UNIVERSITÄT BERN

Per-Protokoll-Analyse von klinischen Studien – schwieriger als gedacht

Marcel Zwahlen

Institute of Social and Preventive Medicine

http://www.ispm.unibe.ch/about_us/staff/zwahlen_marcel

Themen

- Klären folgender Begriffe in der Analyse von RCTs
- Intention-to-treat Analyse
- Per-Protokoll Analyse
- Point vs Sustained Treatments <-> Per-Protokoll Analyse

Three levels of questions in health-related research

- Description
  - How many persons have been Covid vaccinated in Switzerland (by age, region, nationality, BMI group etc)
- Clinical prediction
  - What is the probability of needing intensive care treatment for a (doubly) vaccinated but later SARS-Cov-2 infected person (by age, region, nationality etc)?
- Evaluation of clinical or policy interventions
  - By how much would a 3rd booster Covid vaccine reduce the risk for severe Covid disease in already vaccinated persons of age >75 ?

  → A causal statement about an intervention

30-day mortality after MI with two different treatment approaches

What can you conclude from this data?

	Treatment A			Treatment B		
	Number of patients	Deaths	Proportion dead (percent)	Number of patients	Deaths	Proportion dead (percent)
Total	800	40	5.0	800	81	10.1

Sex, Age and Severity

			Treatment A			Treatment B		
			Number of patients	Deaths	Proportion dead (percent)	Number of patients	Deaths	Proportion dead (percent)
Total	Age	Seve-rity	800	40	5.0	800	81	10.1
Men	<60	Low	200	4	2.0	50	1	2.0
	<60	High	60	6	10.0	100	10	10.0
	60+	Low	100	5	5.0	200	10	5.0
	60+	High	40	10	25.0	160	40	25.0
Women	<60	Low	200	2	1.0	100	1	1.0
	<60	High	60	3	5.0	40	2	5.0
	60+	Low	100	4	4.0	50	2	4.0
	60+	High	40	6	15.0	100	15	15.0

The beauty of randomization

- For a large study with randomized treatement assignment there is «no need to adjust»
  - for confounding by baseline characteristics
  - selection of patients into treatment group

The "magic" of randomization is that it is guaranteed to result in groups of patients that are balanced (give or take the play of chance) with respect to both known and unknown risk factors (regardless of whether those risk factors have been assessed) :

Collins R et al. The Magic of Randomization versus the Myth of Real-World Evidence. NEJM 2020 (Feb 13) 382;7:674-8.

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

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–95)	51.4 (18–95)	51.4 (18–95)
Age category and risk for severe Covid-19 — no. of participants (%)†			
18 to <65 yr, not at risk	8,886 (58.6)	8,888 (58.5)	17,774 (58.6)
18 to <65 yr, at risk	2,535 (16.7)	2,530 (16.7)	5,065 (16.7)
≥65 yr	3,749 (24.7)	3,763 (24.8)	7,512 (24.8)
Risk factor for severe Covid-19 — no. of participants (%)			
Chronic lung disease	744 (4.9)	710 (4.7)	1,454 (4.8)
Significant cardiac disease	744 (4.9)	752 (5.0)	1,496 (4.9)
Severe obesity	1,021 (6.7)	1,025 (6.8)	2,046 (6.7)
Diabetes	1,440 (9.5)	1,435 (9.5)	2,875 (9.5)
Liver disease	96 (0.6)	100 (0.7)	196 (0.6)
Human immunodeficiency virus infection	87 (0.6)	92 (0.6)	179 (0.6)
Body-mass index¶			
No. of participants	15,007	14,985	29,992
Mean ±SD	29.3±6.7	29.3±6.9	29.3±6.8

