Optimizing the Route to Regulatory Approval for a Novel Vaccine

Cecil Nick
Vice President (Technical), Regulatory Strategy
Parexel

© 2024 Parexel International (MA) Corporation.

parexel BIOTECH

Introduction

The positive impact of vaccines on human health has been advanced through the development of new platforms, spurred on by the global threat of COVID-19. This article addresses critical points to consider in order to gain regulatory approval and approaches to streamlining clinical development for a new vaccine.

mRNA vaccines played a crucial role in controlling COVID-19 and are now being developed as prophylaxis against other infectious diseases, as well as cancer. The US FDA granted breakthrough therapy designation to Moderna and Merck's melanoma mRNA vaccine which is deployed in combination with a checkpoint inhibitor (pembrolizumab), and results are looking promising.[1] Aside from infectious diseases and cancer, mRNA vaccines are being developed to treat other conditions such as cystic fibrosis, allergies and potentially autoimmune disease.[2] The safety of mRNA as well as viral-vectored vaccines is supported by their use in billions of people worldwide although, as with any vaccine, rare serious adverse events have been reported.

Viral vector vaccines were an early weapon against SARS-CoV-2 but are no longer widely deployed due to lower protection rates, particularly with the evolution of novel SARS-CoV-2 variants, and the occurrence of a rare, potentially fatal adverse event termed "thrombosis with thrombocytopenia syndrome", discussed later in this article.[3]

DNA vaccines have only, so far, been approved for veterinary use. They are being investigated for cancer indications and treatment of HIV; there are also examples of DNA vaccines being developed against COVID-19.

Virosomes represent yet another approach; they comprise viral envelope phospholipids with the nucleocapsid removed. Reconstituted influenza virosomes are a favored approach, with the hemagglutinin and neuraminidase antigens facilitating delivery to antigen-presenting cells (APC) by binding to sialic acid on the APC surface. To date several vaccines based on various virosome formulations have been commercialized against infections such as influenza and hepatitis A, and further research is ongoing to utilize this approach to develop vaccines against SARS CoV-2, HIV-1, human papilloma virus (HPV), and cancer.[4]

While novel vaccines offer exciting opportunities to control infectious disease, development of improved adjuvants represent another approach to enhancing the effectiveness of classical sub-unit vaccines. Aluminum has been used as an adjuvant for over a century, but it is important to note upper allowable limits of 1.25 mg per WHO regulations[5] and 0.85 to 1.25 mg as per US FDA guidelines.[6] Since the 1990s, newer and more effective adjuvants have come into use drawing on a growing understanding of the innate immune system.

© 2024 Parexel International (MA) Corporation.

Early phase studies

Optimized development of new vaccines requires the integration of multi-disciplinary expertise from key contributors, such as non-clinical experts, clinicians, regulatory professionals, statisticians, and immunologists. The clinical development of vaccines, like all medicinal products, follows a logical sequential program, starting with small exploratory Phase 1 studies.

The starting dose in first in human studies is informed by non-clinical data and, when available, historical clinical data. Typically, clinical development begins with dose escalation studies in tens up to about one hundred healthy adults and, subsequently, is expanded to cover the full spectrum of the target population.

The inclusion of multiple exploratory endpoints can help to predict the potential therapeutic value of a vaccine early in its development. EMA guidelines[7] recommend evaluating secondary endpoints such as induction of immune memory; cross-reactive antibodies; cross-priming (e.g. induction of immune memory to a different antigen); cell-mediated immunity (CMI); correlation between cytokine or gene expression profiles and an immune correlate of protection.

Human challenge studies are useful where an infection is expected to be relatively mild or treatable. Such studies have been conducted on influenza, RSV, malaria and recently COVID-19. There are major complexities in designing human challenge studies, including deciding on the challenge dose of infectious agent and the point at which to intervene with antimicrobial or rescue treatment, but challenge studies can play a critical role in gaining rapid proof of concept and supporting granting of breakthrough treatment designation, and, in some circumstances, supporting marketing approval. In 1998, the VRBPAC agreed that human challenge studies could suffice to demonstrate efficacy of a cholera vaccine provided that studies were adequate and well-controlled and conducted under the provisions of GCP.[8] Nevertheless, use of challenge studies to demonstrate efficacy does not exclude the requirement for adequate safety data as discussed later in this article.

