the other 92 pages report presented the same day.

Illustration 35 : Pfizer Clinical Study Report-- December 10th, 2020 – Suspected COVID-19 cases – 53 pages report

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.

Source : https://www.fda.gov/media/144245/download

It states that during the trial, 3410 COVID 19 were suspected but not confirmed, 1594 occurred in the vaccine group versus 1816 in the placebo group.

Suspected cases that occurred within 7 days of any vaccination were **409** in the vaccine group versus **287** in the placebo group.

The remaining question is why 3410 cases were not confirmed by PCR test.

Were the cases unconfirmed because the PCR test was negative or unconfirmed because the PCR test was not performed by the center?

Therefore, the number of PCR tests performed for the 3410 suspected but non confirmed COVID 19 cases should be available.

If the primary endpoint had been based on the number of symptomatic participants, which is a relevant endpoint since the symptomatic patients are those who are hospitalized, we would have had, at a minimum, 417 cases for BNT162b2 (8+409) and 449 cases for placebo (162+287), which would have resulted in a VE of 6.5% !

Assuming that 30% of these cases were positive from 7 days after dose 2, this would add 123 cases to the 8 cases for the BNT162b2 group, or 131 cases. For the placebo group, we would obtain 86 additional cases to be added to the 162 already observed, i.e. 248 cases.

The efficacy calculation would then be 46.8%, far from the 95% announced.

When the percentage of COVID-19 cases is decreased, the efficacy is increased (see Illustration 3 Vaccine Effectiveness Simulation). This suggests an underestimation of the number of COVID-19 cases due to lack of PCR testing.

This suggests an underestimation of the number of COVID-19 cases due to lack of PCR testing.

Illustration 36 : Simulation Vaccine Efficacity according to positive % rate among the non confirmed cases

Hypothesis % of + cases	IRR	VE
30%	0,532	46,8 %
25%	0,473	52,7 %
20%	0,414	58,6 %
15%	0,118	88,2 %
10%	0,056	94,4 %

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.**

Illustration 37 : FDA - Development and Licensure of Vaccines to Prevent COVID-19 – Efficacy threashold

E. Statistical Considerations

- To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is >30%.
  - The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy.
  - A lower bound ≤30% but >0% may be acceptable as a statistical success criterion for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.

Source: Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry (fda.gov) - U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research June 2020 - https://www.fda.gov/media/139638/download

It is interesting to note that the vaccine efficacy was lower, **82%**, when taking into account **symptomatic COVID-19 cases from dose 1**.

This shows how much the choice of the primary efficacy criterion affects the result since there is a 13% loss when counting from dose 1 and not from dose 2.

Illustration 38 : Pfizer - Rapport clinique du 10 décembre 2020 - Résultats d'efficacité – Résultats d'efficacité COVID-19 symptomatiques à partir de la dose 1 - Rapport de 92 pages

Table 11. Vaccine Efficacy – First COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population

	Vaccine Group (as Randomized)					
	BNT162b2 (30 µg) (N[a]=21669)		Placebo (N[a]=21686)			
Efficacy Endpoint Subgroup	n1[b]	Surveillance Time[c] (n2[d])	n1[b]	Surveillance Time[c] (n2[d])	VE (%)	(95% CI[e])
First COVID-19 occurrence after Dose 1	50	4.015 (21314)	275	3.982 (21258)	82.0	(75.6, 86.9)
After Dose 1 to before Dose 2	39		82		52.4	(29.5, 68.4)
Dose 2 to 7 days after Dose 2	2		21		90.5	(61.0, 98.9)
≥7 Days after Dose 2	9		172		94.8	(89.8, 97.6)

Abbreviations: VE = vaccine efficacy.
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 Dose 1 to the end of the surveillance period.
d. n2 = Number of subjects at risk for the endpoint.
e. Confidence interval (CI) for VE is derived based on the Clopper and Pearson method (adjusted for surveillance time for overall row).
PFIZER CONFIDENTIAL SDTM Creation: 17NOV2020 (09:48) Source Data: adc19ef Table Generation: 18NOV2020 (17:06)
(Cutoff Date: 14NOV2020, Snapshot Date: 16NOV2020) Output File: ./nda2_unblinded/C4591001_Efficacy_FA_164/adc19ef_ve_cov_pd1_aai

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

For severe cases within 7 days after dose 2 (page 65 of the report), the reported vaccine efficacy (VE) results were 66.4%, however, the VE confidence interval of (-124.8, 96.3) **did not support a difference between BNT162b2 and placebo for this endpoint**.

Illustration 39 : Pfizer Clinical Study Report-- December 10th, 2020 – Efficacy results – Severe COVID-19 – 92 pages Report

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

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

As of December 10, 2020, it was therefore incorrect to conclude that BNT162b2 protected against severe cases as defined in the protocol.

Concerning the reactions reported by the participant on the electronic diary, only the 53-page report gives the numbers and proportions of participants with an event, the 92-pages report presenting only graphs making the percentages difficult to read.

In the subpopulation of participants aged 18-55 years with access to electronic diaries, 2045 BNT162b2 and 2053 placebo after dose 2 (pages 35 and 36 of the report), there was significantly more use of antipyretics in the BNT162b2 group (45%) than in the placebo group (12.6%).

The presence of a fever ≥ 38, chills, muscle pain are also much more reported with, respectively 15.8%, 35.1% and 37.3% versus 0.5%, 3.8% and 8.2% for placebo.

The results were similar for those over 55 years of age (pages 37 and 38 of the report) in terms of the difference between BNT162b2 and placebo but with less symptom reported, possibly due to the use of the electronic diary, which may indicate an underestimation of symptoms in older participants.

Illustration 40 : Pfizer Clinical Study Report-- December 10th, 2020 – Solicited events after dose 2 – 18-55 years Population / > 55 years old Population

	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)

Source : https://www.fda.gov/media/144245/download

It should be noted that the reactogenicity population is a subpopulation of the general population, so **it would have been important to ensure that it represents the general population in terms of age, sex, comorbidities**...

Regarding the duration of protection assessed by antibody assay, Illustration 41 shows the average neutralizing antibody assay for participants aged 18 to 55 years (page 26 of the report), while Illustration 41 (page 27 of the report) shows the average neutralizing antibody assay for participants over 65 years of age for phase 1/2.

It is important to note that the laboratory was aware of the products administered to each participant since it was not blinded (see section 6.3.3-*Blinding of the Sponsor* of the protocol).

It can be noted that, under the 2 graphs, the cutoff date was August 24, 2020 and not November 14 (date of the database extraction) as for the other results. The neutralizing antibody assays were presented for days D1, D21, D28, D35 and D52, D28 to 52 being performed after dose 2.

A decrease in immunity was already observed at D52 whatever the dose 10 µg, 20 µg or 30 µg, the dose finally chosen on July 27. It is very surprising that no results were available after August 24 for the unfinished Phase 1 when one sees the laboratory's eagerness to manage the progress of its clinical trials.

Illustration 41 : Pfizer Clinical Study Report-- December 10th, 2020 –Immunogenicity results – Phase 1,2 – 18-55 years old – 92 pages report

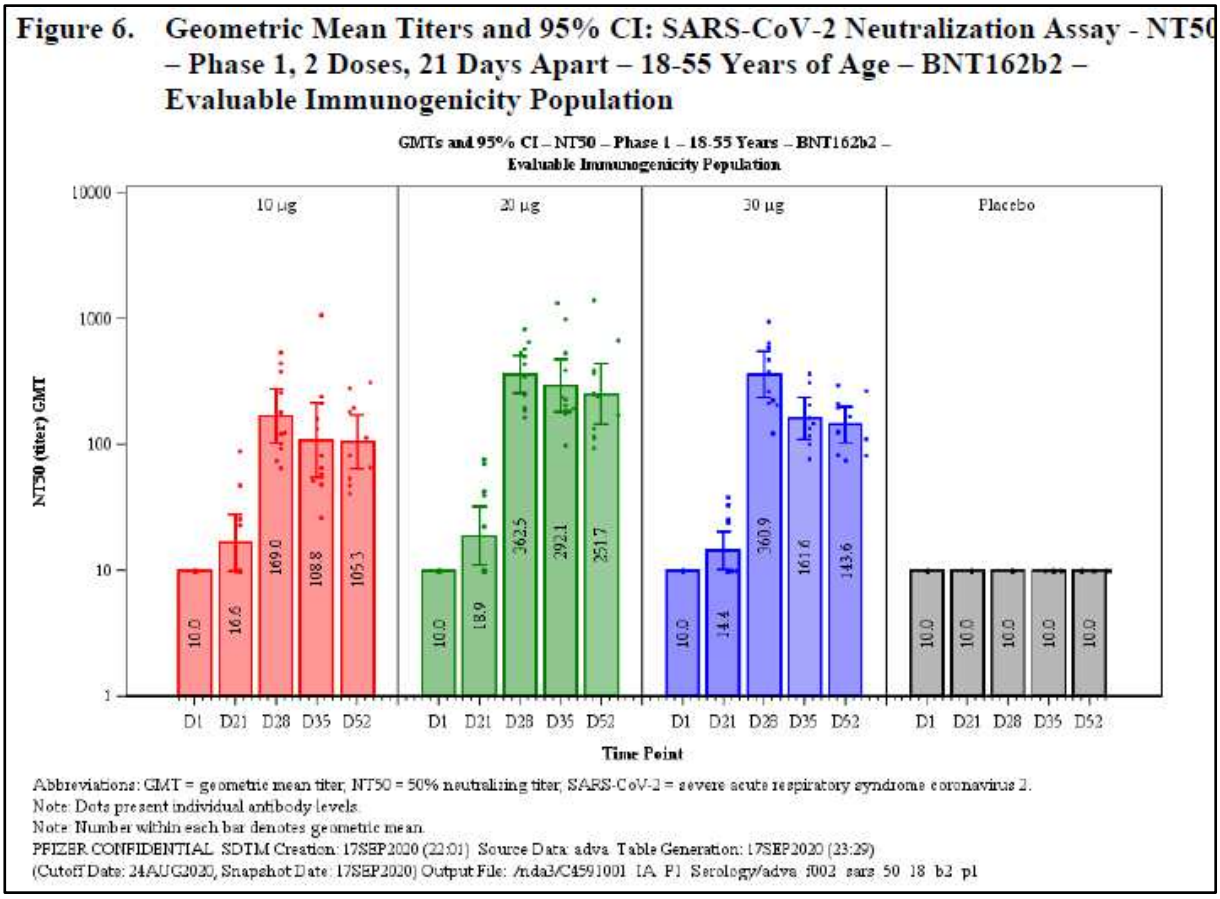
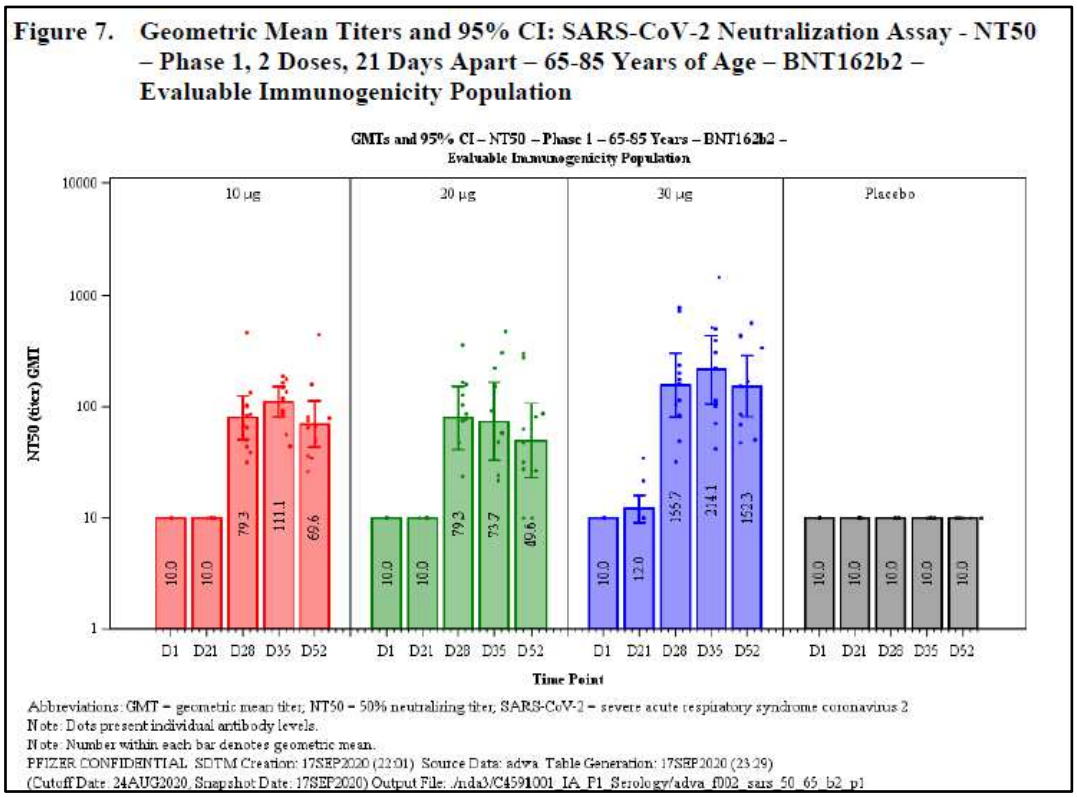
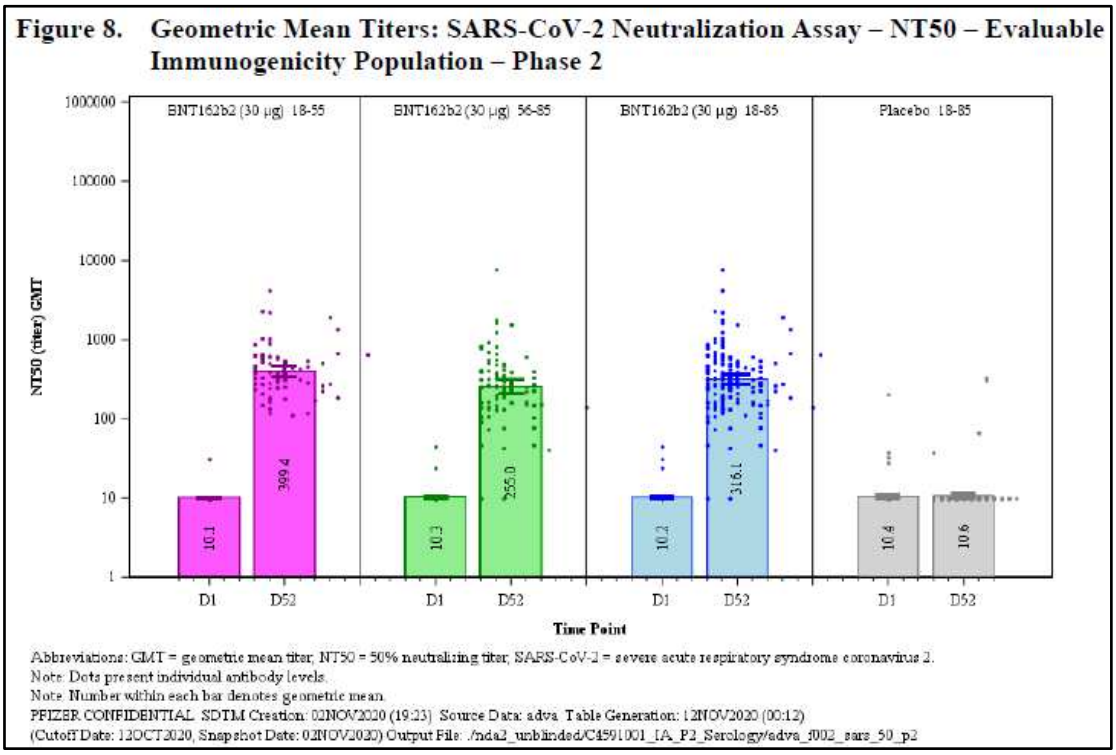