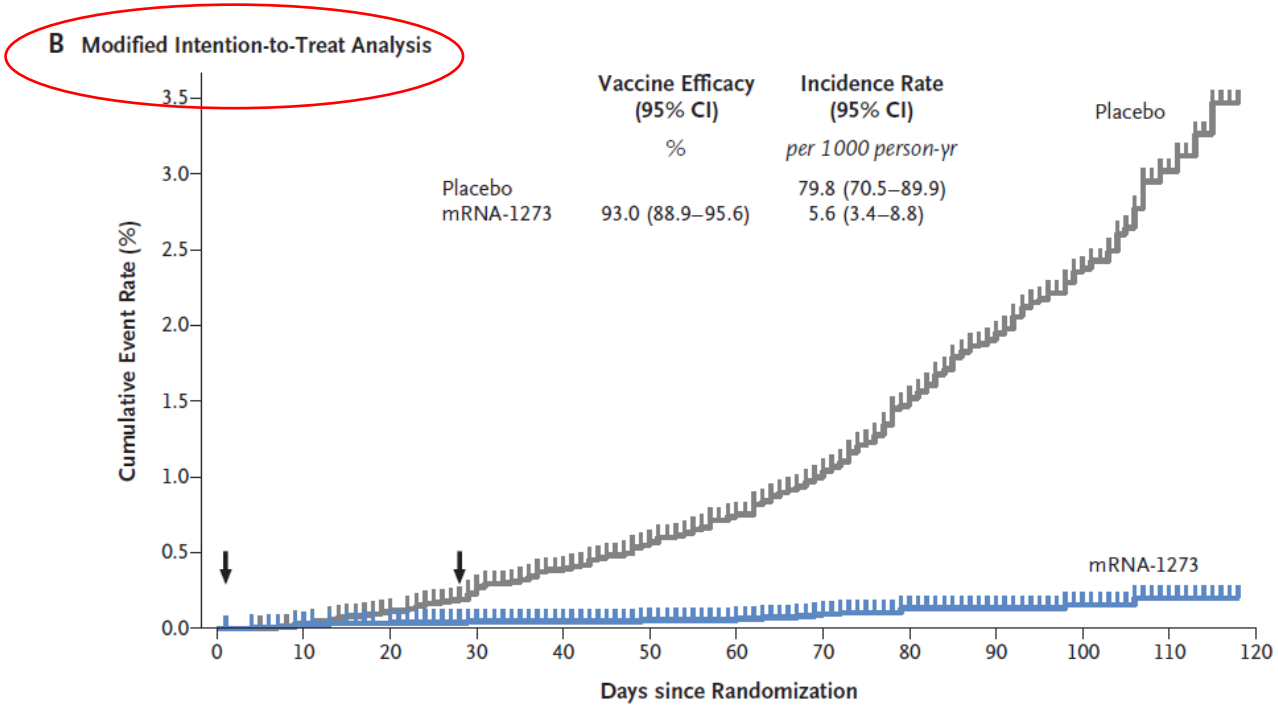
«Moderna» Trial. NEJM 2020 (Dec 30) ;384:403-16

We expect an ITT (intention-to-treat)-analysis

From the glossary of the 1998 FDA Guidance for Industry

E9 Statistical Principles for Clinical Trials

Intention-to-treat principle: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance with the planned course of treatment.