Immune correlates

On proceeding to confirmatory clinical studies, prior knowledge can help to reduce the scale of the requisite trials, particularly if immune correlates of protection (ICP) are known. EU guideline defines an ICP as the "type and amount of immunological response that correlates with vaccine-induced protection against an infectious disease and that is considered predictive of clinical efficacy[8]" Generally, ICPs are expressed as levels of neutralizing antibodies or neutralizing or opsonizing activity. It is critical that all assays used to monitor ICPs are validated and, where available, international reference standards are used.

© 2024 Parexel International (MA) Corporation.

Widely accepted and well-supported ICPs exist for a range of infectious diseases and can be useful in extrapolating data generated from prior efficacy studies. ICPs allow for assessment of individual and population immunity as well as bridging vaccine effectiveness across populations or related strains of the pathogen. Establishing ICPs varies in complexity and are easiest to establish when protection is reliant on neutralization, as would be the case for an anti-capsular or anti-toxin antibody response. In the case of influenza, EU guidance defines seroconversion in terms of hemagglutination inhibition (HI).[9] However, that level is protective only at 50 to 70%, which makes this a relative rather than an absolute correlate of protection and which further varies with emergence of new strains.[10]

The importance of cellular immunity

The mechanisms by which vaccines exert their protective effect extend beyond that of neutralizing antibodies. T-cell response also plays an important role in protection, sometimes the dominant role. It is generally believed that cellular immunity induced by *Mycobacterium bovis* (BCG) is the key protective function against tuberculosis. In the case of rotavirus, neutralizing antibodies, non-neutralizing antibodies, secretory antibodies, and cellular immune responses all may play a role, depending on the situation.[11] In the case of SARS CoV2, while the focus has been on neutralizing antibody titer, in fact, immune memory and cellular immunity are also reported to be of importance. For these reasons, ICPs cannot always be reliably applied from one vaccine platform to another, since the effect of vaccination may vary in terms of how the antigen is presented to the immune system, which can affect the nature of the immune response including humoral versus cellular response. Also, the correlation between neutralizing antibody levels and protection may vary from one age group, gender or major histocompatibility complex (MHC) group to another and be impacted by the emergence of new strains. So the relevance of an ICP needs to be carefully considered and its use justified to the regulators.

In some cases, immune correlates can be used in place of efficacy trials, particularly if such trials are not feasible or ethical. Such an approach has been considered for the development of a vaccine against Chikungunya virus (CHIKV) by the FDA and the Vaccines and Related Biological Products Advisory Committee (VRBPAC) in 2019,[12] as outbreaks caused by Chikungunya are unpredictable, making it impractical to conduct a clinical effectiveness study. The FDA and VRBPAC agreed that a CHIKV-neutralizing antibody titer that is reasonably likely to predict protection could be established from passive transfer of human antibodies to non-human primates followed by challenge with wild-type CHIKV. A similar approach could be considered for developing vaccines against Ebola and Marburg virus.

© 2024 Parexel International (MA) Corporation.

Immuno-bridging

An immuno-bridging approach represents an alternative to reliance on ICPs but requires demonstration of non-inferiority against an active comparator. In the case of development of new COVID-19 vaccines, the challenge now is to demonstrate efficacy in a setting of widespread public vaccination and where it is unethical to withhold vaccine in lieu of placebo. Comparative trials against an approved vaccine require demonstration of non-inferiority or superiority in terms of immunogenicity compared to an approved vaccine. In the EU, immuno-bridging may be accepted in lieu of clinical effectiveness data in the development of new COVID-19 vaccines although clinical effectiveness data is still recommended in FDA COVID-19 guidance.[13] The non-inferiority margin should be clinically justified taking into consideration the mortality rate and the risk of serious permanent sequelae from the infection to be prevented.[14, 15] Immunogenicity outcomes are also used in the development of combination or multivalent vaccines and to investigate efficacy against emergent strains.

