Societat Catalana de Farmacologia.
Sessió Científica:

Disseny i interpretació dels estudis clínics de les vacunes COVID-19

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Disclaimer

The opinions expressed today are personal views and should not be understood or quoted as being made on behalf of any organization.

- **Regulatory**
  - Spanish Medicines Agency (AEMPS)
  - European Medicines Agency (EMA)
    - Scientific Advice Working Party (ex-SAWP)
    - Biostatistics Working Party (BSWP)
  - Catalan Heath Service (CatSalut)
    - Advisory Board of the Hospital Medication (CAMH)
- **Hospital - Academic - Independent Research**
  - IDIBAPS. Hospital Clinic Barcelona
  - Autonomous University of Barcelona (UAB)
  - SCReN & ECRIN Spanish & European Clinical Trials Platforms

2

The role of statistics

"Thus statistical methods are no substitute for common sense and objectivity. They should never aim to confuse the reader, but instead should be a major contributor to the clarity of a scientific argument."

The role of statistics. *Pocock SJ . Br J Psychiat 1980; 137:188-190*

3

European Medicines Agency

September 1998
CPMP/ICH/363/96

ICH Topic E 9
Statistical Principles for Clinical Trials

Step 5

NOTE FOR GUIDANCE ON
STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
(CPMP/ICH/363/96)

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Key Issues

- Vaccine Efficacy (VE)
- Multiplicity
  - Outcomes
  - Interim Analyses
  - Subgroups
- Super-(Supra)-Efficacy
- Sample Size
- Application with 1. Meta-analyses; 2. One pivotal study
- Pfizer, Moderna, Oxford/AZ, Janssen

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Vaccine Efficacy (VE)

VE=90%??

90% efficacy in Vaccine?
90% more efficacy in Vaccine?

VE=(1-RR)*100

RR=0.10 VE=90%

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Vaccine Efficacy (VE)

Vaccine Efficacy (VE)	(1-RR)*100	=>	**90.0%**
Rate Ratio (RR)	$Rate_{Vaccine}/Rate_{Contro}$	=>	0.100
	Control	**Vaccine**	
Patients	10,000	10,000	
Cases	50	5	
Rate	**0.50%**	**0.05%**	
***"Efficacy"* (100-rate**	**99.50%**	**99.95%**	

Orenstein WA et al. Bull World Health Organ. 1985;63(6):1055-68

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Vaccine Efficacy (VE)

VE	Control		Vaccine	Absolute Diff.
90.0%	0.50%	x 0.1	0.05%	0.45%
	2.00%		0.20%	1.80%
60.0%	0.50%	x 0.4	0.20%	0.30%
	2.00%		0.80%	1.20%

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Multiplicity

- K independent hyp… H_{02} , … , H_{0K}
- S significant result…

- Pr ($S \geq 1 \mid H_{01} \cap H$ … $= H_{0.}$) = 1 - Pr ($S=0 \mid H_{0.}$)

K	Pr(S>=1|Ho.)
1	0.0500
2	0.0975
3	0.1426
4	0.1855
5	0.2262

K	Pr(S>=1|Ho.)
10	0.4013
15	0.5367
20	0.6415
25	0.7226
30	0.7854

$\alpha)^K$

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Group sequential methods (cont.)

	O'Brien & Fleming		Peto		Pocock	
K	z	α'	z	α'	z	α'
1	2.782	0.005	2.576	0.010	2.178	0.029
2	1.967	0.049	1.969	0.049	2.178	0.029
1	3.438	0.001	2.576	0.010	2.289	0.022
2	2.431	0.015	2.576	0.010	2.289	0.022
3	1.985	0.047	1.969	0.049	2.289	0.022
1	4.084	0.000	3.291	0.001	2.361	0.018
2	2.888	0.004	3.291	0.001	2.361	0.018
3	2.358	0.018	3.291	0.001	2.361	0.018
4	2.042	0.041	1.969	0.049	2.361	0.018
1	4.555	0.000	3.291	0.001	2.413	0.016
2	3.221	0.001	3.291	0.001	2.413	0.016
3	2.630	0.009	3.291	0.001	2.413	0.016
4	2.277	0.023	3.291	0.001	2.413	0.016
5	2.037	0.042	1.969	0.049	2.413	0.016

O'Brien PC and Fleming TR. Biometrics. 1979;35:549-56.
Peto R, et al. Br J Cancer. 1976;34:585-612.
Pocock SJ. Biometrika. 1977;64:191-9.