No. at Risk

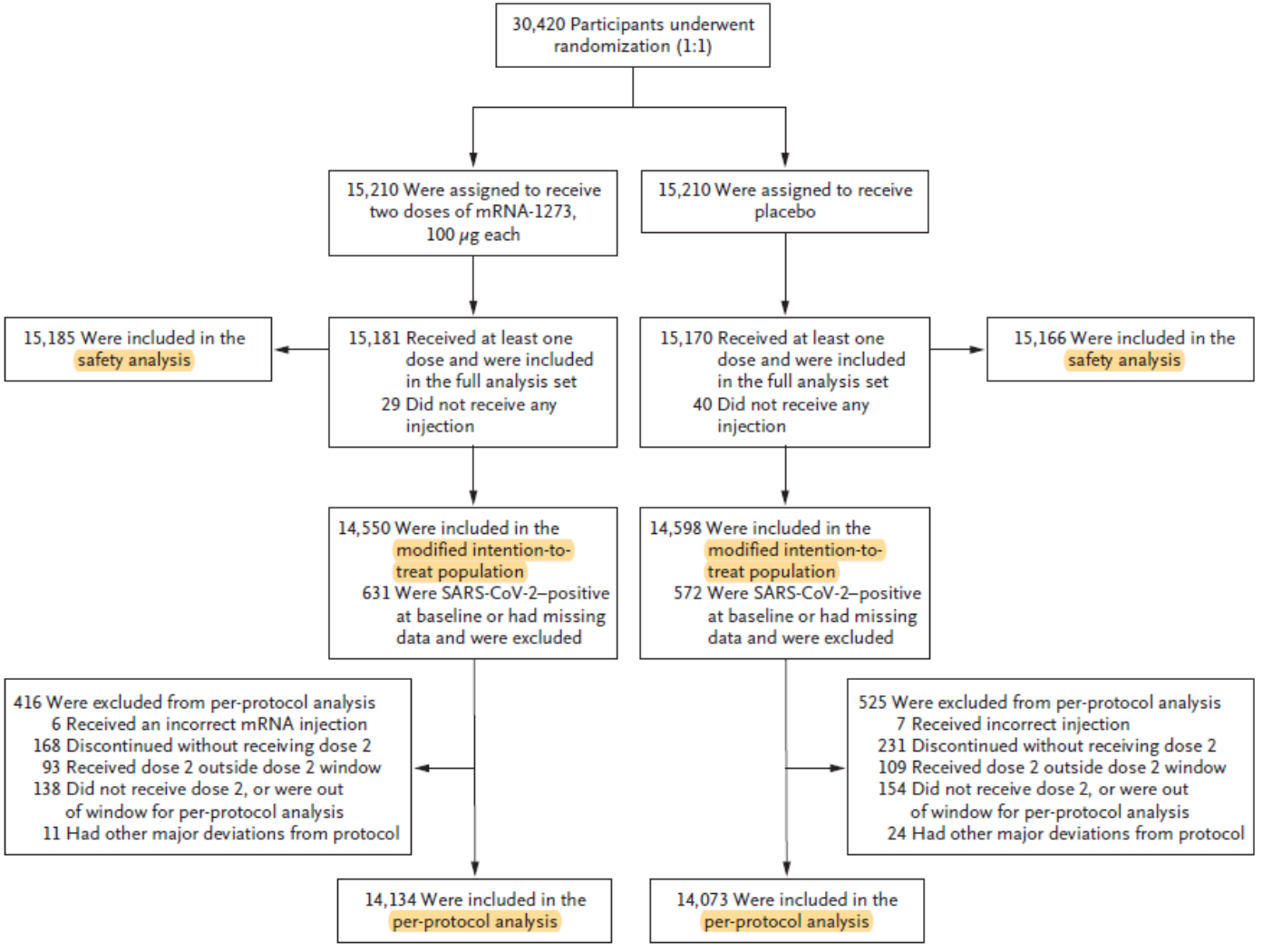
Placebo	14,598	14,590	14,567	14,515	13,806	12,352	12,694	11,450	9736	6729	4067	1200	0
mRNA-1273	14,550	14,543	14,532	14,504	13,825	13,398	12,791	11,573	9911	6871	4179	1238	0