Considerations for later phase studies

Vaccine efficacy trials may require very large sample sizes, upward of 10,000 participants, in which case a single pivotal trial may be acceptable if compliant with regulatory guidelines.[16] The actual number of participants recruited will depend on both the virus attack rate and the expected level of protection provided by the vaccine. It is evident that in the case of clinical efficacy trials for vaccination against a rare infection, trial sizes would become unmanageably large and immuno-bridging or use of a non-clinical model may represent the only possible approaches but would need to be agreed with key regulatory agencies.

Where placebo-controlled trials are considered unethical, the only option may be to undertake a comparison against an active control. This approach can be challenging as, for one thing, procurement of the licensed vaccine, particularly during a pandemic, is likely to be difficult. An alternative is to apply a staggered approach with delayed vaccination as a comparator, but this does have disadvantages such as lower power because of compressed timelines and the potential to introduce bias.[17]

Applying a seamless and/or adaptive approach

Rapid development of vaccines can be facilitated by applying a seamless and/or adaptive approach, whereby the trial is expanded based on decisions taken as the data become available, in order to accelerate development. A recent example of an aggressive seamless design was the Phase 1/2/3, dose-finding study to evaluate a SARS-COV-2 RNA vaccine candidate, conducted by Pfizer. In this study, each group in Phase 1 comprised 15 participants (12 receiving active vaccine and 3 receiving placebo). Many groups were studied simultaneously to select a dose and formulation to carry into Phase 2/3. More than 20,000 participants were recruited into Phase 2/3 with phased interim analyses. As the study progressed, 12- to 15-year-olds were recruited into a separate stratum of about 2,000 participants. Further, the intention was to recruit 40% of participants > 55 years old to ensure broad population coverage.[18]

© 2024 Parexel International (MA) Corporation.

Another interesting adaptive approach relates to a trial designed to demonstrate the efficacy of a nine-valent vaccine against nine strains of the human papilloma virus (9V-HPV), which was compared against the approved four-valent vaccine (4V-HPV). In this trial, roughly 1,250 participants were equally randomized into four arms (low dose, medium dose, high dose and approved 4V-HPV as a comparator) with the primary objective of comparing immunogenicity. This enabled dose selection for the Phase 3 confirmatory doses. At Phase 3, approximately 13,400 participants were randomized (1:1) to either the selected medium dose 9V-HPV arm or 4V-HPV arm with vaccine efficacy rather than immunogenicity as the primary endpoint. This resulted in approximately 14,200 participants in both stages for the efficacy assessment. Of these, only 620 participants were rolled over from Phase 2, but they contributed roughly 10% of the person-years of follow-up due to the longer observation period. Generally, regulatory agencies do not allow participants used for dose selection to be reused, but the sponsor pointed out that there was a small correlation between biomarker endpoint in Phase 2 and efficacy endpoint in Phase 3. A data monitoring committee was responsible for the decisions on trial adaptation, with all personnel directly involved in trial conduct kept blinded.[19]

Innovative approaches to demonstrating vaccine efficacy.

Other approaches to investigating levels of clinical protection in people at high risk of exposure exist, some of which are discussed below.

- **Cluster design:** Participants are recruited in institutions or areas where high levels of transmission exist. This is feasible only where the dynamics of infection allow for a response to the vaccine before the infection becomes symptomatic. Areas of high population density or where a lack of adoption of social distancing measures exist can also represent fertile grounds for high viral transmission rates.
- **Platform trials:** In pandemic situations, platform trials offer the opportunity to test multiple vaccines against a single placebo group. An example is the WHO "Solidarity Vaccine Trial" for a vaccine against COVID-19.[20] The trial contributed patients from Philippines, Mali and Colombia in the development of vaccines by Medigen and Inovio but, to a large degree, was eclipsed by the rapid development of vaccines sponsored by some other major companies.