Illustration 42 : Pfizer Clinical Study Report-- December 10th, 2020 – Immunogenicity results – Phase 1,2 – 65-85 years old – 92 pages report



For phase 2, results were presented only for D1 and D52, as intermediate assays were suppressed for an unknown reason (see below page 35 of the report).

Illustration 43 : Pfizer Clinical Study Report-- December 10th, 2020 – Immunogenicity results – 65-85 ans – Rapport de 92 pages



Source : https://www.fda.gov/media/144245/download

It should be noted that the FDA's Emergency Use Authorization for Vaccines to Prevent COVID-19 states that **no immune markers have been identified to establish protection against COVID-19**. Therefore, neutralizing antibodies were used, for lack of a better term, to assess immunogenicity.

4. Assays for assessment of immunogenicity endpoints

The assays used to assess immunogenicity endpoints of clinical studies should be identified. Even though an immune marker predictive of protection against COVID-19 has not been established to date, depending on the vaccine construct, neutralizing antibody may be considered a relevant measure of immunogenicity.

Source : « Emergency Use Authorization for Vaccines to Prevent COVID-19 - Guidance for Industry » , « Autorisation d'Urgence pour les vaccins contre la COVID-19 ».https://www.fda.gov/media/142749/download

4.3.2 April 9, 2021 Clinical Study Report on the 12-15 year old population

In the April 9, 2021 report, the results of the analyses are presented for 2260 participants aged 12-15, 1,131 who received BNT162b2 injection, 1,129 who received placebo.

As for the population over 16 years of age, the follow-up time does not exceed 3 months with 42% being followed for less than 2 months, or 60 days as shown by the Illustration 44 (page 13 of the report).

Illustration 44 : Pfizer Clinical Study Report-April 9, 2021- Participants' follow-up

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

	Vaccine Group (as Administered)		
	BNT162b2 (30 µg) (N[a]=1131)	Placebo (N[a]=1129)	Total (N[a]=2260)
Length of Follow-up[c]	n[b] (%)	n[b] (%)	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)

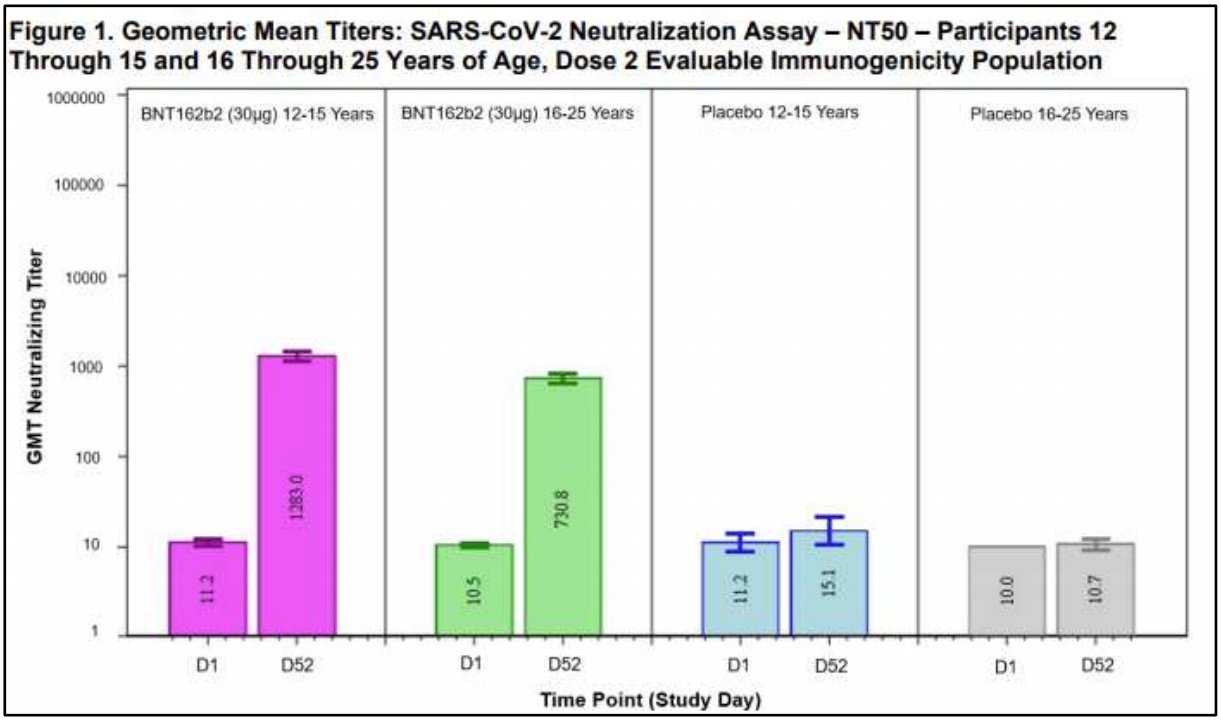
Source: EUA 27034.132, eua-amend-12-15-years.pdf, Table 3, page 20.
[a] N=number of subjects in the specified group, or the total sample. This value is the denominator for the percentage calculations.
[b] n=number of subjects with the specified characteristic.
[c] Length of follow-up is the total exposure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

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

As in the previous report, antibody assays are presented only at day 1 and day 52, because of the short follow-up time, no results were provided at more than 2 months (page 20 of the report).

Illustration 45 : Pfizer Clinical Study Report-April 9, 2021– Immunogenicity results (p 20)

Figure 1. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay – NT50 – Participants 12 Through 15 and 16 Through 25 Years of Age, Dose 2 Evaluable Immunogenicity Population



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

On page 38 of this same report, the unknown benefits and data gaps associated with Pfizer's COVID-19 vaccine when used in adolescents aged 12 to 15 years are listed (see Illustration 46), they are the same as those detailed in the memorandum authorizing the vaccine for emergency use in persons aged 16 years and older.

Illustration 46 : Pfizer Clinical Study Report-April 9, 2021 – Unknown benefits and data gaps

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.

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

The long list of missing information on a product that has been used for nearly 6 months in real life on millions of people is more than worrisome.

Pfizer recognizes here, although in a roundabout way, the **impotence of its vaccine to act against asymptomatic infections** and thus to slow down the transmission of the virus, as already demonstrated earlier in this report, the main criterion chosen not being able to claim any effectiveness in this matter.

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

The October 26, 2021 clinical report present results based on the data extracted on the 08 October 2021 (cut-off date).

The randomization scheme was 2:1, with twice as many participants in the group BNT162b2 as in placebo group.

On this very young population of **2,238 children aged 5 to 11 years** (safety population), as in previous reports, the median follow-up time after Dose 2 was only 2 months, with 95.1% of participants being observed between 2 and 3 months with a maximum of 2.5 months (page 26 of the report).

Illustration 47 : Pfizer Clinical Study Report - October 26th, 2021 – Participants' follow-up

BNT162b2
VRBPAC Briefing Document

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)