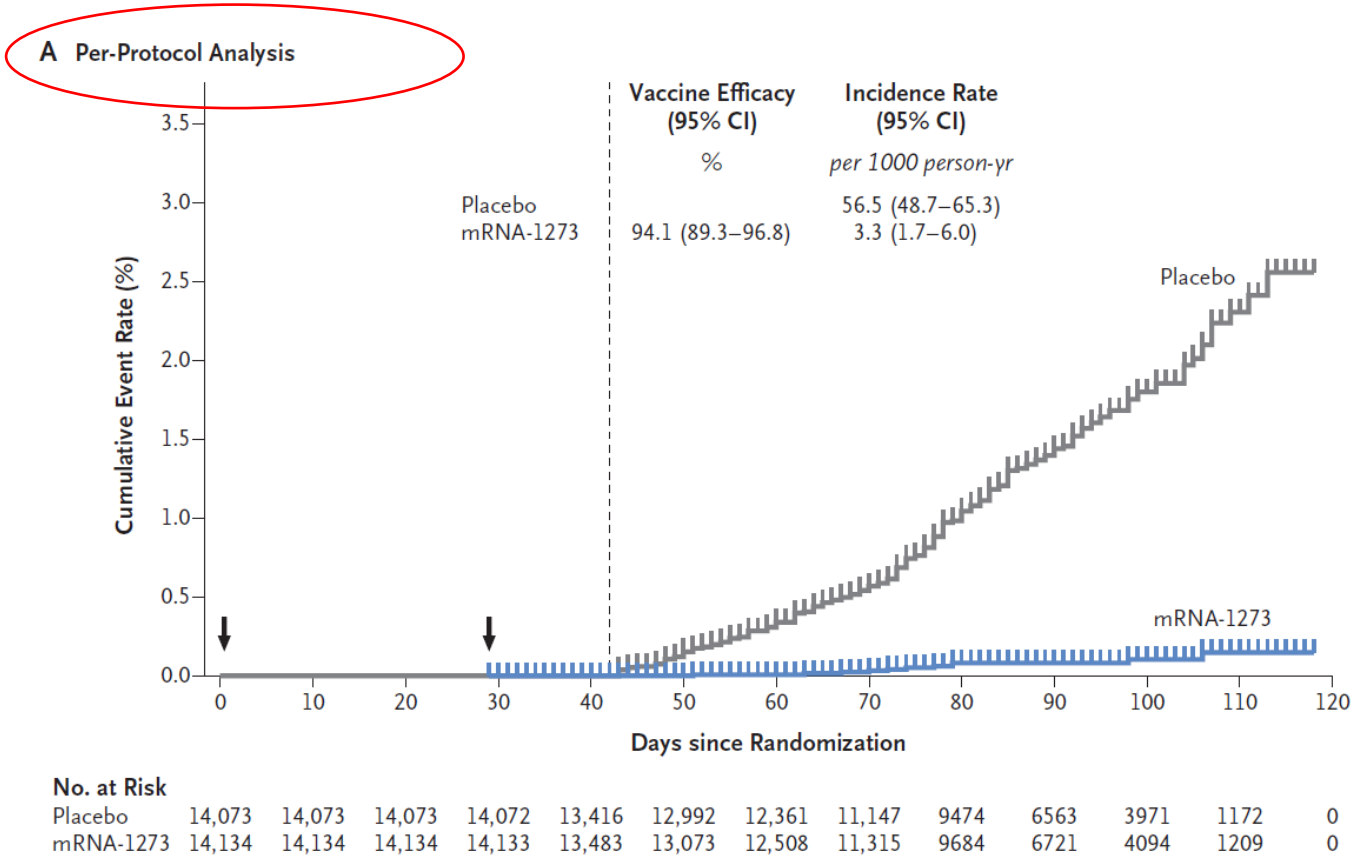
Restriction to those «at risk» of SARS-CoV-2 infection at start of trial

Table 1. Demographic and Clinical Characteristics at Baseline.*

Baseline RT-PCR test — no. of participants (%)			
Negative	14,923 (98.4)	14,917 (98.3)	29,840 (98.3)
Positive	95 (0.6)	87 (0.6)	182 (0.6)
Missing data	152 (1.0)	177 (1.2)	329 (1.1)
Baseline bAb anti–SARS-CoV-2 assay — no. of participants (%)			
Negative	14,726 (97.1)	14,690 (96.8)	29,416 (96.9)
Positive	303 (2.0)	305 (2.0)	608 (2.0)
Missing data	141 (0.9)	186 (1.2)	327 (1.1)

Vaccine efficacy was assessed in the full analysis population (randomized participants who received at least one dose of mRNA-1273 or placebo), the modified intention-to-treat population (participants in the full analysis population who had no immunologic or virologic evidence of Covid-19 on day 1, before the first dose), and the per-protocol population (participants in the modified intention-to-treat population who received two doses, with no major protocol deviations).


30,420 Participants underwent randomization (1:1)
15,210 Were assigned to receive two doses of mRNA-1273, 100 μg each
15,210 Were assigned to receive placebo
15,185 Were included in the safety analysis
15,181 Received at least one dose and were included in the full analysis set
29 Did not receive any injection
15,170 Received at least one dose and were included in the full analysis set
40 Did not receive any injection
15,166 Were included in the safety analysis
14,550 Were included in the modified intention-to-treat population
631 Were SARS-CoV-2–positive at baseline or had missing data and were excluded
14,598 Were included in the modified intention-to-treat population
572 Were SARS-CoV-2–positive at baseline or had missing data and were excluded
416 Were excluded from per-protocol analysis
6 Received an incorrect mRNA injection
168 Discontinued without receiving dose 2
93 Received dose 2 outside dose 2 window
138 Did not receive dose 2, or were out of window for per-protocol analysis
11 Had other major deviations from protocol
525 Were excluded from per-protocol analysis
7 Received incorrect injection
231 Discontinued without receiving dose 2
109 Received dose 2 outside dose 2 window
154 Did not receive dose 2, or were out of window for per-protocol analysis
24 Had other major deviations from protocol
14,134 Were included in the per-protocol analysis
14,073 Were included in the per-protocol analysis