© 2024 Parexel International (MA) Corporation.

- **Real-world data (RWD):** Applying RWD and synthetic arms can be useful when designing trials that require recruitment of tens of thousands of patients. In some circumstances, historical data can be used as a control allowing for a single arm study, this is termed a synthetic or external controlled arm. Alternatively, data from a small, limited control arm within the study could be supplemented by external data. In general external control arms are not favored by regulators and require strong justification. FDA has published its expectations for agreeing to an external control and these include rare disease, serious unmet medical need, circumstances where a randomized trial would be unethical and where severe logistical challenges to including a comparator arm exist. Epidemiological and statistical methods exist to ensure an external control provides sufficiently robust comparison.[21] In some cases, historical data on the incidence and severity of an infectious disease, from disease surveillance networks or registries, can be used as a baseline for estimation of vaccine efficacy. A validated predefined approach to collection of RWD is important and requires support of an epidemiologist with specialist knowledge. Such information can be collated while preclinical studies are ongoing. Observational cohort studies, case-control or case-cohort studies represent approaches to generating real-world evidence. Case-control studies are a common approach and compare the proportion of immunized participants with infection to unvaccinated participants matched for risk factors. Clearly, good immunization records and clear case definitions are required. Such an approach, using an external control arm, has confirmed efficacy of HIB conjugate vaccines.[22]

Generating safety data

Since most adverse reactions to vaccines occur within the first few days after each dose, participants should be closely monitored for about the first week after administration and longer in the case of replication-competent live vaccines (e.g. 10-14 days or sometimes more), depending on what is known about the vaccine.[7] For replication-competent live vaccines, shedding has implications in terms of any potential risks to contacts of vaccinees.

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to regulatory agencies. An appropriate grading system to assess severity should be pre-defined in the study protocol. FDA has published a scale to categorize adverse events observed during a clinical trial that they advise may assist in monitoring safety and making required reports,[23] nevertheless, FDA points out that these guidelines are supplementary to and do not replace standard regulatory safety and data analysis requirements.

Vaccine programs are usually designed to detect adverse events with an incidence greater than between 1/100 and 1/1000 vaccinated persons, requiring a minimum of 3000 participants ex-posed to the vaccine.[13]

Extremely rare serious and very rarely fatal adverse reactions have been reported following vaccination; these include anaphylaxis and autoimmune related events.[24] Examples of these include TTP associated with adeno-vector based COVID-19 vaccines. Recent information suggests an incidence of 3 to15 per million doses.[25] Earlier clinical recognition and awareness of TTP has reduced mortality from as high as 50 percent initially to 5 percent in a recent analysis from Australia.[26]

© 2024 Parexel International (MA) Corporation.

Thrombocytopenia not directly associated with thrombotic events has been reported as the main adverse event following MMR vaccination, usually occurring within 6 weeks at a risk rate of 1:22,000–25,000 doses. However, this frequency needs to be set against the risk of thrombocytopenia of 1:6000 for measles and 1:3000 for rubella induced by the infection, which affected almost every child prior to the introduction of the vaccine[27].

Myocarditis and pericarditis at an incidence of less than 1 per 10,000 have been observed with COVID-19 messenger RNA vaccines but in general, have been mild to moderate in severity; this too needs to be considered against the fact that nearly one-fourth of those hospitalized with COVID-19 have been diagnosed with cardiovascular complications, which have contributed to roughly 40% of all COVID-19-related deaths.[28]
In assessing the risk-benefit of a vaccine it is, therefore, important to weigh the known and potential risks associated with the target infection and whether a more effective and/or safer alternative vaccine is available.

As events such as those discussed above are extremely rare, often less than one in a million, they cannot be identified in clinical trials, making post-marketing safety monitoring a crucial final phase in vaccine development.