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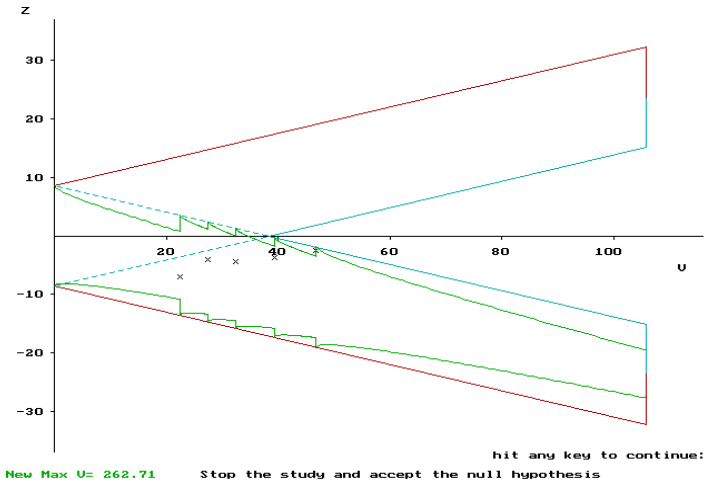
Truncated SPRT (sequential probability ratio test)



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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

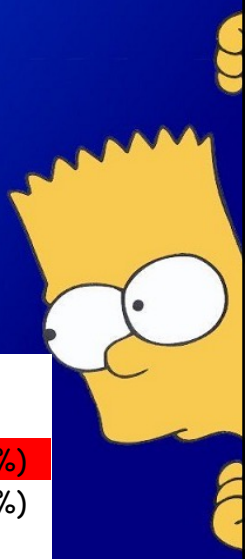
31 January 2019
EMA/CHMP/539146/2013
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the investigation of subgroups in confirmatory clinical trials

16

Simpson's Paradox

Simpson EH. The interpretation of interaction in contingency tables. J R Stat Soc Series B Stat Methodol 1951; 13: 238–241.



		Experimental n (%)	Control n (%)
ALL	Succes	70 (70%)	60 (60%)
	Failure	30 (30%)	40 (40%)
		100	*100*

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Simpson's Paradox cont.

		Experimental n (%)	Control n (%)
MALE	Succes	10 (33%)	24 (40%)
	Failure	20 (67%)	36 (60%)
		30	*60*
FEMALE	Succes	60 (86%)	36 (90%)
	Failure	10 (14%)	4 (10%)
		70	*40*

		Experimental n (%)	Control n (%)
ALL	Succes	70 (70%)	60 (60%)
	Failure	30 (30%)	40 (40%)
		100	*100*

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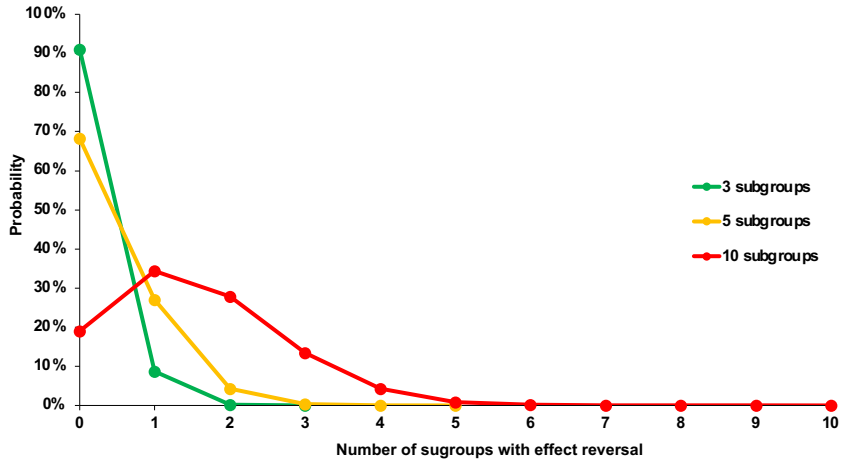
"Effect Reversals", where the treatment effect is positive overall but numerically negative in some subgroups are to be expected in Phase III subgroup analyses