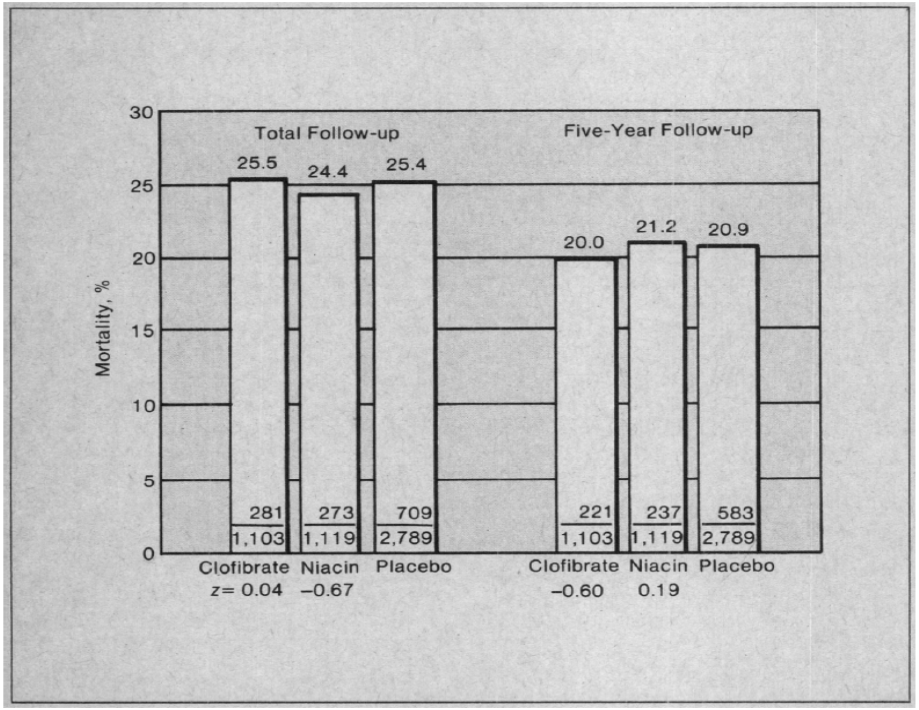


No. at Risk

Placebo	14,073	14,073	14,073	14,072	13,416	12,992	12,361	11,147	9474	6563	3971	1172	0
mRNA-1273	14,134	14,134	14,134	14,133	13,483	13,073	12,508	11,315	9684	6721	4094	1209	0

The Coronary Drug Project «Story»

Fig 3.—Mortality for all causes, for first five years of follow-up and for total follow-up experience.



«As previously reported, three of the Coronary Drug Project treatment regimens were discontinued before the scheduled completion of the project.”

The Coronary Drug Project. Clofibrate and niacin in coronary heart disease. JAMA 1975;231:360-81.

The Coronary Drug Project and the «adherence question» to a long-term treatment

INFLUENCE OF ADHERENCE TO TREATMENT AND RESPONSE OF CHOLESTEROL ON MORTALITY IN THE CORONARY DRUG PROJECT

THE CORONARY DRUG PROJECT RESEARCH GROUP

Abstract The Coronary Drug Project was carried out to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term treatment of coronary heart disease.

NEJM 1980;303:1038

Separate analysis for patient's cumulative adherence

Table 1. Five-Year Mortality in Patients Given Clofibrate or Placebo, According to Cumulative Adherence to Protocol Prescription.

ADHERENCE *	TREATMENT GROUP	
	CLOFIBRATE	
	no. of patients	*% mortality* †
<80%	357	24.6±2.3 (22.5)
≥80%	708	15.0±1.3 (15.7)
Total study group	1065	18.2±1.2 (18.0)

*A patient's cumulative adherence was computed as the estimated number of capsules actually taken as a percentage of the number that should have been taken according to the protocol during the first five years of follow-up or until death (if death occurred during the first five years).

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Table 1. Five-Year Mortality in Patients Given Clofibrate or Placebo, According to Cumulative Adherence to Protocol Prescription.