In some cases, a larger database might be needed, for example, if novel technologies are being employed, or safety concerns arise from the nonclinical program or from related vaccines. On the other hand, a reduced safety database may be justifiable in some circumstances, e.g. if extensive clinical safety data are already available from related approved vaccines.

In general, it would usually be expected that at least some safety data are available from all target groups for which the use of the vaccine is approved (e.g. age sub-groups) and a minimum number of participants within a certain age range or with specific host characteristics may be required to be exposed.[7]

Recently a new syndrome, "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA) has been linked to the use of several adjuvants. ASIA syndrome may be underreported because of unawareness and failure to connect the syndrome with exposure.[29] The term was first coined in 2011 and describes a heterogenous mix of autoimmune and inflammatory conditions. An international registry of ASIA syndrome was created in 2011. A preliminary analysis of 300 patients in 2016 showed that most (nearly 90%) of the ASIA syndrome patients were female and had a mean age around 40 years. The most commonly reported disease was undifferentiated connective tissue disease (UCTD), found in 26% of the cases.[29] Macrophagic myofasciitis (MMF) is an example of an extremely rare adverse event that can occur many years after the vaccination was administered. MMF has been attributed to aluminum deposits in muscle following immunization with aluminum containing vaccines. MMF lesions are now universally recognized as indicative of a long-lasting persistence of aluminum adjuvant at the site of prior intramuscular immunization.[30]

© 2024 Parexel International (MA) Corporation.

Late-occurring adverse events are very rare but cannot be discounted and it is important to monitor for these during long-term follow-up, over a period of at least 12 months but may be longer. During long-term follow-up it may be acceptable that only serious adverse events and adverse events of special interest are captured. The duration of safety follow-up will be based on a number of factors including the nature of the candidate vaccine, the choice of adjuvant and prior knowledge.

Potential for vaccines to exacerbate subsequent infection

There are rare specific cases where vaccines, instead of protecting against infection, may exacerbate the illness. Antibody-dependent enhancement (ADE) of disease is a mechanism that facilitates viral entry into host cells and has been reported following prior infection with several viruses including Dengue, Ebola and HIV[31]. Another mechanism by which vaccines might give rise to exacerbation of disease is a process known as enhanced respiratory disease exacerbation (ERD), which was observed to be associated with a formaldehyde-inactivated vaccine against respiratory syncytial virus (FI-RSV) being developed in the 1960's. This resulted in a few vaccinated infants suffering a more severe disease following natural infection. ERD is caused by an imbalance between Th1 and Th2 response, leading to pulmonary allergic inflammation.[32]

Clearly, the potential for vaccines to enhance rather than protect against infection through the two mechanisms of ADE and ERD highlights the need for studies in animal models before commencing clinical trials and long-term follow-up after completion of the clinical trial.

Population diversity: important considerations in vaccine development

Another critical consideration in the global development of vaccines is the need to account for varied response and level of protection across populations. This is impacted by factors such as age, gender, ethnicity, prior exposure to the target infection, strain variants, gut microbiota and general health and these need to be considered in any vaccine clinical development program.

A multitude of regional factors can impact vaccine response, such as seasonal occurrence of infection, circulation of different subtypes of the infectious agent and the impact of other infections circulating in the community. If different subtypes are endemic in different parts of the world, this needs to be accounted for in the design of the clinical development program. Prior exposure to the target infection is also important, as the vaccinated participant would likely be already immune but in some cases the reverse may be true with immunological imprinting reducing the effectiveness of the vaccine or in the case of Antibody Dependent Enhancement (ADE), vaccination might enhance the risk of severe disease following infection.[33]

© 2024 Parexel International (MA) Corporation.