Senn, S and Harrell, F. On wisdom after the Event. *J Clin Epidemiol*, 1997. 50(7):749-751.

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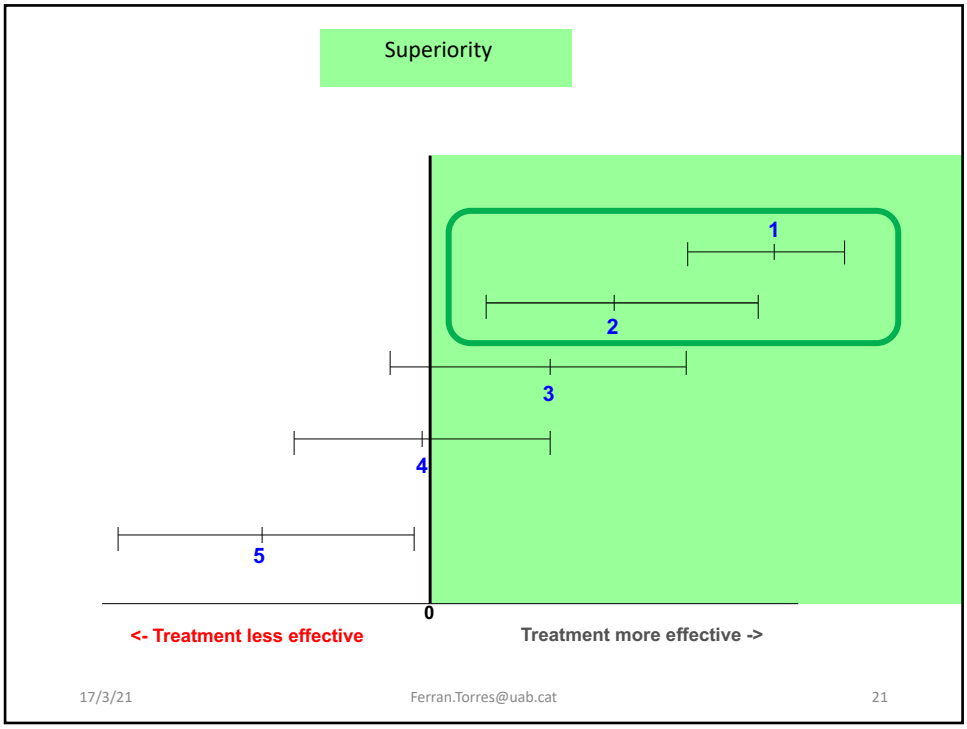
Superiority
1
2
3
4
5
0
<- Treatment less effective
Treatment more effective ->
17/3/21
Ferran.Torres@uab.cat
21