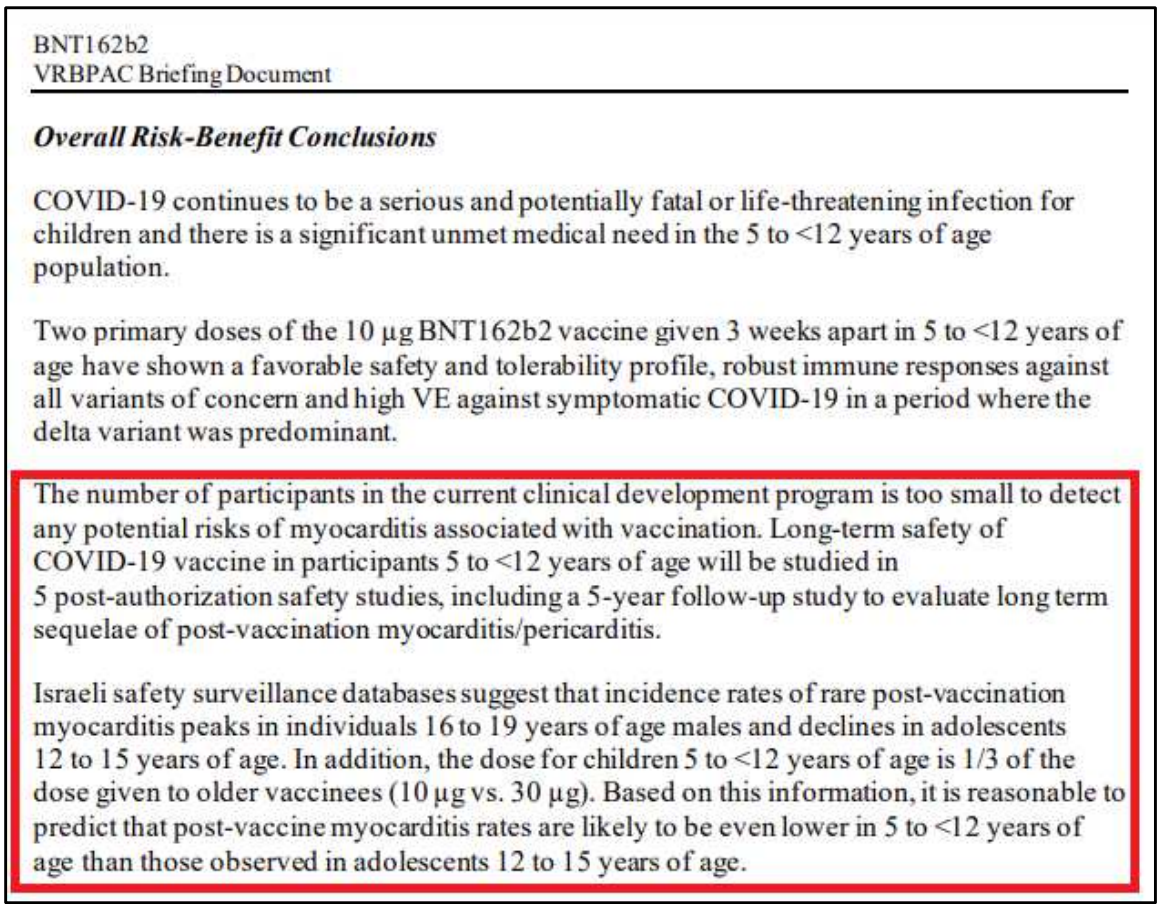
Note: Follow-up time was calculated from Dose 2 to the cutoff date or withdrawal date or the date of unblinding (per protocol), whichever date was earlier. Follow-up time after Dose 2 for participants who did not receive Dose 2 was counted as 0.
a. N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
b. n = Number of participants with the specified characteristic.

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

In the benefit/risk assessment section, it is clearly established that the sample size of this young population "***is too small to detect potential risks of myocarditis associated with vaccination.***" *(see* Illustration 48 page 11 of the report).

As for other populations studied, the long-term safety of the COVID-19 vaccine could not be assessed without post-approval safety studies, *including a 5-year follow-up study to assess long-term sequelae of post-vaccination myocarditis/pericarditis*."

Illustration 48 : Pfizer Clinical Study Report - October 26th, 2021 – Overall Risk/Benefit Conclusion



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.

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

This admission that serious events such as myocarditis/pericarditis cannot appear in the safety results of the clinical trial is evidence that the calculated sample size does not allow for the detection of serious adverse events. **This is therefore an admission of the invalidity of the safety results presented in the report provided**.

5 Real-life adverse events

As required by the Pharmacovigilance regulations, the sponsor remains responsible for the management of post-marketing safety data.

The reported effects come from multiple sources

- The laboratory's own database of spontaneously reported cases
- Cases reported to health authorities
    - EudraVigilance in Europe, https://dap.ema.europa.eu/analytics/saw.dll?PortalPages
    - VAERS (Vaccine Adverse Event Reporting System) in the US, www.vaers.hhs.gov
- Cases published in the medical literature,
- Cases from marketing programs sponsored by the laboratory,
- Identified cases of non-interventional studies
- Cases of serious adverse events reported in clinical trials,

All cases must be reported; independently of the evaluation of causality, it is the analysis of cases that will allow the calculation of safety signals for the detection of adverse drug reactions not highlighted in clinical trials and to evaluate potential causal associations between an event and the product and to update the list of risks identified when people take the product.

5.1 Pfizer Adverse Event Analysis

« 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, 42,086 case reports are in the database, 25,379 medically confirmed and 16,707 non-medically confirmed, containing 158,893 events 34,762 in the United States, 13,739 in the United Kingdom, 13,404 in Italy 7,324 were distributed in 56 other countries.

Among the 42,086 reports, 1,223 deaths were reported, or nearly 3% (see below).

Illustration 49 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – February 28th, 2021 – General Analysis

BNT162b2
5.3.6 Cumulative Analysis of Post-authorization Adverse Event Reports

Table 1 below presents the main characteristics of the overall cases.

Table 1. General Overview: Selected Characteristics of All Cases Received During the Reporting Interval

Characteristics		Relevant cases (N=42086)
Gender:	Female	29914
	Male	9182
	No Data	2990
Age range (years): 0.01 -107 years Mean = 50.9 years n = 34952	≤ 17 18-30 31-50 51-64 65-74 ≥ 75 Unknown	175[a] 4953 13886 7884 3098 5214 6876
Case outcome:	Recovered/Recovering	19582
	Recovered with sequelae	520
	Not recovered at the time of report	11361
	Fatal	1223
	Unknown	9400

a. in 46 cases reported age was <16-year-old and in 34 cases <12-year-old.

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

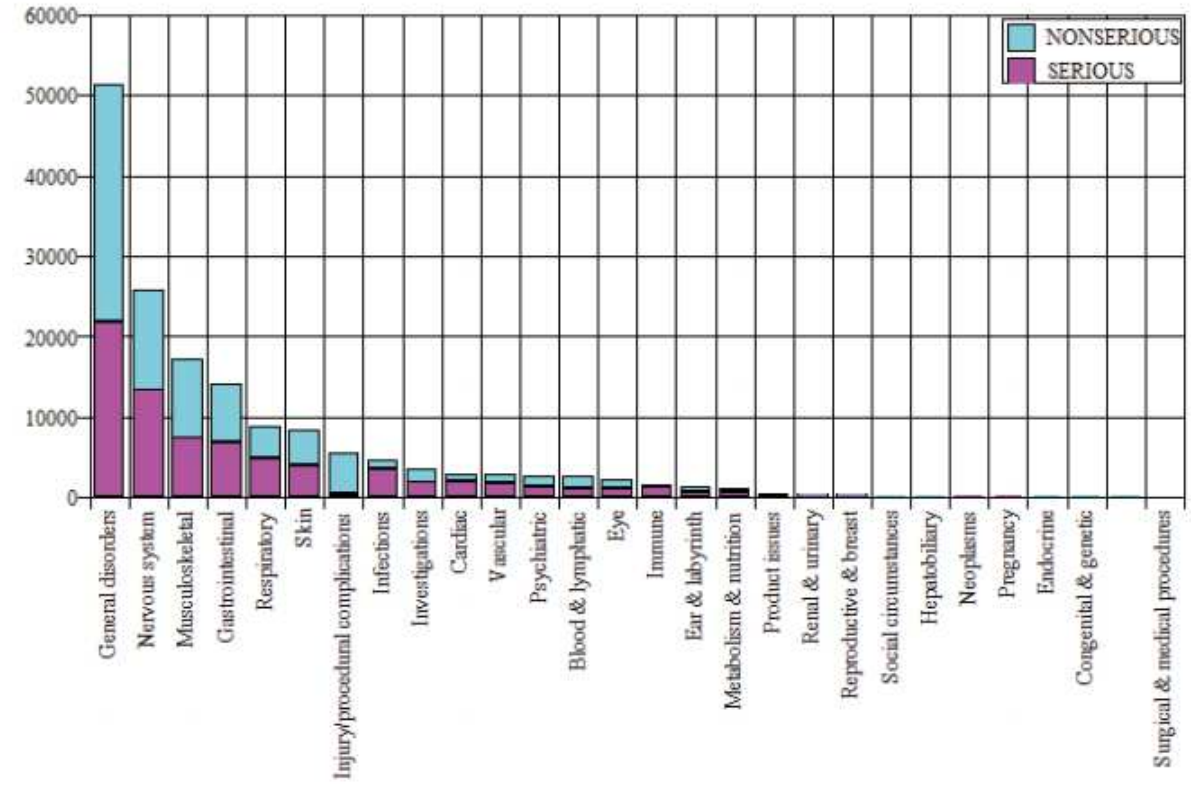
The most reported adverse events (AEs) were general disorders and administration site conditions (51,335 AEs), nervous system disorders (25,957), musculoskeletal and connective tissue disorders (17,283) gastrointestinal disorders (14,096), skin and subcutaneous tissue disorders (8,476), respiratory, thoracic, and mediastinal disorders (8,848), infections and infestations (4,610), injuries, poisonings, and procedural complications (5,590), and investigations (3,693).

Illustration 50 shows a **high proportion of serious events** (indicated in purple), more than 50% of the reported effects were serious for almost all categories, and more particularly among cardiac diseases, infections, autoimmune diseases.

Illustration 50 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – February 28th, 2021 - Total Number of Adverse Events by Organ Class and Seriousness

BNT162b2
5.3.6 Cumulative Analysis of Post-authorization Adverse Event Reports

Figure 1. Total Number of BNT162b2 AEs by System Organ Classes and Event Seriousness



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

It is interesting to note that **1,927 COVID-19 out of 42,086 were reported (**4.6%) in the Infections and infestations class (System Organ Class of the MedDRA dictionary) as mentioned into the table below.

Illustration 51 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – February 28, 2021 - Events reported ≥ 2% Cases

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**

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 real life of 4.6% was more than 100 times equal to the infection rate of the clinical trial which was 0.044%**.

This confirms the major bias in the choice of the primary endpoint.

The report also highlighted the occurrence of

- Cardiac adverse events myocardial infarction, arrhythmia, heart failure, cardiogenic shock; coronary heart disease, myocardial infarction, tachycardia, cardiomyopathy
- Hematological adverse events: leukopenia, neutropenia, thrombocytopenia, hemorrhage
- Facial paralysis or paresis ...

Although pregnant women were excluded from the clinical trials, they were also vaccinated in real life, and the report mentions 270 pregnant women among whom 26 spontaneous abortions or neonatal deaths were reported.

Illustration 52 : Pfizer - Cumulative Analysis of Post-authorization Adverse Event Reports – February 28th, 2021 - Pregnant women

Pregnancy cases: 274 cases including:

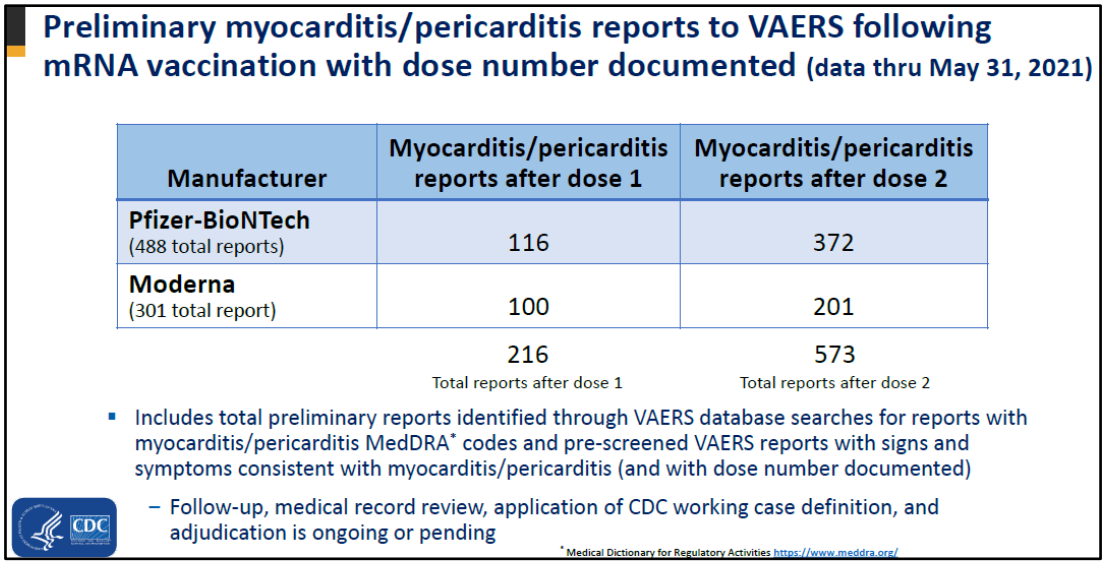
- 270 mother cases and 4 foetus/baby cases representing 270 unique pregnancies (the 4 foetus/baby cases were linked to 3 mother cases; 1 mother case involved twins).
- Pregnancy outcomes for the 270 pregnancies were reported as spontaneous abortion (23), outcome pending (5), premature birth with neonatal death, spontaneous abortion with intrauterine death (2 each), spontaneous abortion with neonatal death, and normal outcome (1 each). No outcome was provided for 238 pregnancies (note that 2 different outcomes were reported for each twin, and both were counted).