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	CLOFIBRATE		PLACEBO	
	no. of patients	*% mortality* †	*no. of patients*	*% mortality* †
<80%	357	24.6±2.3 (22.5)	882	28.2±1.5 (25.8)
≥80%	708	15.0±1.3 (15.7)	1813	15.1±0.8 (16.4)
Total study group	1065	18.2±1.2 (18.0)	2695	19.4±0.8 (19.5)

*A patient's cumulative adherence was computed as the estimated number of capsules actually taken as a percentage of the number that should have been taken according to the protocol during the first five years of follow-up or until death (if death occurred during the first five years).

Table 2. Prevalence of Base-Line Characteristics in Patients Given Placebo, According to Cumulative Adherence to Protocol Prescription.

Base-Line Characteristic	Per Cent Prevalence	
	<80% Adherence	>80% Adherence
Depression of ST-segment	31.4	21.6
Use of diuretics	20.0	14.7
New York Heart Association Class 2	58.7	50.5
Ventricular conduction defect	3.1	4.5
Heart rate >70 on electrocardiogram	48.2	42.8
Cardiomegaly (definite or suspected)	20.9	16.3
>2 previous myocardial infarctions	22.9	18.2
Intermittent claudication (definite or suspected)	10.5	7.4
Serum cholesterol >250 mg/dl (>6.47 mmol/liter)	48.4	47.4
White-cell count >7500	49.3	42.2
Light physical activity	72.6	68.2
Ventricular premature beats	2.9	2.5
Serum total bilirubin >0.50 mg/dl (>8.55 μmol/liter)	52.0	51.1
Q/QS patterns	64.8	60.4
Use of oral hypoglycemic agents	6.1	5.7
Serum triglycerides >5.0 meq/liter (>1.67 mmol/liter)	54.8	52.1
Use of antiarrhythmic agents	4.2	4.3
Serum uric acid >7.0 mg/dl (>0.42 mmol/liter)	43.1	44.1
Fasting plasma glucose >100 mg/dl (5.55 mmol/liter)	42.5	41.9
Use of antihypertensive agents	10.8	8.3

Separate analysis for patient's cumulative adherence

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The figures in parenthesis are adjusted for 40 baseline characteristics

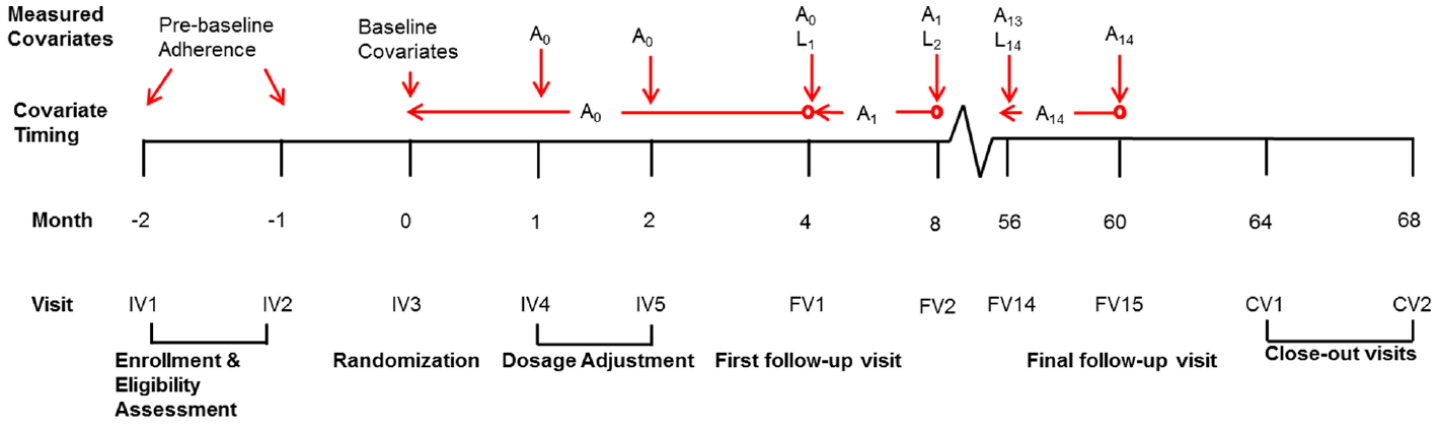
The Coronary Drug Projet re-analysed and re-discussed

Table 1. Replication of the original results reported by Coronary Drug Project Research Group.[4]