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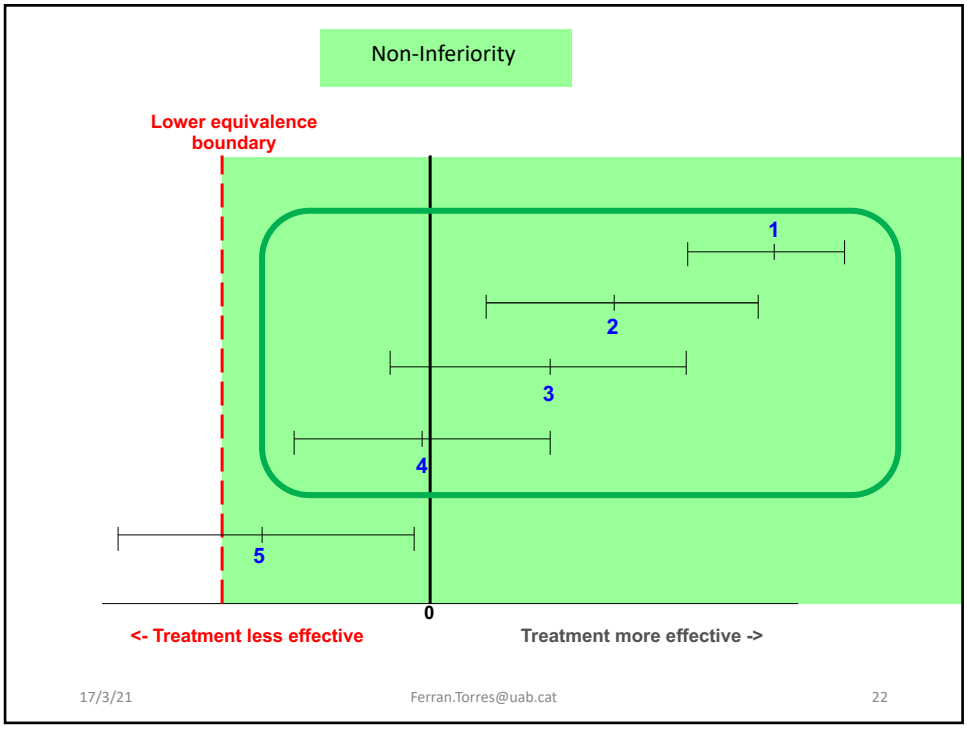
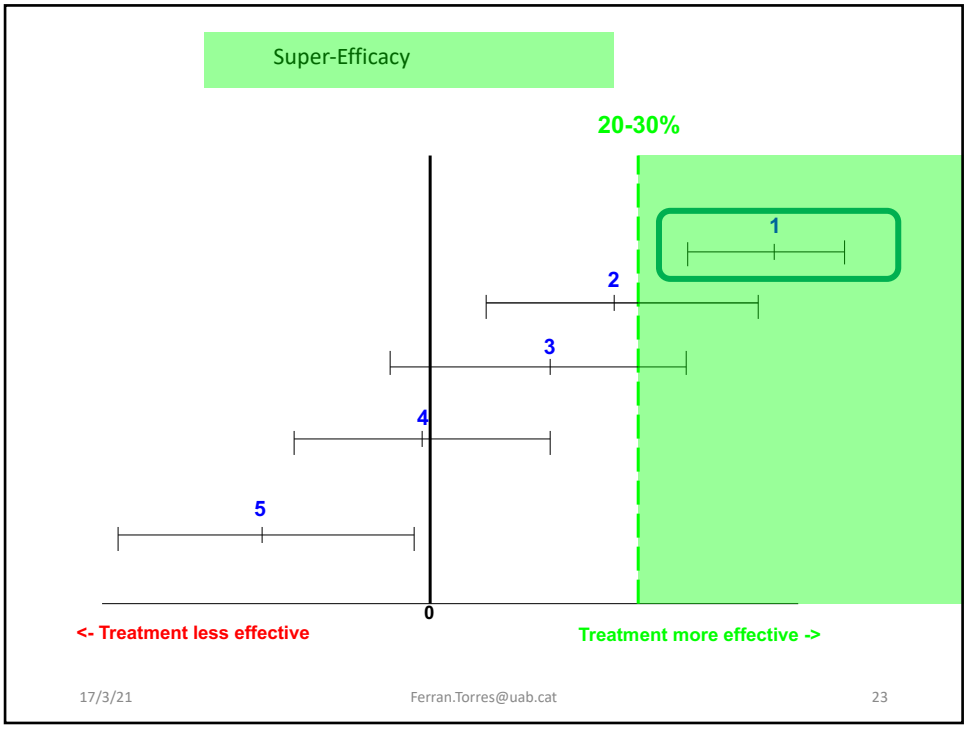