Although half of the events analysed were serious, the laboratory confirmed a favourable benefit/risk ratio for BNT162b2.

5.2 Centers for Disease Control and Prevention (CDC) evaluation of safety signals

At its June 10, 2021, CDC safety Updates safety meeting, CDC counted **216 myocarditis/pericarditis after Pfizer and Moderna doses 1, 573 after dose 2, for a total of 789 identified from the VAERS site**.

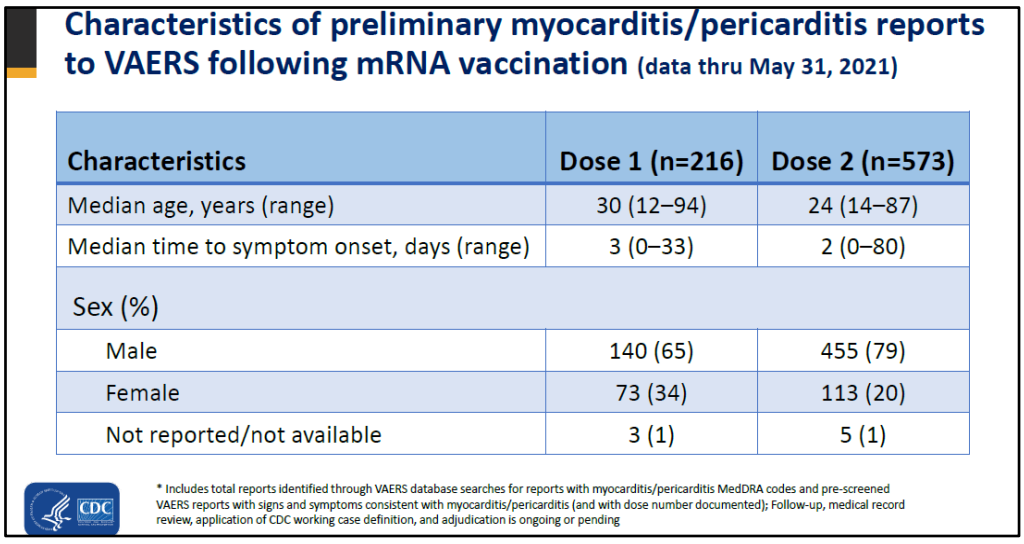
Illustration 53 : CDC safety Updates - June 10th, 2021 – Number of myocarditis/pericarditis



Source : CDC safety Updates Vaccines and Related Biological Products Advisory Committee (VRBPAC), Tom Shimabukuro - https://www.fda.gov/media/150054/download

50% of the events were observed in subjects under 30 years of age after dose 1 and in subjects under 24 years of age after dose 2 (see median age line Illustration 54) with events occurring on the same day after injection up to 80 days (Illustration 54 line Median time to symptom).

Illustration 54 : CDC safety Updates - June 10th, 2021 – Age of patients with myocarditis/ pericarditis



Source : CDC safety Updates Vaccines and Related Biological Products Advisory Committee (VRBPAC), Tom Shimabukuro - https://www.fda.gov/media/150054/download

Of the 789 myocarditis/pericarditis events, **only 60** were considered, i.e., only 7.6% in the calculation of the signals supposed to warn of an adverse effect in real life. Indeed, due to the calculation method, only events occurring within **21 days after injection** were counted.

Illustration 55 : CDC safety Updates - June 10th, 2021 – Myocarditis/Pericarditis Risk Assessment

Outcome events in the VSD in 21-day risk interval after either dose of any mRNA vaccine compared with outcome events in vaccinated comparators on the same calendar days

(thru May 29, 2021)

Pre-specified outcome event	Events in risk interval	Adj Rate Ratio*	95% CI	Signal
Acute disseminated encephalomyelitis	2	.	0.07– .	no
Acute myocardial infarction	560	1.00	0.86–1.17	no
Appendicitis	608	0.82	0.71–0.95	no
Bell's palsy	454	1.02	0.85–1.21	no
Cerebral venous sinus thrombosis	4	1.07	0.17–9.36	no
Disseminated intravascular coagulation	26	0.62	0.33–1.19	no
Encephalitis / myelitis / encephalomyelitis	15	1.06	0.38–3.41	no
Guillain-Barré syndrome	10	0.63	0.20–2.14	no
Stroke, hemorrhagic	224	0.89	0.70–1.14	no
Stroke, ischemic	944	0.97	0.86–1.10	no
Immune thrombocytopenia	43	1.04	0.58–1.92	no
Kawasaki disease	0	0.00	0.00–6.53	no
Myocarditis / pericarditis	**60**	**0.94**	**0.59–1.52**	**no**
Seizures	233	1.01	0.79–1.31	no
Transverse myelitis	2	0.50	0.04–15.32	no
Thrombotic thrombocytopenic purpura	5	2.04	0.33–17.36	no
Thrombosis with thrombocytopenia syndrome (TTS)	60	0.76	0.49–1.18	no
Venous thromboembolism	530	1.06	0.90–1.25	no
Pulmonary embolism	459	1.00	0.84–1.19	no

* Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. ne=not estimable

Source : CDC safety Updates Vaccines and Related Biological Products Advisory Committee (VRBPAC), Tom Shimabukuro - https://www.fda.gov/media/150054/download

As a result, the safety signal for the occurrence of this serious effect, which could lead to the death of the patient, was minimized. One could have expected, on the contrary, a calculation rather unfavourable to the product, as it is usually done in the pharmaceutical industry, in order not to miss severe risks, especially for a product developed in such a short time and to be distributed worldwide.

In contrast to all the emergency measures taken for COVID-19, no specific steps have been taken to further monitor real-life vaccine adverse events.

In the previous illustration, it should be noted that a significant number of vascular accidents (1168 cases), whether haemorrhagic (Stroke, haemorrhagic) or ischemic (Stroke, ischemic), the same for thrombotic events (5+ 60 +530 + 459 = 1054).

Assuming that, as with myocarditis/pericarditis, the CDC did not count even 10% of reported cases, there would have been more than 12,000 cases of vascular events and more than 12,000 thrombotic events for all COVID-19 vaccines as of June 11.

As of October 25, 2021, the same Tom Shimabukuro presented an update on the risks for myocarditis and pericarditis. Of 1640 reported cases, 877 were retained in the assessment, **which concluded, as expected, that Pfizer/BioNTech and Moderna vaccines increased the risk of both conditions in 12-39 year olds**.

Illustration 56 : CDC Safety Updates – October 25th, 2021 - Number of Myocarditis/

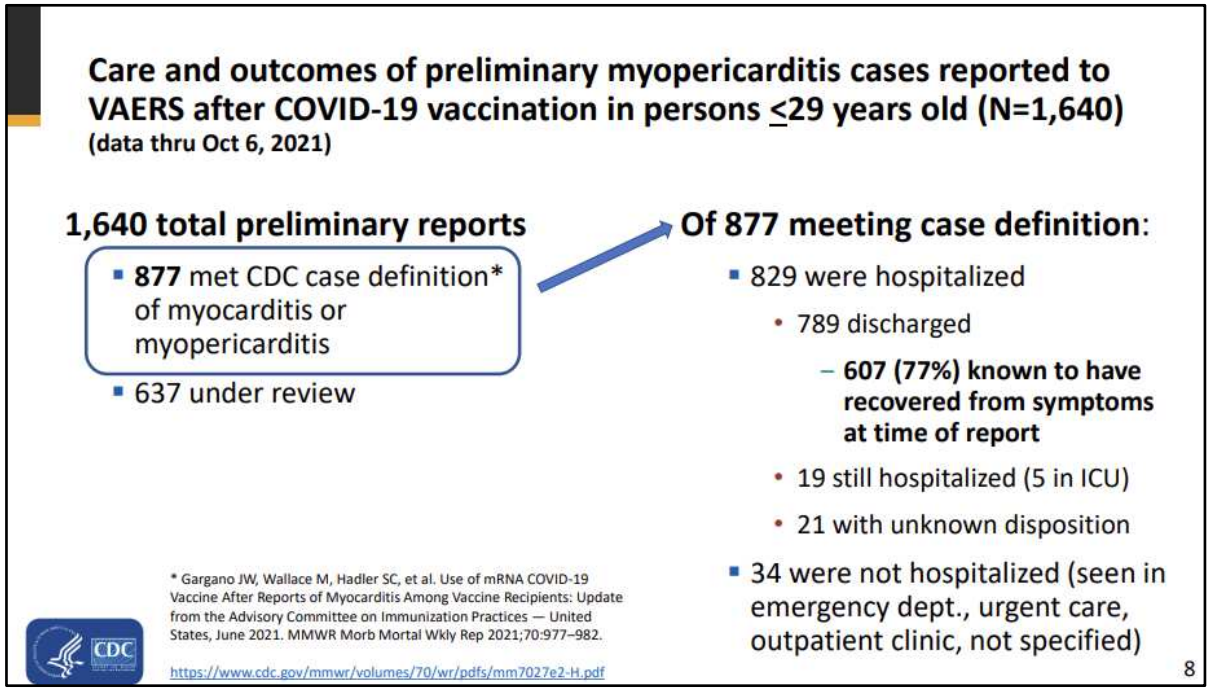
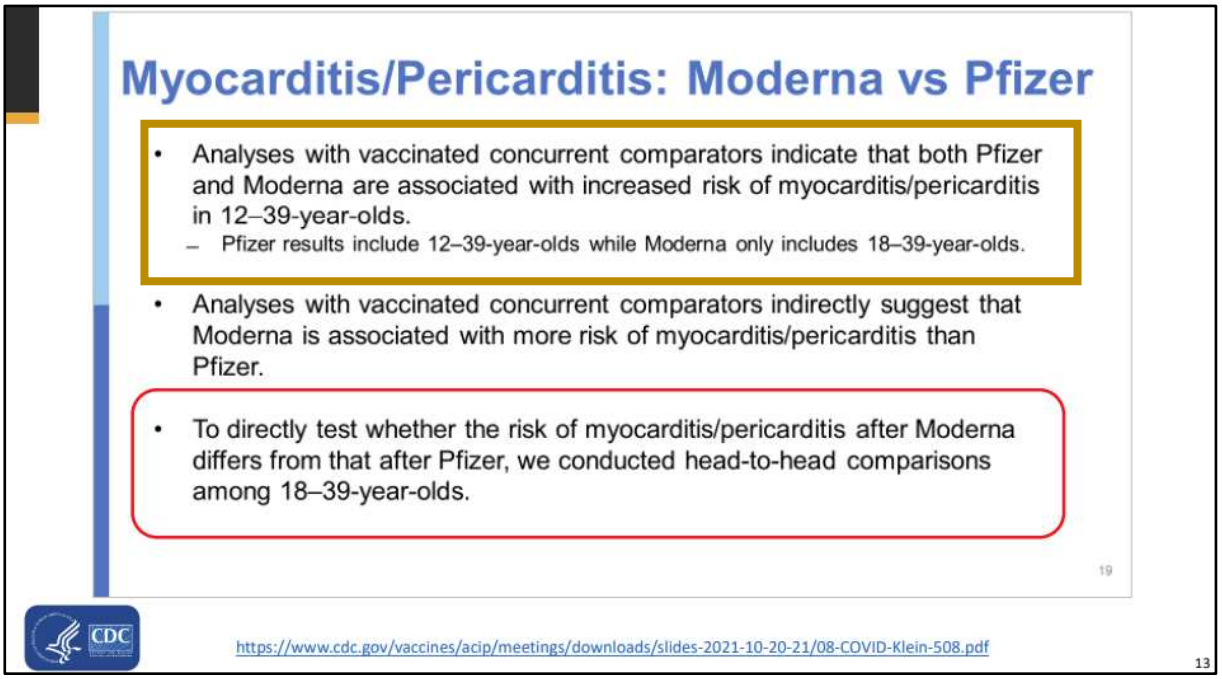


Illustration 57 : CDC Safety Updates – October 25th, 2021 – Myocarditis/Pericarditis Risk Assessment



Source : *Myocarditis Following mRNA -COVID-19 Vaccination- WHO COVID-19 Vaccines Research - Tom Shimabukuro, MD, MPH, MBA - Vaccine Safety Team*
https://cdn.who.int/media/docs/default-source/blue-print/shimabukuro_who-blueprint_myocarditis_who-vr-call_25oct2021.pdf?sfvrsn=40e99d51_7

Scientific papers, which we will not mention in this report as they deserve a report of their own, are regularly published concerning adverse events and deaths after vaccination, **they are signs of incomplete evaluation of tolerance during clinical trials**, so much so that some health authorities have already taken measures to compensate people who have suffered adverse events, or even to suspend use in certain populations.