More interestingly, recent reports suggest that the human microbiota may also modulate vaccine response[34, 35, 36] and that this may be most important during early life when many vaccines are administered. In view of these observations, it is important to ensure that vaccines trials include adequate representation from different socio- economic groups. FDA encourages the inclusion of diverse populations in all phases of vaccine clinical development. In the case of COVID-19 vaccine programs, FDA strongly encourages the enrolment of populations most affected, specifically racial and ethnic minorities.[13]

Vaccine development generally takes place in a stepwise fashion from adults to children. However, for many global diseases the pediatric population could face greater mortality or morbidity than the adult population because adults may already be immune. Documented differences in vaccine response between adults, children and infants mean it is not possible to extrapolate results from adults directly to children and vaccine studies in infants or children early in development may be indicated. Pediatric Study Plans (US)/ Pediatric Investigation Plans (EU) will need to be included with the initial marketing application for all new medicines including vaccines unless a waiver or deferral is granted by the respective regulatory agency.

In the case of COVID-19, the early phase trials included patients aged over 18 years. The Pfizer program quickly expanded to include patients over the age of 16 years and within about six months included just over 2,000 participants of 12 to <16 year-old into a separate stratum of their seamless Phase 1/2/3 study; this supported FDA emergency use authorization (EUA) and EU approval, about six months after the initial adult EUA was granted. The study showed comparable immunogenicity to adults in this younger age group with 100% protection over the trial period. Moderna initiated a separate Phase 2/3 study in the 12 – 17-year-old group in December 2020 once early safety data were available from their adult study. Over the following year, studies demonstrating comparable immunogenicity and safety to adults were conducted sequentially in younger age groups: >6 to <12 years; 24 months to <6 years; and 6 months to 23 months leading to regulatory approvals up to June 2022 for these age groups. Generally, 1500 to 3000 participants were included for each age group with fewest being in the youngest groups. FDA is now requiring data for these COVID-19 vaccines to be generated also in the <6 months age group as a post-approval commitment.

Dose-finding studies are also required for vaccines to be used in older adults and should cover all age groups e.g. 65-74 years, 75-84 years and 85 years or more to determine whether different doses and/or regimens are needed as age increases.[7]

© 2024 Parexel International (MA) Corporation.

Health status particularly some types of immune deficiencies also impact response to vaccines. EMA guidelines do not recommend studying vaccine response in a broad immunodeficient population and suggest focusing on well-defined sub-populations with immune deficiencies that have been selected based on their likelihood to affect the immune response to a specific vaccine.[7] In the case of COVID-19 vaccines seroconversion was much lower in immune-compromised patients being only 50% as likely, for example, in patients with hematological malignancies, this was improved by a second booster dose and further improvement could be gained with a third dose but further research is needed.[37]

Conclusion

New approaches to vaccination are safe, highly effective and have led to the end of the COVID pandemic. Rapid delivery of the benefits of new vaccines to patients requires streamlining vaccine development by applying novel approaches to trial design; this is an important focus area for all involved in vaccine development. Better understanding of the immunobiology underlying protection will enable the further improvement of next-generation candidates for global use in all at-risk populations.

References

1) Reuters. Positive Moderna, Merck cancer vaccine data advances mRNA promise, shares rise. Published 202, December 13, 5:35 PM GMT. Available at: Positive Moderna, Merck cancer vaccine data advances mRNA promise, shares rise | Reuters

2) Flemming A. mRNA vaccine shows promise in autoimmunity. Nat Rev Immunol 21, 72 (2021). Available at: mRNA vaccine shows promise in autoimmunity | Nature Reviews Immunology

3) WHO. Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19). Published 2023, April 20. Available at: https://www.who.int/publications/i/item/9789240061989

4) Asadi K and Gholami A. Virosome-based nanovaccines; a promising bioinspiration and biomimic approach for preventing viral diseases: A review. Int J Biol Macromol. 182:648–658 (2022). doi:10.1016/j.ijbiomac.2021.04.005

5) World Health Organization. Requirements for diphtheria, tetanus, pertussis and combined vaccine, in Tech. Rep. Series 800, WHO, Geneva, Switzerland, 87–179 (1990) Available at: Requirements for Diphteria, Tetanus, Pertussis and Combined Vaccines (who.int)