Non-Inferiority
Lower equivalence boundary
1
2
3
4
5
0
<- Treatment less effective
Treatment more effective ->
17/3/21
Ferran.Torres@uab.cat
22

22



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VE Null: 30% - 20%

- Point estimate >>50%
- Lower bound for VE:
  - 30%:
    - Krause P et al. Lancet. 2020 Sep 12;396(10253):741-74
    - WHO target product profiles for COVID-19 vaccines
    - FDA. Development and licensure of vaccines to prevent COVID-19: guidance for industry
  - 20%:
    - CHMP. EMA/592928/2020 EMA considerations on COVID-19 vaccine approval

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Sample size

$$n = \frac{C \times \textbf{Variance}}{(MICD)^2}$$

C: function of α and β

typically:

7.85 for α=0.05 and β=0.2
10.5 for α=0.05 and β=0.1

MICD: Minimum Important Clinically Difference

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Sample Size Estimation for Demonstrating Super Efficacy

STATISTICS IN MEDICINE, VOL. 9, 1447–1454 (1990)

TEST STATISTICS AND SAMPLE SIZE FORMULAE FOR COMPARATIVE BINOMIAL TRIALS WITH NULL HYPOTHESIS OF NON-ZERO RISK DIFFERENCE OR NON-UNITY RELATIVE RISK

CONOR P. FARRINGTON AND GODFREY MANNING
PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, U.K.

Farrington CP, Manning G. Stat Med. 1990 Dec;9(12):1447-54
Nauta J. Statistics in Clinical and Observational Vaccine Studies. 2nd edition. Springer Nature Switzerland. AG 2020
Nauta J. Statistics in Clinical Vaccine Trials. Springer-Verlag Berlin Heidelberg 2011.

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Sample Size Estimation for Demonstrating Super Efficacy

alpha =2.5% (1-sided)
power =90%

Control rate =0.5%

Expected VE = 60% (RR=0.4)

Null VE **=30%** (RR=0.7)

Farrington CP, Manning G. Stat Med. 1990 Dec;9(12):1447-54
Nauta J. Statistics in Clinical and Observational Vaccine Studies. 2nd edition. Springer Nature Switzerland. AG 2020
Nauta J. Statistics in Clinical Vaccine Trials. Springer-Verlag Berlin Heidelberg 2011.

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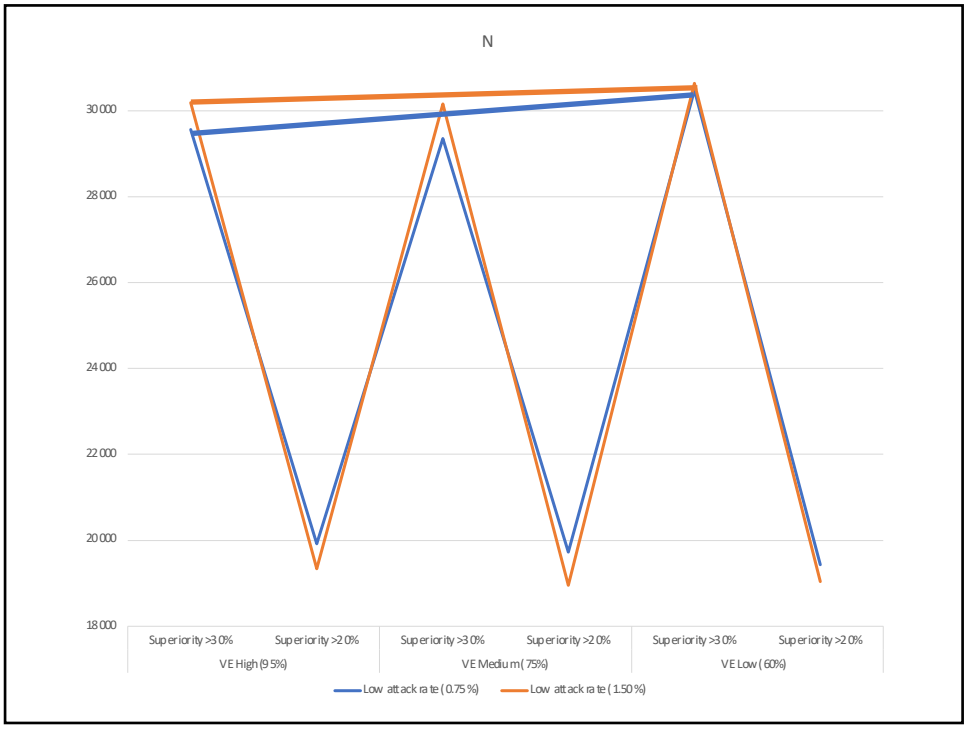
N
30 000
28 000
26 000
24 000
22 000
20 000
18 000
Superiority >30%
Superiority >20%
VE High (95%)
VE Medium (75%)
VE Low (60%)
Low attack rate (0.75%)
Low attack rate (1.50%)