In September 2020, the Australian Federal Department of Health in fact launched a website for people suffering from vaccine side effects offering compensation capped at $5,000, by November 2020, more than 10,000 people had already made a claim. That means it would cost at least $50 million if each claim is approved. A new service will soon be available for uncapped claims that can run into the hundreds of thousands or even millions of dollars for major brain or heart injuries or even deaths. Claims over $20,000, including death claims, must be evaluated by a panel of independent legal experts and compensation will be paid based on their recommendations.

Source : https://www.lesechos.fr/idees-debats/editos-analyses/covid-les-effets-secondaires-du-vaccin-vont-couter-cher-a-laustralie-1364543

In the United States, the INJURY COMPENSATION PROGRAMS reports, as of November 1, 2021, 2299 claims for adverse events due to COVID-19 vaccines; 108 deaths are reported, 103 myocarditis/pericarditis, 67 anaphylactic reactions ...

https://www.hrsa.gov/cicp/cicp-data#table-1

The Japanese Ministry of Health has alerted to the problems of myocarditis/pericarditis in young men as possible serious side effects of Moderna and Pfizer's COVID vaccines.

Source : https://www.japanbullet.com/news/health-ministry-warns-of-vaccines-side-effects

Taiwan, on the other hand, has suspended the 2nd ème dose of Pfizer vaccine for 12-17 year olds due to myocarditis.

Source : https://www.msn.com/en-in/news/world/taiwan-suspends-2nd-dose-pfizer-covid-vaccine-for-12-17-ages-amid-myocarditis-cases/ar-AAQD03t

6 Uncertainties and Persistent Risks

6.1 Identified risks

In response to identified real-life adverse events, based on the emerging signal of myocarditis and pericarditis following COVID-19 mRNA vaccines discussed at the June 10, 2021, FDA and CDC Vaccines and Related Biological Products Advisory Committee (VRBPAC) meetings, the Comirnaty Vaccine Emergency Authorization Fact Sheet was revised on June 25, 2021, to add a warning for myocarditis and pericarditis. The Pharmacovigilance Plan was also amended to include myocarditis and pericarditis as significant risks identified.

All of this is clearly explained in the Clinical Review Memorandum written by Drs. Susan Wollersheim and Ann Schwartz on August 23, 2021 (page 14).

Source: https://www.fda.gov/media/152256/download

The Risk Management Plan of September 24, 2021 therefore includes myocarditis/pericarditis in the significant risks identified (page 82).

Illustration 58 : Risk Management Plan - September 24, 2021 – Important identified risks

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Anaphylaxis

Risk-benefit impact

Anaphylaxis is a serious adverse reaction that, although very rare, can be life-threatening.

Important Identified Risk: Myocarditis and Pericarditis

Risk-benefit impact

Myocarditis and pericarditis are serious conditions that may occur concomitantly and that may range in clinical importance from mild to life-threatening.

Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

The other risks, Anaphylaxis and Vaccine-associated enhanced disease (VAED) including Vaccine associated enhanced respiratory disease (VAERD) listed have been present since the first version of the Risk Management Plan.

These three risks are still present in the Risk Management Plan of November 25, 2021.

Illustration 59 : Risk Management Plan, November 25, 2021 – Important identified risks

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Anaphylaxis

Risk-benefit impact

Anaphylaxis is a serious adverse reaction that, although very rare, can be life-threatening.

Important Identified Risk: Myocarditis and Pericarditis

Risk-benefit impact

Myocarditis and pericarditis are serious conditions that may occur concomitantly and that may range in clinical importance from mild to life-threatening.

Important Potential Risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)

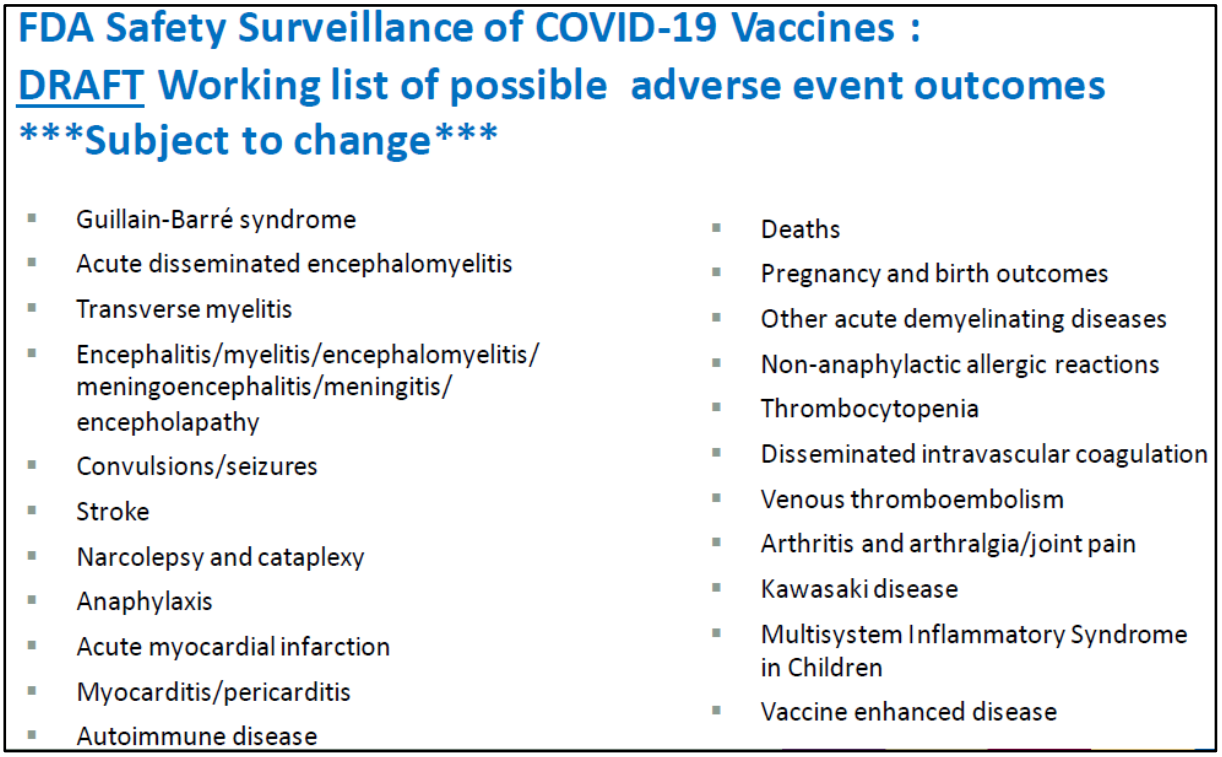
Risk-benefit impact

Although not observed or identified in clinical studies with COVID-19 vaccines, there is a theoretical risk, mostly based on non-clinical betacoronavirus data, of VAED occurring either before the full vaccine regimen is administered or in vaccinees who have waning immunity over time. If VAED were to be identified as a true risk, depending on its incidence and severity, it may negatively impact the overall vaccine benefit risk assessment for certain individuals.

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

All this was more than foreseeable given the reduced follow-up time of the participants in the analyses provided by Pfizer especially since, as early as October 22, 2020, a document presented by the FDA itself mentioned an impressive list of side effects to be followed up, those that appear in real life since the use of the Comirnaty vaccine, the Risk Management Plan mentioning only a small part of it.

Illustration 60 : FDA - October 22nd, 2020 – Vaccines surveillance COVID-19



Source:
CBER Plans for Monitoring COVID-19 Vaccine Safety and Effectiveness Steve Anderson, PhD, MPP Director, Office of Biostatistics & Epidemiology

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

6.2 Missing Information

The Risk Management Plan already mentioned in chapter SVII.3.2 "**Presentation of the Missing Information**" the missing information **as of April 29, 2021**.

- Use in pregnancy and while breast feeding
- Use in immunocompromised patients
- Use in frail patients with co-morbidities (i.e. 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

Illustration 61 : Risk Management Plan, April 29th, 2021 – Missing Information

BNT162b2
Risk Management Plan 29 April 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*.

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 44. 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

This information is still missing in the November 25, 2021 Risk Management Plan.

Illustration 62 : Risk Management Plan, November 25th – Missing information

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

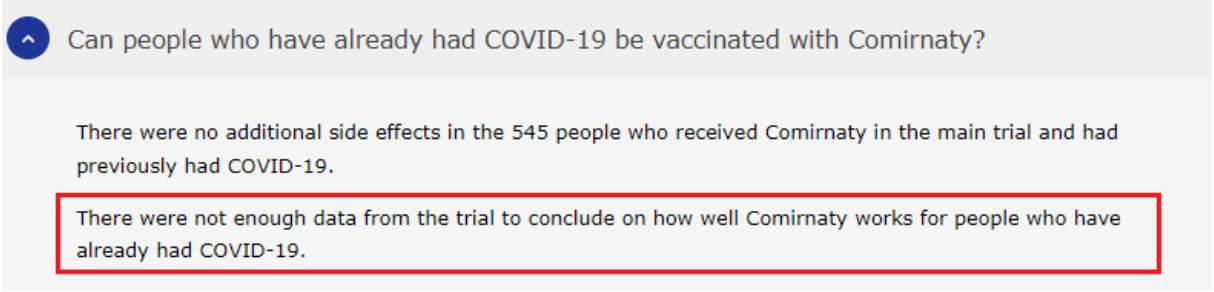
Important identified risks	Anaphylaxis Myocarditis and Pericarditis
Important potential risks	Vaccine-associated enhanced disease (VAED) including Vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breast feeding
	Use in immunocompromised patients
	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

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

Several clinical trials are therefore planned or on going to address these many persistent uncertainties about the subpopulations involved.

The European Medicines Agency (EMA) website is sufficient to summarize the limited knowledge about the vaccine by summarizing the points of the Risk Management Plan
https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

- Not enough information to conclude on side effects of vaccine action in people who have had a COVID-19 infection

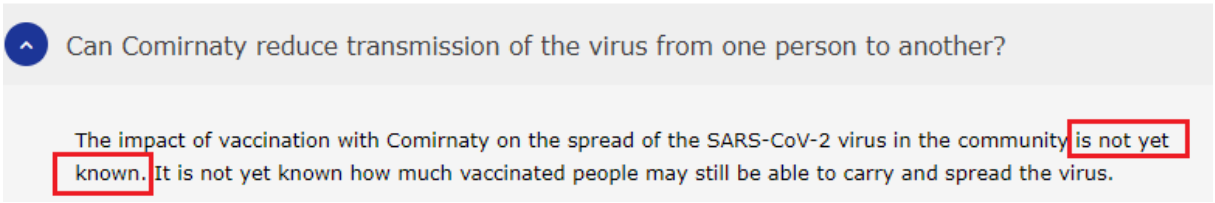


Can people who have already had COVID-19 be vaccinated with Comirnaty?

There were no additional side effects in the 545 people who received Comirnaty in the main trial and had previously had COVID-19.

There were not enough data from the trial to conclude on how well Comirnaty works for people who have already had COVID-19.

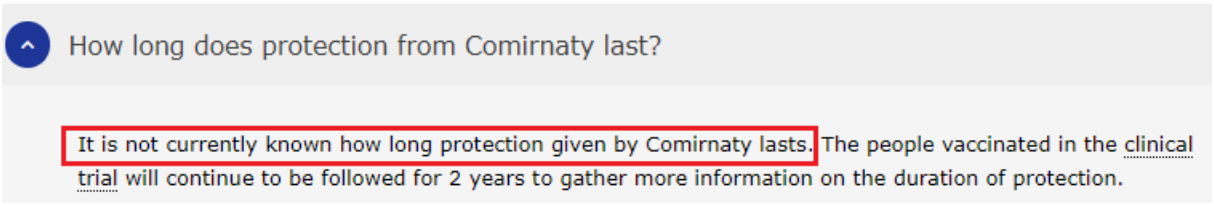
- Impact on transmission not yet known



Can Comirnaty reduce transmission of the virus from one person to another?