	Five-year mortality, % (95% CI)			
	Unadjusted		Adjusted for baseline variables	
	Cumulative adherence <80%	Cumulative adherence ≥80%	Cumulative adherence <80%	Cumulative adherence ≥80%
Placebo arm: Original 1980 analysis[4]	28.2 (25.3–31.1)	15.1 (13.5–16.7)	25.8 (22.9–28.7)	16.4 (14.8–18.0)
Replication	29.7 (26.6–33.0)	15.5 (13.8–17.2)	27.4 (24.5–30.3)	16.5 (14.8–18.2)

Murray E & Hernan M. Clinical Trials 2016;13:372-8

Timing of study visits and variable measurement



L_t is the vector of post-randomization covariates measured at visit t

A_t is an indicator for adherence level for the period from t to just before t + 1 measured at visit t + 1

A_0 is measured at follow-up visit 1 (FV1) or, for individuals who died or dropped out before FV1, at IV4 and IV5.

Per-Protocol Analyses of Pragmatic Trials

Table 1. Data Requirements for the Definition and Estimation of the Per-Protocol Effect in Randomized Trials with Sustained Treatment Strategies.

Available Data	Example	Identification of Adherence to the Protocol	Estimation of the Per-Protocol Effect
Randomization group assignment and outcome	A large, simple trial	Not possible	Not possible
Group assignment and outcome plus treatment received after randomization	A trial that records pill counts but not clinical information at each visit	Not possible	Not possible
Group assignment and outcome plus treatment received after randomization plus protocol-specified clinical events that either mandate or allow treatment changes	A trial that records data on protocol-specified toxic effects and contraindications	Possible	Possible if adherence is independent of prognosis
Group assignment and outcome plus treatment received after randomization plus prerandomization and postrandomization prognostic factors associated with adherence	A trial that records detailed clinical data at and after randomization	Possible	Possible; g-methods are required if prognostic factors are affected by previous treatment

Hernan& Robins. NEJM 2017;377:1391-8.

Table 2. Comparison of original and updated estimates for the placebo arm, Coronary Drug Project.

	Five-year mortality risk difference, % (95% CI)			
	Unadjusted	Adjusted for baseline variables[a] via linear regression	Adjusted for baseline variables[a] via logistic regression[b]	Further adjusted for post-randomization variables[c]
Replication of 1980 analysis (N = 2630)	14.3 (10.8–17.8)	10.9 (7.5–14.4)	10.6 (7.3–14.0)	N/A
Updated 2015 analysis (N = 2401)	11.0 (6.5–15.6)	7.4 (3.0–11.8)	7.0 (2.7–11.2)	2.5 (−2.1–7.0)

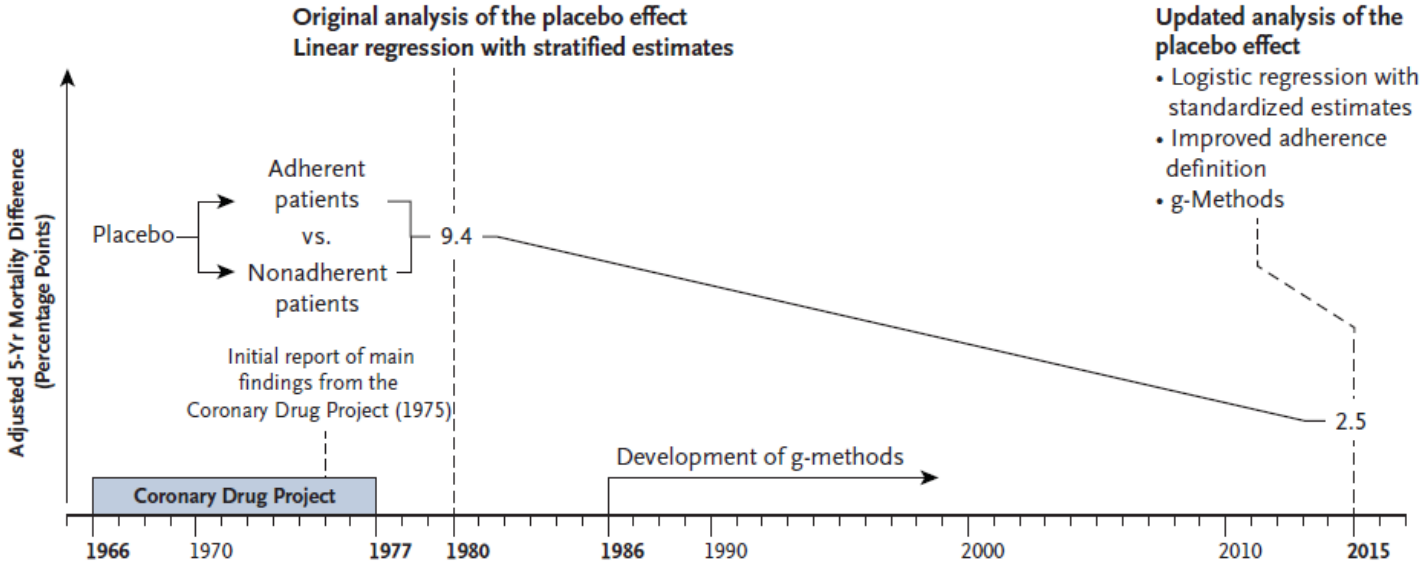
CI: confidence interval; ECG: electrocardiogram; MI: myocardial infarction.