6) May JC, Progar JJ, and Chin R. The aluminum content of biological products containing aluminum adjuvants: determination by atomic absorption spectrometry. J. Biol. Stand. 12:175–183 (1984). doi:https://doi.org/10.1016/s0092-1157(84)80051-7

7) European Medicines Agency. Guideline on clinical evaluation of vaccines (europa.eu). EMEA/CHMP/VWP/164653/05 Rev. 1. Published 2023, January 16. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-vaccines-revision-1_en.pdf

8) Vaccines and Related Biological Products Advisory Committee meeting, May 26-27, 1998. Available at: Advisory Committees: CBER 1998 Meeting Documents (archive-it.org)

9) European Medicines Agency Guideline on Influenza Vaccines - Non-clinical and Clinical Module EMA/CHMP/VWP/457259/2014. Published 2016, July 21. Available at: Guideline on Influenza Vaccines - Non-clinical and Clinical Module (europa.eu).

10) Plotkin SA. Correlates of Protection Induced by Vaccination. Clin Vaccine Immunol. 17(7): 1055–1065. (2010) doi: 10.1128/CVI.00131-10

11) Plotkin SA and Gilbert PB. Nomenclature for Immune Correlates of Protection After Vaccination. Clinical Infectious Diseases 54(11)1615–1617(2012). doi: https://doi.org/10.1093/cod/cis238

12) Food and Drug Agency. Vaccines and related biological products advisory committee November 8, 2019, meeting announcement (2019). Available at: 2023-02-01 10:30 | Archive of FDA (pagefreezer.com)

13) Food and Drug Agency. Guidelines for Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry 6/2020. Updated: 2023, March 13. Available at: Development and Licensure of Vaccines to Prevent COVID-19; Guidance for Industry (fda.gov)

14) European Medicines Agency Guideline on Non-inferiority Margin (europa.eu). EMEA/CPMP/EWP/2158/99. Published 2005, July 27 Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf#:~:text=In%20order%20to%20demonstrate%20non-inferiority%2C%20the%20recommended%20approach,principles%20can%20be%20used%20to%20provide%20general%20guidance

15) Food and Drug Administration guideline on non-inferiority clinical trials. Published November 2016. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials.

© 2024 Parexel International (MA) Corporation.

16) Points to consider on application with 1. Meta-analyses; 2. One pivotal study. Doc. Ref. CPMP/EWP/2330/99; Published 2001 May 31. Available at: Points to consider on application with 1. meta-analyses; 2. one pivotal study (europa.eu).

17) Dean NE, Halloran ME, Longini IM. Design of vaccine trials during outbreaks with and without a delayed vaccination comparator. Ann. Appl. Stat. 12(1):330 (2018). doi: https://doi.org/10.1214/17-aoas1095

18) Protocol C4591001. A Phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-COV-2 RNA vaccine candidates against Covid-19 in healthy individual. Study Intervention Number: PF-07302048 US IND Number: 19736. EudraCT Number: 2020-002641. Available at: https://media.tghn.org/medialibrary/2020/11/C4591001_Clinical_Protocol_Nov2020_Pfizer_BioNTech.pdf

19) Liu M, Li Q, Lin J, Lin Y, Hoffman E. Innovative Trial Designs and Analyses for Vaccine Clinical Development. Contemp Clin Trials. 2021 Jan; 100: 106225. Published online: 2020, Nov 21. doi: https://doi.org/10.1016/j.cct.2020.106000

20) World Health Organization. Technical document. Solidarity Trial Vaccines (STV) presentation. Published: 2022, May 11. Available at: https://www.who.int/publications/m/item/solidarity-trial-vaccines-(stv)-presentation

21) Food and Drug Agency. Published: 2023, February. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Considerations for the Design and Conduct of Externally Con-trolled Trials for Drug and Biological Products (fda.gov).