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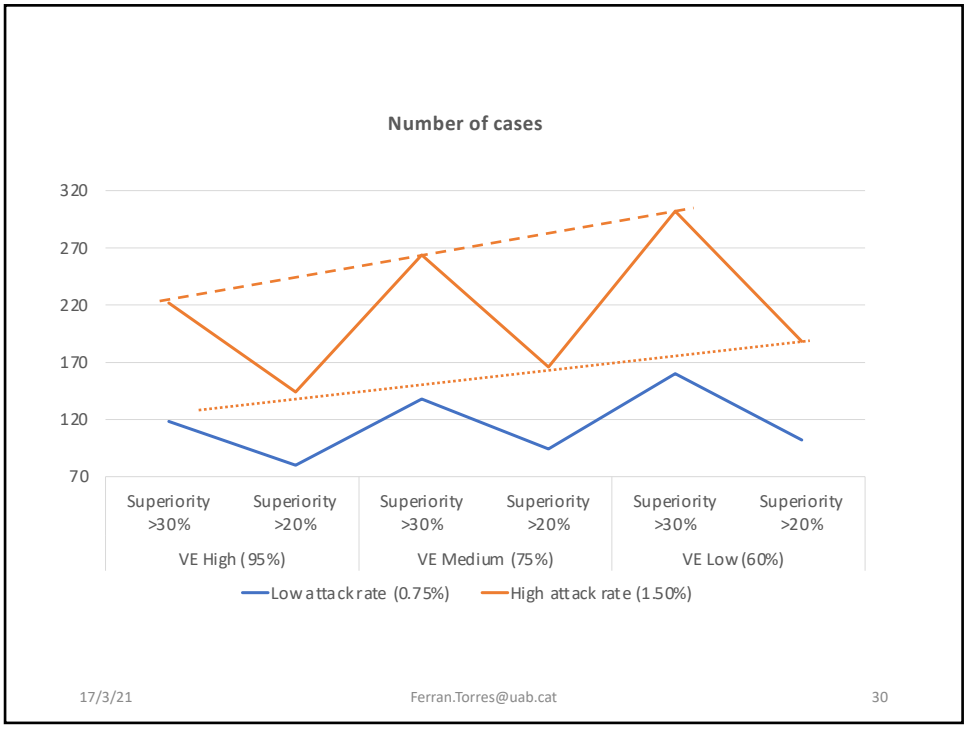
Number of cases
320
270
220
170
120
70
Superiority >30%
Superiority >20%
VE High (95%)
VE Medium (75%)
VE Low (60%)
Low attack rate (0.75%)
High attack rate (1.50%)
17/3/21
Ferran.Torres@uab.cat
30

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The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 31 May 2001
CPMP/EWP/2330/99

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER ON APPLICATION WITH 1. META-ANALYSES; 2. ONE PIVOTAL STUDY

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III ONE PIVOTAL STUDY

III.1 The need for replication

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III.2 Prerequisites for one pivotal study applications

In cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling, and in the regulatory evaluation special attention will be paid to:

- The internal validity. There should be no indications of a potential bias.
- The external validity. The study population should be suitable for extrapolation to the population to be treated.
- Clinical relevance. The estimated size of treatment benefit must be large enough to be clinically valuable.
- The degree of statistical significance. Statistical evidence considerably stronger than $p<0.05$ is usually required, accompanied by precise estimates of treatment effects, i.e. narrow confidence intervals. The required degree of significance will depend on factors such as the therapeutic indication, the primary endpoint, the amount of supportive data and whether the alternative analyses demonstrating consistency are pre-specified. When the aim is to demonstrate non-inferiority, one study is more likely to be accepted if the lower 95% confidence bound is well away from the non-inferiority margin.
- Data quality.
- Internal consistency. Similar effects demonstrated in different pre-specified sub-populations. All-important endpoints showing similar findings.
- Centre effects. None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect.
- The plausibility of the hypothesis tested.

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The use of a meta-analysis to provide the pivotal evidence in an application will always be problematic. One really robust trial supported by smaller trials is stronger than either a meta-analysis of studies, none of which is convincing on its own or a meta-analysis of seemingly conflicting results. There are, however, a number of accepted regulatory purposes for meta-analysis. These include:

II META-ANALYSES

II.1 Pre-specification

Thus, when the need for a meta-analysis is prospectively identified, the protocol for the meta-analysis **should be prospectively specified during the planning of the clinical development** program.

II.1.3 Regulatory prerequisites of retrospective meta-analyses

....

Some studies clearly positive

....

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Oxford/AZ - Overview studies

Study Identifiers Region	COV001 UK	COV002 UK	COV003 Brazil	COV005 South Africa
Start Date / Status	April 2020	May 2020	June 2020	June 2020
Phase	I/II	II/III	II/III	I/II
Planned number of participants	~ 1077	~12390	~10300	~2070
Characteristics of participants	18-55 yr, healthy	≥ 18 yr, healthy	≥ 18 yr, healthy	≥ 18-65 yr, healthy
Number of doses	1 or 2 (based on study group)	1 or 2 (based on study group)	2	2
AZD1222 dose levels [a]	SD: 5×10^{10} vp LD: 2.5×10^{10} vp	SD: 5×10^{10} vp LD: 2.2×10^{10} vp	SD: 5×10^{10} vp	SD: 5×10^{10} vp LD: 2.2×10^{10} vp[b]
Control	MenACWY	MenACWY	MenACWY (first dose) Saline Placebo (second dose)	Saline Placebo
Planned Dose interval	4 – 8 wk	4 – 6 wk	4- 12 wk	4 wk

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Vaccine	Status	More information
Comirnaty	Conditional marketing authorisation granted	Clarification of Comirnaty dosage interval Extra dose from vials of Comirnaty COVID-19 vaccine EMA recommends first COVID-19 vaccine for authorisation in the EU Clinical data (login required) Paediatric investigation plan
COVID-19 Vaccine AstraZeneca	Conditional marketing authorisation granted	EMA recommends COVID-19 Vaccine AstraZeneca for authorisation in the EU Paediatric investigation plan
COVID-19 Vaccine Janssen	Conditional marketing authorisation granted	EMA recommends COVID-19 Vaccine Janssen for authorisation in the EU Paediatric investigation plan
COVID-19 Vaccine Moderna	Conditional marketing authorisation granted	EMA recommends COVID-19 Vaccine Moderna for authorisation in the EU Clinical data (login required) Paediatric investigation plan