[a]Adjusted for 39 baseline variables: age, race, risk group, number of prior MIs, relative body weight, medical history, prescriptions of non-study medications, lab findings, blood pressure, cardiomegaly, ECG findings, cigarette smoking, and physical activity level (see Supplementary Table A1 for details).

[b]The original 1980 analysis did not include logistic regression; we include it here for comparison purposes.

[c]Adjusted for the 39 baseline variables (age, race, risk group, prior MIs, and relative body weight were baseline only) and 34 post-randomization variables: medical history, prescriptions of non-study medications, lab findings, blood pressure, cardiomegaly, ECG findings, cigarette smoking, and physical activity level (see Supplementary Table A1 for details). Comparing individuals with $<80\%$ versus $\geq 80\%$ at each visit.

Murray&Hernan Clinical Trials 2016;13:372-8



Hernan& Robins NEJM 2017;377:1391-8.

Conclusions I

- ITT analysis of RCTs is simple
- Definition of a «per-protocol population» in a RCT for a «point intervention» (eg. single shot vaccination) is reasonaly straightforward

Conclusions II :
Situation for RCTs on sustained treatments is different and more difficult

- ITT analysis might not be the final answer of interest
- «Naive» per-protocol (or adherence) analysis is flawed
- More appropriate «adjusting methods» exist

  But for proper (planned) per-protocol analysis

  «Data collection» must be
  - Adapted
  - Much larger with controlled data qualtiy
  - Must have good «time resolution»

STATISTICS IN MEDICINE

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References

1. The Coronary Drug Project. Clofibrate and niacin in coronary heart disease. JAMA 1975;231(4):360-81.

2. The Corornary Durg Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the coronary drug project. N Engl J Med 1980;303(18):1038-41.

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4. Hernan MA, Hernandez-Diaz S. Beyond the intention-to-treat in comparative effectiveness research. Clinical Trials 2012;9(1):48-55.

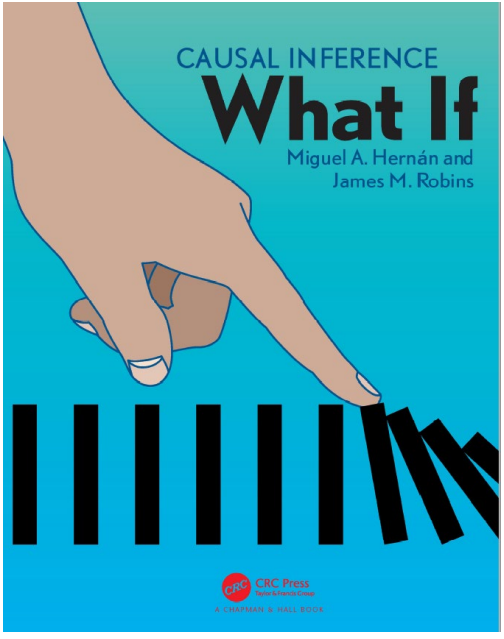
5. Murray EJ, Hernan MA. Adherence adjustment in the Coronary Drug Project: A call for better per-protocol effect estimates in randomized trials. Clin Trials 2016;13(4):372-8.

6. Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. New England Journal of Medicine 2017;377(14):1391-8.

7. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. New England Journal of Medicine 2020;384(5):403-16.

g-methods?

Miguel Hernán



https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/