The impact of vaccination with Comirnaty on the spread of the SARS-CoV-2 virus in the community is not yet known. It is not yet known how much vaccinated people may still be able to carry and spread the virus.

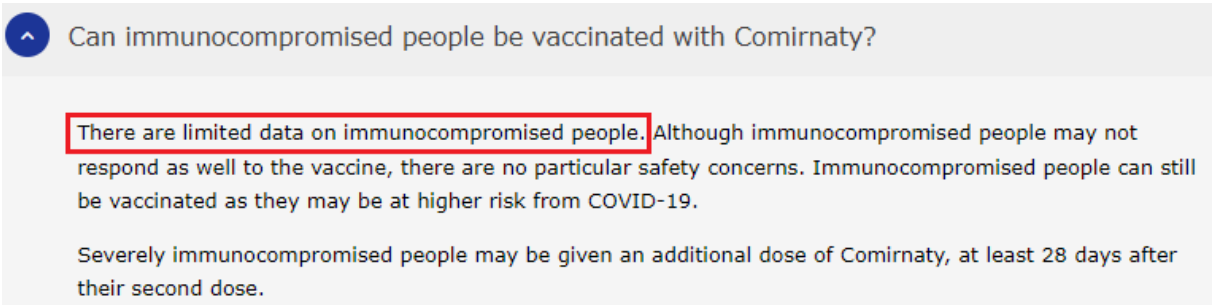
- Duration of protection not yet known



How long does protection from Comirnaty last?

It is not currently known how long protection given by Comirnaty lasts. The people vaccinated in the clinical trial will continue to be followed for 2 years to gather more information on the duration of protection.

- Limited data on immunocompromised people

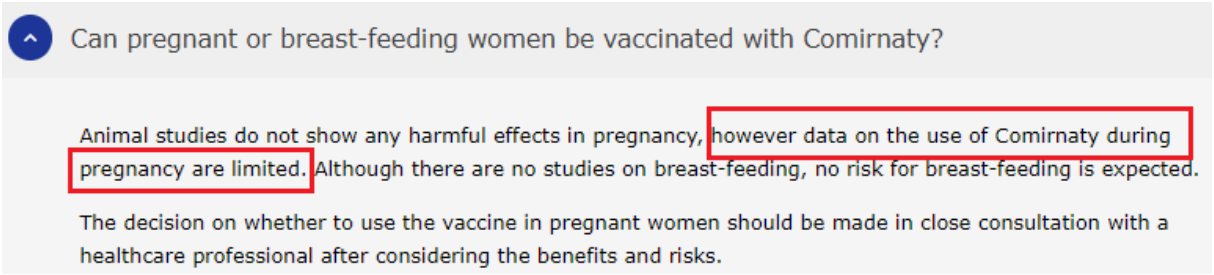


Can immunocompromised people be vaccinated with Comirnaty?

There are limited data on immunocompromised people. Although immunocompromised people may not respond as well to the vaccine, there are no particular safety concerns. Immunocompromised people can still be vaccinated as they may be at higher risk from COVID-19.

Severely immunocompromised people may be given an additional dose of Comirnaty, at least 28 days after their second dose.

- Limited data on pregnant women



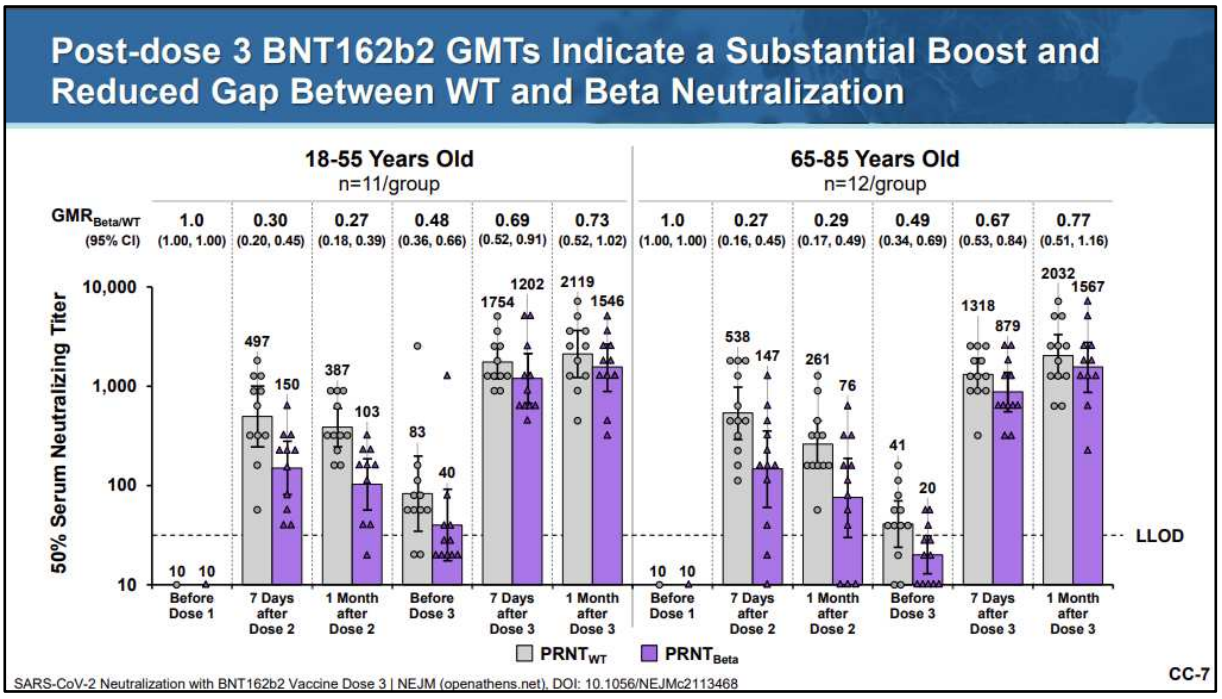
Despite the lack of information clearly documented by the laboratory itself and the EMA for months, these populations are undergoing real-life vaccination.

6.3 Waning of protection

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).

The graph presented below for the dosage clearly indicates a decrease in the antibody level before dose 3 (before booster), a booster dose put in place to compensate for the protection of the vaccine.

Illustration 63 : Pfizer Presentation – September 22nd, 2021 – Immunogenicity Evaluation



Source: BNT162b2 [COMIRNATY® (COVID-19 Vaccine, mRNA)] Booster (Third) Dose - William C. Gruber, MD, FAAP, FIDSA, FPIDS September 22, 2021 -Senior Vice President -Vaccine Clinical Research and Development - Pfizer Inc

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

In summary, while in real life billions of doses were administered, the calculation of surveillance signals by the authorities have underestimated for months the real level of risk for myocarditis/pericarditis while this event was observed in young patients (50% in those under 24 years old).

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 real life was more than 100 times equal to the infection rate of the clinical trial.** This confirms the underestimation of the number of symptomatic COVID-19 cases, the primary endpoint of the trial.

The long list of unknown or missing elements in the April 9, 2021 report was a backhanded admission of the vaccine's **inability to act against asymptomatic infections** and thus, in fact, to curb the transmission of the virus, the main criterion of efficacy chosen, not being able to claim any efficacy in this matter.

As of September 22, 2021, Pfizer publicly admitted a drop in antibodies 6 to 8 months after the second dose, this would have been observed earlier if the interim analysis had been performed at 6 months instead of the median 2 months as authorized by the FDA Emergency use and if the trial had planned visits between 1 month after the 2ndème dose and 6 months after the 2ndème dose, which seems to be common sense even for such an innovating vaccine

The design of the trial therefore helped to mask this drop, which was however predictable from the first report in December 2020, as the antibody level at D52 was lower than the level at D35.

The lack of long-term safety data and the lack of data on the sub-populations cited in the different versions of the Risk Management Plan and in the April 2021 clinical report summarized on the European Medicines Agency website clearly demonstrate that **the risk assessment presented in the clinical reports is totally incomplete**, thus distorting the benefit/risk ratio based on which the emergency use was authorized

7 Doubts about data quality, the Ventavia and Madeline de Garay "cases

According to an article in the British Medical Journal, Ms. BrookJackson regional director with 20 years of experience in clinical trial coordination and management, hired by CRO Ventavia Research Group (https://www.ventaviaresearch.com/) on September 7, 2020, to oversee operations, recruitment and quality assurance for the company's clinics, is alleging serious breaches of Good Clinical Practice and other misconduct.

Source: Thacker P D. Covid-19: Researcher blows the whistle on data integrity issues in Pfizer's vaccine trial BMJ 2021; 375 :n2635 https://www.bmj.com/content/375/bmj.n2635

During her months on Pfizer. BioNTech's Phase 2/3 COVID-19 trial, Ms. Jackson and two other employees who wished to remain anonymous accused Ventavia for.

- Having stored vaccines at the **wrong temperature**,
- Having falsified data,
- **Having not respected the anonymization of patients**, as the staff of the centres should not be informed of the product actually administered to the different participants since the trial was intended to be blinded
- Having employed inadequately trained vaccinators
- Having delayed in following up on reported adverse events as evidenced by the email sent by ICON CRO, the CRO chosen by Pfizer to manage the trial "*subject reported severe symptoms/reactions... As per protocol, subjects with Grade 3 local reactions should be contacted. Please confirm if an UNPRECEDENTED CONTACT was made and update the corresponding form appropriately*." According to the trial protocol, telephone contact should have occurred "to obtain additional details and determine if a site visit is clinically indicated."
- Having made **gross errors** in sample handling (mislabelled samples) as evidenced by the "laboratory processing logs" completed by staff.
- Having for not being able to complete the data entry within the required timeframe, for which he was called to order by the ICON CRO,
  "*The expectation for this study is that all requests will be processed within 24 hours*."
- **Not having performed PCR tests for all participants with COVID-19 symptoms to validate or not the presence of the case.**

  Ventavia did not have enough staff to collect samples from all trial participants who reported COVID-19-like symptoms to test for infection.
  This information could partly explain the famous symptomatic but PCR-unconfirmed COVID-19 cases and thus confirms the doubts about the validity of the number of COVID-19 cases calculated for the primary endpoint.

Brook Jackson says they were unable to quantify the types and number of errors found when reviewing clinical trial documents for quality control because they were so numerous.

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

The CRO issued a statement of denial, saying that "no part of its job responsibilities involved the clinical trials at issue," but two former Ventavia employees corroborate Jackson's claims. Yet recruitment of participants was suspended to address the list of "common" quality control failures to be investigated, Ventavia did not inform Pfizer of the reason for the pause, as required, and allegedly engaged in a policy of concealing its wrongdoing.

Brook Jackson reportedly holds a document with a list of Ventavia's outstanding "action items," which include discussions with trial coordinators about serious data integrity violations putting patients at risk.

The Ventavia case only concerns 3 centres that included 1000 participants but, if the facts are true, this highlights that the main criterion is erroneous and that the trial was not properly controlled and supervised by Pfizer, which casts suspicion on the management of all the other centres.

The elements cited in the Ventavia case (storage of products at the wrong temperature, failure to respect anonymization, errors in handling samples, chaotic follow-up of serious adverse events ....) **are particularly serious facts in clinical trials since they are serious violations of Good Clinical Practices**.

The FDA states on its vaccine page, in its "Supporting Documents / Approval History, Letters, Reviews, and Related Documents - COMIRNATY" section, and more specifically in the "Bioresearch Monitoring Discipline Review Memo, August 13, 2021 - COMIRNATY" document, that it **has conducted an inspection of 6 sites out of the 153 clinical sites** that included Phase 3 participants.

The FDA justifies this low 3.9% audit rate on a product with such innovative features as Comirnaty by the fact that, of the 153 sites, 131 were in the United States and 22 sites outside the United States. Due to travel restrictions related to the COVID-19 pandemic, only domestic sites were considered for on-site BIMO (bioresearch monitoring) inspection.

Yet, the containment restrictions did not visibly hinder the recruitment and follow-up of 44,000 participants.

The FDA states in the document that it has audited 3 additional sites before approving the vaccine for use in ages 12 and older.