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	Pfizer	Moderna	AZ-Oxford	Janssen	
alpha 1-sided	0.025	0.025	0.025	0.025	
Adjusted alpha	0.02134	0.02229	0.01914		
Power	90%	90%	90%	90%	
Incidence rate placebo	1%	0.75%	2.80%	1.50%	
VE	60%	60%	70%	60%	
Drop-out rate	20%	2%			
IA	4	2	no	SPRT-T	
	32,62,92,120	47,110	???	154	
	20%,38%,56%,73%	30%,70%	???	-	
Futility	yes	no	no	no	
Sample Size					
Planned	30480	30138	???	40000	
Observed	36523	28207	9000	39321	
Number of Cases					
Planned	185	151	105	154	
Observed	177	196	98	464	259

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Cases assessment

Doses:	Pfizer	21 days apart
	Moderna	21 days apart
	Oxford/AZ	4 to 26 weeks (28 to 182 days)
	Janssen	Single dose

PEP:	Pfizer	1st PEP: ≥7 days after Dose 2 without past SARS-CoV-2
		2nd PEP: ≥7 days after Dose 2 with/without past SARS-CoV-2
	Moderna	Illness ≥14 days after dose 2
	Oxford/AZ	Symptomatic ≥ 15 days after dose 2
	Janssen	Moderate to severe/critical COVID-19
		(1) at least 14 days
		(2) at least 28 days

When:	Pfizer	28d post-Rnd
	Moderna	42d post-Rnd
	Oxford/AZ	43d – 197d (≈43-99d)
	Janssen	14d/28d

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Pfizer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

This article was published on December 10, 2020, at NEJM.org.

Polack FP et al. N Engl J Med. 2020;383(27):2603-2615

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Pfizer

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (1,7411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.
§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

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Moderna

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

This article was published on December 30, 2020, at NEJM.org.

Baden LR et al. N Engl J Med. 2020 Dec 30:NEJMoa2035389. doi: 10.1056/NEJMoa2035389

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Moderna

Subgroup	Placebo (N=14,073)	mRNA-1273 (N=14,134)	Vaccine Efficacy (95% CI)
	no. of events/total no.		
All patients	185/14,073	11/14,134	94.1 (89.3–96.8)
Age			
≥18 to <65 yr	156/10,521	7/10,551	95.6 (90.6–97.9)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Age, risk for severe Covid-19			
18 to <65 yr, not at risk	121/8403	5/8396	95.9 (90.0–98.3)
18 to <65 yr, at risk	35/2118	2/2155	94.4 (76.9–98.7)
≥65 yr	29/3552	4/3583	86.4 (61.4–95.2)
Sex			
Male	87/7462	4/7366	95.4 (87.4–98.3)
Female	98/6611	7/6768	93.1 (85.2–96.8)
At risk for severe Covid-19			
Yes	43/3167	4/3206	90.9 (74.7–96.7)
No	142/10,906	7/10,928	95.1 (89.6–97.7)
Race and ethnic group			
White	144/8916	10/9023	93.2 (87.1–96.4)
Communities of color	41/5132	1/5088	97.5 (82.2–99.7)

Figure 4. Vaccine Efficacy of mRNA-1273 to Prevent Covid-19 in Subgroups.

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Oxford-AZ

Articles

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

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	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil: all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)

Table 2: Efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population

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		cases	Overall n	%
Pfizer	w/out	170	36523	0.465%
	all	178	40137	0.443%
Moderna		196	28207	0.695%
AZ	SD/SD	98	8895	1.102%
Janssen	14d	464	39321	1.180%
	28d	259	39321	0.659%

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		Control			Vaccine			Efficacy		
		cases	n	%	cases	n	%	VE	95%CI	
Pfizer	w/out	162	18325	0.88%	8	18198	0.04%	95.0%	90.3%	97.6%
	all	169	20172	0.84%	9	19965	0.05%	94.6%	89.9%	97.3%
Moderna		185	14073	1.31%	11	14134	0.08%	94.1%	89.3%	96.8%
AZ		71	4455	1.59%	27	4440	0.61%	62.1%	40.0%	76.1%
Janssen	14d	348	19691	1.77%	116	19630	0.59%	66.9%	59.0%	73.4%
	28d	193	19691	0.98%	66	19630	0.34%	66.1%	55.0%	74.8%

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