22) Jackson C, Mann A, Mangtani P, Fine P. Effectiveness of Haemophilus influenzae Type B vaccines administered according to various schedules: systematic review and meta-analysis of observational data. Pediatr Infect Dis J 32(11):1261-9 (2013, November). doi: https://doi.org/10.1097/inf.0b013e3182a14e57

23) Food and Drug Agency. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Published: 2007, September. Available at: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials | FDA

24) Omidi F, Hajikhani B, Kazemi SN, Tajbakhsh A, Riazi S, Mirsaeidi M, Ansari A, Ghanbari Boroujeni M, Khalili F, Hadadi S, Nasiri MJ. COVID-19 and Cardiomyopathy: A Systematic Review. Front Cardiovasc Med. 8:695206 (2021, June 17). Available at: Frontiers | COVID-19 and Cardiomyopathy: A Systematic Review (frontiersin.org).

25) Cines DB and Greinacher A. Vaccine-induced immune thrombotic thrombocytopenia. Blood 141(14): 1659–1665 (2023). doi: https://doi.org/10.1182/blood.2022017696

26) Bussel JB, Connors JM, Cines *DB*, et. al. Vaccine-induced Immune Thrombotic Thrombocytopenia. Last updated: 2022, May 9. Available at: Thrombosis with Thrombocytopenia Syndrome - Hematology.org

27) De Mattia D, Del Vecchio GC, Russo G, et al.(AIEOP-ITP Study Group). Management of chronic childhood immune thrombocytopenic purpura: AIEOP consensus guidelines. Acta Haematol.123(2):96-109 (2010). doi: https://doi.org/10.1159/000268855

28) Williamson L. What COVID-19 is doing to the heart, even after recovery. American Heart Association. Available at: What COVID-19 is doing to the heart, even after recovery

29) Watad A, Bragazzi NL, McGonagle D, et. al. Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) demonstrates distinct autoimmune and autoinflammatory disease associations according to the adjuvant subtype: Insights from an analysis of 500 cases. Clin Immunol. 3:1-8 (2019, Jun 20). doi: 10.1016/j.clim.2019.03.007. Epub 2019 Mar 25..

30) Gherardi RK, Coquet M, Cherin P. Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle. Brain. 2001;124:1821–1831. doi: 10.1093/brain/124.9.1821

31) Kuzmina NA, Younan P, Gilchuk P, Santos RI, Flyak AI, Ilinykh PA, Huang K, Lubaki NM, Ramanathan P, Crowe JE Jr, Bukreyev A. Antibody-Dependent Enhancement of Ebola Virus Infection by Human Antibodies Isolated from Survivors. Cell Rep. 2018 Aug 14;24(7):1802-1815.e5. doi: https://doi.org/10.1016/j.celrep.2018.07.035

32) World Health Organization. Respiratory Syncytial Virus (RSV) disease (who.int) available at: Respiratory Syncytial Virus (RSV) disease (who.int)

33) Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system – working in harmony to reduce the risk of infection. Nutrients12(1):236 (2020). doi: https://doi.org/10.3390/nu12010236

34) Impact of the host microbiome on vaccine responsiveness: Lessons Learned and Future Perspective Stefanetti G , Kasper DL. Biochemistry 61(24): 2849–2855 (2022). doi: https://doi.org/10.1021/acs.biochem.2c00309

35) Jordan A, Carding SR, Hall LJ. The early life gut biome and vaccine efficacy. Lancet 3(10):e787-e794 (2022, September 18). doi: https://doi.org/10.1016/S2666-5247(22)00185-9-

36) Hagan T. et al. Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans. Cell 178, 1313–1328 (2019).

37) Lee AR, WongSY, Chai LYA et.al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *BMJ* 2022; 376 (2022, March 2) doi: https://doi.org/10.1136/bmj-2021-068632

 © 2024 Parexel International (MA) Corporation.

With Heart™

We're always available for a conversation

Parexel International Corporation
2520 Meridian Pkwy, Durham, NC 27713, USA
+1 919 544-3170

Offices across Europe, Asia, and the Americas
www.parexel.com

© 2024 Parexel International (MA) Corporation

parexel® BIOTECH