Illustration 64 : FDA audit of August 13, 2021

In response to the PHE, BIMO reviewers proactively performed a review of the sponsor's investigational new drug application (IND 19736) and issued the necessary BIMO inspections to review the study conduct of Protocol C4591001, "*A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of SARS-COV-2 RNA Vaccine Candidates Against COVID-19 in Healthy Individuals.*"

Protocol C4591001 was a multi-center study conducted at a total of 153 clinical sites: 131 study sites in the United States and 22 sites outside of the United States. Due to the COVID-19 pandemic travel restrictions, only the domestic sites were considered for an on-site BIMO inspection. Initially, six (6) study sites were inspected, before FDA issued the original Emergency Use Authorization for individuals 16 years of age and older. Subsequently, three (3) additional sites were inspected before FDA authorized use of the vaccine in those 12 and older. All of the study sites were selected based on subject enrollment, previous inspectional history, and other information submitted in IND 19736.

The inspections were conducted in accordance with FDA's Compliance Program 7348.811, Inspection Program for Clinical Investigators, focusing primarily on the study conduct, human subject protection and compliance with related FDA regulations. The data integrity and verification portion of the BIMO inspections were limited because the study was ongoing, and the data required for verification and comparison were not yet available to the IND. The table below summarizes the domestic study site information and the outcome of each BIMO inspection:

Illustration 65 : FDA audit of August 13, 2021– Listing of audited sites

Site ID	Site Location	Form FDA 483 Issued	Final Classification
1007	Cincinnati Children's Hospital Medical Center Cincinnati Center for Clinical Research Cincinnati, OH	No	No Action Indicated (NAI)
1009	J. Lewis Research Inc./ Foothill Family Clinic South, Salt Lake City, UT	No	NAI
1044	Virginia Research Center, LLC. Midlothian, VA	No	NAI
1056	Indago Research and Health Center, Inc. Hialeah, FL	No	NAI
1109	Deland Clinical Research Unit DeLand, FL	No	NAI
1118	Meridian Clinical Research, LLC. Binghamton, NY	No	NAI
1125	Meridian Clinical Research, LLC Norfolk, NE	No	NAI
1133	Research Centers of America Hollywood, FL	No	NAI
1149	Collaborative Neuroscience Research, LLC at two locations: Long Beach & Garden Grove, CA	No	NAI

Source : Bioresearch Monitoring Discipline Review Memo, August 13, 2021 – COMIRNATY - Approval History, Letters, Reviews, and Related Documents – COMIRNATY
https://www.fda.gov/vaccines-blood-biologics/comirnaty

According to the FDA, the audits did not raise any major issues.

However, in its letter, the FDA states that the inspection program focused primarily on the conduct of the study, protection of participants, and compliance with related FDA regulations. It states that "***The data integrity and verification portion of the BIMO [biological research monitoring] inspections was limited because the study was ongoing and the data required for verification and comparison were not yet available for the IND [investigational new drug]***"(see Illustration 64))

It is surprising that the sites managed by Ventavia (located in Dallas, Galveston, Texas, Houston) are not among the sites inspected despite the letter sent by Ms. Jackson who had reported major violations of Good Clinical Practices to the FDA.

It is also very surprising that the data required for an inspection was not available at the time of the audit, since the Trial Master File containing all the documents must be updated regularly and it is highly unlikely that the FDA did not notify the centres so that they could retrieve the missing elements in order to present them to the auditor.

Even more surprisingly, no problems were identified at the Cincinnati Children's Hospital Medical centre, which had enrolled Garay's Maddie who participated in the Pfizer Phase 3 trial for 12-15 year olds.

Maddie suffered multiple adverse events after receiving the second dose of vaccine, severe abdominal and chest pain, gastroparesis, nausea, vomiting, erratic blood pressure, heart rate and memory loss. Maddie's mom says she had great difficulty reaching the centre.

Source : https://www.foxnews.com/media/ohio-woman-daughter-covid-vaccine-reaction-wheelchair

Although Maddie is still in a serious condition, she is fed through a gastric tube because she still cannot digest food, she no longer walks intermittently, Maddie's case appears as "abdominal pain" instead of "permanent paralysis". in the clinical report on the 12-15 year old population.

Illustration 66 : Pfizer Clinical Study Report – April 9, 2021 – Serious Adverse Events

SAEs

Dose 1 through 1 month after Dose 2

12-15-year-olds: SAEs from Dose 1 through up to 30 days after Dose 2 in ongoing follow-up were reported by 0.4% of BNT162b2 recipients and 0.1% of placebo recipients. A total of 5 SAEs were reported by 5 recipients (4 BNT162b2, 1 placebo), all who had no history of prior SARS-CoV-2 infection (SARS-CoV-2 negative at baseline).

BNT162b2:

- 3 participants, all with pre-existing anxiety and depression, were hospitalized for medical management of depression exacerbation that started 7 days after Dose 1, 1 day after Dose 2, and 15 days after Dose 1, respectively. All 3 participants reported treatment with a selective serotonin reuptake inhibitor (SSRI) that began within 1-2 months prior to vaccination. Worsening suicidal ideas with initial SSRI treatment in adolescents is a recognized risk and provides a reasonable alternative explanation for depression exacerbation in these BNT162b2 recipients.

- One participant experienced an SAE reported as generalized neuralgia, and also reported 3 concurrent non-serious AEs (abdominal pain, abscess, gastritis) and 1 concurrent SAE (constipation) within the same week. The participant was eventually diagnosed with functional abdominal pain. The event was reported as ongoing at the time of the cutoff date.

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

On August 23, 2021, the medical review by Drs. Wollersheim and Schwartz reported in section 3.2 Compliance with Good Clinical Practice and Submission Integrity on 7 investigators with conflicts of interest out of the 1,834 who participated in the clinical studies (see pages 15 and 16 of the report).

In addition, they named the efforts made to eliminate bias in the studies. These included the following:

- **The trial was double-blind and multicenter**
  The number of participants at each center is not known at this time, and no analysis by center was provided to conclude that the multicenter design of this study was free of bias.

- **The statistical methods used are in accordance with the statistical analysis plan.**
  This is not a proof of the absence of bias, and it is the case for almost all clinical trials. There is no discussion of the identification of symptomatic COVID-19 cases, which is a more than questionable point.

- **Frequent monitoring of investigators' trial sites and auditing of study sites.**
  The monitoring elements are not sufficiently explicit in the reports provided to be able to conclude that the monitoring of the sites was done adequately, especially in the middle of a pandemic, any remote verification of the data being less reliable than on-site visits by the CRAs.

- **The validity of the data collected was confirmed by standard monitoring procedures.**
  In other words, no special procedures were implemented to manage this critical trial, even though the vaccine was expected to be administered to billions of people.

- **Data processing involved cleaning checks (querying data through electronic edit checks) to ensure that errors were identified and corrected.**
- **Data were reviewed by clinicians and queries were generated in case of inconsistencies during the course of the trial**
  These arguments refer to the checks programmed by the data managers to retrieve missing data and correct inconsistent data. This is the least that can be done in a serious clinical trial.

- **The study report was reviewed by the project team and quality control.**
  It would be interesting to know what comments were made on the reports.

- **The study sites performing the safety assessments were deemed acceptable based on appropriate certification or historical performance and/or qualifications and credentials.**
  Again, it is the least we can do to recruit competent investigators to participate in a study of this importance.

According to the report, "*No major statistical issues were identified by CBER CBER (Center for Biologics Evaluation and Research) statistical reviewers in this application. The key statistical analyses for safety and efficacy were confirmed by CBER statistical reviewers*".

The editors conclude in section "4.7 Risk and Benefit Assessment" that

- *"the benefit-risk estimates are limited by **uncertainties** associated with the dynamics of pandemics."*
- *"The major uncertainties in benefits are related to potential changes in COVID-19 incidence over time and vaccine efficacy and duration of protection in the face of emerging virus **variants**."*
- *"The major risk uncertainty is the data on **vaccine-related myocarditis cases***
- *and **deaths**."!*

Source : https://www.fda.gov/media/152256/download

In summary, the current "cases" seem to confirm the **dubious quality of the data**, both for efficacy (PCR tests not carried out) and for tolerance, and the impossibility of reporting serious effects, thus considerably distorting the evaluation of the real number of effects and therefore the evaluation of the real risks run by people who are vaccinated

This underestimation of serious effects can only be amplified by the workload of the investigating centers, which have broken records in recruiting participants.

The results of the FDA audits cannot be taken into account to comfort on the integrity of the data since, against all expectations, and for reasons of sanitary restrictions, they have not been subject to on-site verification.

The medical review report of August 25, 2021 is not particularly comforting on the quality of the controls carried out, as it refers to classic and obvious validations in the pharmaceutical industry, the conclusions are more than trivial.

8 Conclusion

This report highlights the following points.

Regarding the evaluation of efficacy

Regarding the calculation of the primary endpoint, first occurrence of symptomatic COVID-19 from 7 days after dose 2, defined by

- **Presence of at least one of the following symptoms reported by the participant among:**
  - 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.

  And

- **Positive PCR tests** during or within the 4 days before or after the symptomatic. The nasal should be sent to a central laboratory in order to get homogenous results for all participants.
  If no central result was available, the result of a local laboratory should be to confirm a COVID-19 case.

In order to diagnose a potential COVID-19, the participant was invited to immediately contact the investigator site having included him in the clinical trial in order to report the symptoms mentioned above but was also encouraged to consult his usual physician (see sections 8.1 and 8.13 of the protocol[1]; Illustration 21 and Illustration 26).

In order to ensure that the symptoms were correctly reported, the participant had the following means at his disposal (see Illustration 27) :

- *Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate,* ***to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness*** *(COVID-19 illness e-diary; see Section 8.13).*
- *An alert in the event that the participant is hospitalized.*
- *Visit reminders.*
- *Messages of thanks and encouragement from the study team.*
- *A platform for recording local reactions and systemic events (reactogenicity e-diary) – see Section 8.2.2.*

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

The first 6000 participants included (the so-called reactogenicity population) had an access to an electronic diary to report possible reactions to the tested products such as fever, chills, muscle aches, diarrhea, vomiting, the whole population having to note all COVID-19 symptoms including the previous ones on another electronic diary.

When the participant had these symptoms that overlap possible vaccine reactions (fever, chills, muscle aches, diarrhea, vomiting) and that he contacted the site directly, it is specified in the protocol (see Illustration 18) that "these symptoms should not trigger a visit for a potential COVID-19 disease, except

- *If, in the opinion of the investigator, such a visit was necessary.*
- *If, in the opinion of the investigator, the clinical picture was more indicative of possible COVID-19-related disease than vaccine reactogenicity.*
- *If, in the opinion of the investigator, the symptoms were more likely to be vaccine reactogenicity,* ***a local test for SARS-CoV-2*** *could be performed.*

The PCR test was therefore not systematically performed for all participants but only for participants reporting symptoms and on the advice of the investigator.

This approach has the following biases:

Any erroneous assessment or incomplete reporting of symptoms by the participant does not trigger PCR testing to confirm or not the presence of COVID-19.

For a study of this importance, carried out on an innovative product, in a record time frame, leaving the participant to report his/her symptoms, with all the errors of judgment that this entails, since the participant does not have the clinical competence to assess his or her health status, is particularly questionable

Pfizer was well aware of the importance of symptom carry-over since section 8.14 of the protocol insists on this point (see Illustration 27).

"***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***."

Any participant with at least one of the symptoms listed in the primary endpoint determination should logically have been prompted to perform an immediate PCR test to classify the symptom as an adverse event or as a COVID-19 case.

This constitutes a major bias in the evaluation of the primary endpoint, since it is impossible to be certain that COVID-19 symptoms were not classified as adverse events because of the lack of PCR testing, since **it is clear that no PCR testing means no symptomatic COVID-19**.

The need for participants to call the investigating site to report their symptoms also means that site staff must respond very quickly to calls so that PCR testing can be performed as quickly as possible.

In the case where, the participant had directly consulted his GP, he had to call the investigator site to inform him of the result of his PCR test carried out by a local laboratory. This also implied a great reactivity of the investigator site in order to note the result in the database and possibly to plan a visit on site.
Any late response from the site or even non-response also leads to an underestimation of the number of symptomatic COVID-19 cases.
Given the number of participants recruited per clinical investigation center (on average 293) in record time, in the middle of the COVID-19 pandemic and travel restrictions, did the investigative sites have the capacity to respond to all participating calls?
The Maddie de Garay case confirms **the difficulty some participants had in reaching the investigator site and obtaining participant management**.

This major methodological bias is confirmed by the existence of the **3410 suspected but non confirmed cases of COVID-19 by PCR test (409 suspected cases identified in the vaccine group versus 287 in the placebo group within 7 days of any vaccination)** reported in one of the two clinical reports submitted on December 10th 2020 to the FDA (see Illustration 35 : Pfizer Clinical Study Report– December 10th, 2020 – Suspected COVID-19 cases – 53 pages report).

Were these cases unconfirmed because the PCR test was negative, or unconfirmed because the PCR test was not performed by the center?
This paragraph no longer appears in the second Pfizer report, which was submitted to the Food and Drug Administration on the same day.

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.

Finally, the authorized use of antipyretic treatments makes the very symptoms (fever, pain) that were supposed to trigger the PCR test to confirm or not the presence of COVID-19 disappear.

As such, it introduces an additional bias in the evaluation of the primary endpoint since the number of participants who used an antipyretic was significantly higher in the BNT162b2 group than in the placebo group. Any participant with symptoms resolved by antipyretic use is not required to undergo PCR testing and is therefore de facto classified as a treatment success.

This bias could have been managed at the time of analysis by taking into account the use of antipyretics in the statistical modelling.

Based on the above, we can conclude that 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.

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 real life of 4.6% was more than 100 times equal to the infection rate of the clinical trial which was 0.044%**.

These results confirm the underestimation of the number of COVID-19 cases in the clinical trial.
The results are also not reliable for other all efficacy criteria based on confirmed cases, such as the number of severe COVID-19 cases.

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, as asymptomatic cases are also vectors of the disease.

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

As such, the information on the product insert itself is therefore incorrect.

«*Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is a vaccine used for preventing COVID-19 caused by SARS-CoV-2* virus».

The laboratory could, at most, write:

"The Pfizer-BioNTech/Comirnaty COVID-19 mRNA vaccine is a vaccine used to prevent symptomatic COVID-19 caused by the SARS-CoV-2 virus.

Illustration 67 : Packaging leaflet: Information for the user

Package leaflet: Information for the user

Pfizer-BioNTech/Comirnaty concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

Read all of this leaflet carefully before you receive this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is and what it is used for
2. What you need to know before you receive Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine
3. How Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is given
4. Possible side effects
5. How to store Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine
6. Contents of the pack and other information

1. What Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is and what it is used for

Pfizer-BioNTech/Comirnaty COVID-19 mRNA Vaccine is a vaccine used for preventing COVID-19 caused by SARS-CoV-2 virus.

Source : https://www.fda.gov.ph/wp-content/uploads/2021/11/Pfizer-BioNTech-and-Comirnaty-Product-Information-for-vaccine-recipients.pdf

Pfizer cannot claim to have respected the usual format of vaccine protocols since, in the context of a global pandemic that gave rise to exceptional emergency measures allowing the start of a development phase of their product without the previous one being completed, the protocol should also have been adapted so as not to leave the participants to their own, without offering them systematic and regular tests, as one might have expected.

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.

The laboratory could have easily determined whether the participant had COVID-19 during the trial by performing anti-Nucleocapsid serology on all participants at the 6-month visit after dose 2. This would also have allowed calculation of vaccine efficacy on transmission and not just on symptomatic patients, and it is surprising that this was not planned for at least those for whom PCR test results were not reported and recorded.

Concerning the evaluation of safety

As for efficacy, between protocol-scheduled visits, it is the participant's reporting of adverse events that is supposed to trigger a consultation at the center to identify the severity of the events.

Garay's Maddie case illustrates the difficulty of reporting adverse events.

Maddie de Garay, 12 years old at the time of her voluntary participation in the Phase 3 trial, suffered 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, she is 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.

Moreover, the October 2021 clinical report[2] on the 5- to 11-year-old population states, by the company's own admission, that "***the number of participants in the current clinical development program is too small to detect potential risks of myocarditis associated with vaccination***. *The long-term safety of the COVID-19 vaccine in participants aged 5 to <12 years will be studied in 5 post-approval safety studies, including a 5-year follow-up study to assess long-term sequelae of post-vaccination myocarditis/pericarditis*." (see Illustration 43 : Pfizer Clinical Study Report - October 26th, 2021 – Overall Risk/Benefit Conclusion).

In all clinical reports, results were developed based on a median 2-month follow-up time (50% of participants followed up less than 2 months, maximum follow-up of months4).

This follow-up time was authorized by the new “Emergency Use Authorization for Vaccines to Prevent COVID-19” [3] issued by the U.S. Food and Drug Administration in October 2020 and contrasts with the 2010 World Health Organization vaccine recommendations[4], which called for one-year follow-up to conclude efficacy and a six-month follow-up to properly assess safety in order to obtain valid and reliable results.

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[2] https://www.fda.gov/media/153409/download
[3] https://www.fda.gov/media/142749/download
[4] https://www.who.int/immunization_standards/vaccine_quality/clinical_considerations_oct10.pdf?ua=1

The short duration of observation of the participants does not allow for the evaluation of long-term safety, which is mentioned in the Comirnaty Risk Management Plan for months in chapter SVII.3.2 "Presentation of the Missing Information (see Illustration 62).

On the basis of the above, we can conclude that the methods used to identify adverse events (trial design, timing of planned visits, no visits between 1 month after the second dose and 6 months after the second dose, method of reporting adverse events, follow-up of the participant by the investigator site, duration of follow-up of participants in intermediate analyses, number of participants in analyses of young populations, etc.) lead to an underestimation of the number of adverse events, making the safety results unreliable.

Concerning the evaluation of immunogenicity

The neutralizing antibody assay presented in the December 10, 2020 report, already indicated a decrease in immunity at less than 2 months after the second dose. The data considered at the time of this analysis were, for some unknown reason, dated August 24, 2020, and not November 14, 2020 (cut-off date), as all other data.

As of September 22, 2021, Pfizer publicly admitted a drop in antibodies 6 to 8 months after the second dose, this would have been observed earlier if the interim analysis had been performed at 6 months instead of the median 2 months as authorized by the FDA Emergency use and if the trial had planned visits between 1 month after the 2ndème dose and 6 months after the 2ndème dose, which seems to be common sense even for such an innovating vaccine

The design of the trial thus contributed to masking the drop in antibodies, which was however predictable from the first report in December 2020, the neutralizing antibody rate at D52 being lower than the rate at D35.

In addition, 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.

Concerning risks and missing information

The missing information about the vaccine was already cited in the April 9, 2021 clinical study report [5] (see Illustration 46)

"The unknown benefits and data gaps associated with Pfizer-BioNTech's COVID-19 vaccine when used in adolescents aged 12 to 15 years are the same as those detailed in the memorandum authorizing the vaccine for emergency use in persons aged 16 years and older. They relate to:

- *Duration of the protection*
- *Effectiveness in selected populations at high risk for severe COVID-19*
- *Effectiveness in persons already infected with SARS-CoV-2*
- *Future vaccine effectiveness influenced by pandemic characteristics*
- *The evolution of the virus and/or the potential effects of co-infections.*
- *Vaccine effectiveness against asymptomatic infection*
- *Vaccine effectiveness against the long-term effects of COVID-19*
- *Vaccine effectiveness against mortality*
- *Vaccine efficacy against SARS-CoV-2 transmission."*

[5] https://www.fda.gov/media/148542/download

Pfizer was admitting here, although in an indirect way, the impotence of its vaccine to act against asymptomatic infections and therefore to slow down the transmission of the virus, as already demonstrated earlier in this report, since the main criterion chosen could not claim any efficacy in this matter.

The missing data were also available in the Comirnaty Risk Management Plan for months, in November 25, 2021 [6], they still concern to

- 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

The Risk Management Plan and the clinical report of April 2021 therefore clearly demonstrate, **due to the huge amount of missing information, that the risk assessment presented is totally incomplete.**

To date, the significant health risks to patients identified in the Comirnaty Risk Management Plan to date are anaphylaxis, myocarditis and pericarditis, and vaccine-associated enhanced disease (VAED).

The Ventavia case [7] highlighted 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.

Nearly 44,000 patients were enrolled and followed between July 27, 2020, and November 14, 2020, by 150 clinical trial sites in the United States, Germany, Turkey, South Africa, Brazil, and Argentina, an average of 293 participants per clinical investigation center in the midst of a COVID-19 pandemic and travel restrictions.

Given the accelerated clinical development of the vaccine through the COVID-19 Emergency Use Procedure drafted by the Food and Drugs Administration in October 2020 and the Fast-track System, method authorized to accelerate development using non-standard methods, it is likely that there **will be numerous deviations from Good Clinical Practices.**

There are therefore serious doubts about the quality of the trial as a whole, in relation to Good Clinical Practices.

To date, the FDA audit, conducted on 9 centers does not resolve these doubts, since, by the FDA's own admission, during the audits conducted on the centers, "the data integrity and verification portion of the BIMO inspections was limited because the study was ongoing and the data required for verification and comparison were not yet available to the IND."

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

[7] *https://www.bmj.com/content/375/bmj.n2635*

Since the use of Comirnaty vaccine in real life, a significant number of serious events have been reported on pharmacovigilance websites, Pfizer had identified a number of them since they were already included in its analysis of cumulative post-authorization safety data from December 1, 2020 to February 28, 2021 (5.3.6 Cumulative Analysis of Post-authorization Adverse Event Reports document). However, the conclusion of the review of effects, in the opinion of the laboratory itself, confirmed a favourable benefit/risk ratio for BNT162b2.

Health authorities have also calculated pharmacovigilance signals, such as the Center Disease Control. However, by taking into account only adverse events within 21 days after the injection, while long-term tolerance data were precisely lacking, the method used by the CDC minimized the real number of events, however serious and even fatal, while one could have expected an even stricter follow-up from the authorities for such an innovative product developed in such a short time, and for which special recommendations were issued in an emergency.

They finally admitted in October 2021 t**hat Pfizer/BioNtech and Moderna vaccines increased the risk of myocarditis and pericarditis in 12-39 year olds**.

The medical review by Drs. Wollersheim and Schwartz of August 25, 2021 is not really comforting about the quality of the controls performed as it reports standard pharmaceutical industry validations, "no major statistical problems were identified".

The editors conclude in section "4.7 Risk and benefit assessment" that

- *"The benefit-risk estimates are limited by **uncertainties** associated with the dynamics of pandemics."*
- *"The major uncertainties in benefits are related to potential changes in COVID-19 incidence over time and vaccine efficacy and duration of protection in the face of emerging virus **variants**."*
- *"The major risk uncertainty is the data on **vaccine-related myocarditis cases***
- *and **deaths**."!*

Final 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, etc.), 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 mentioned in this document, etc.

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 favourable 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 <u>urgently suspend</u> 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 based on this trial.

In order to uncover any errors or attempts at dissimulation, by the laboratory itself or the participating centers, it is necessary to

- Ask Pfizer to provide the provide the complete database of the trial in order to check the calculations (SAS® format).

- Ask Pfizer to provide the files tracking participant phone calls, call-backs by the center, and PCR test results from both the local and central laboratories to clarify the algorithm used to determine symptomatic COVID-19 cases.

- Ask Pfizer to provide the file tracing the values and dates of data entry and modifications by the various participants at the investigation centers, so-called "audit-trail" file that would facilitate the identification of any modification of data aimed to mask a failure in the performance of the main tasks of the trial by the investigation sites, such as the non-performance of the PCR assay for suspected COVID-19 cases, or the absence of follow-up of the participants who reported suffering from adverse events

- More generally, conduct a full audit of the Pfizer/BioNTech phase 1-2-3 clinical trial, preferably by auditors external to any organization involved in the development and approval of the Comirnaty vaccine, by delegating teams of quality assurers to the trial site to review all records available at the sites that could not be verified in person because of Fast Track or Emergency Use procedures that allow for remote verification, including
    - Records related to participants, consent, dates of vaccinations and visits ...
    - Participants' calls to report symptoms or adverse events, telephone reminders by the center,
    - The respect of the non-removal of the decoding of the trial products (protection of the randomization) for the supposedly blinded personnel
    - The storage conditions of the products...
    - As well as all source documents of the center

      Since, by the FDA's own admission, its audit can in no way claim to reassure about the integrity of the data.

The conclusions are identical for any clinical trial on COVID-19 vaccines with a similar primary endpoint and similar calculation and analysis methods.