Leids Universitair Medisch Centrum

Causal inference 1

Week 2: design

Part 4.1 and 4.2 of r-causal.org (4.3 in exerices)

Recap week 1

An exposure *X* with two values (0/1)

Potential outcomes

- $Y(1)$: The outcome if the exposure value is set to the level 1
- $Y(0)$: The outcome if the exposure value is set to the level 0

Individual causal contrast

$$Y(1)\text{-}\ Y(0)$$

Average causal contrast in a certain population

$$E\big(Y(1)\big) - \ \mathrm{E}(Y(0))$$

Estimating causal contrasts from data

Three assumptions needed

Consistency: If $X = x$ then $Y(x) = Y$, for all x

well defined exposure

Exchangeability: X is independent of $Y(x)$, for all x

Exposed and unexposed group are comparable

Positivity: $\Pr(X = x) > 0$, for all x

All participants should have the possibility to receive all levels of exposure

PLUS:

No interference

The outcome for any individual does not depend on another individual's exposure

How can we meet the causal assumptions?

Linking causal estimands to data

- Design of the study
  - Collect appropriate data
- Analysis
  - Use methods which address potential sources of bias

- Today: design.

Two types of designs

- Experimental designs
  - The researcher has an active rol. Assigns the exposure.
  - Examples
    - The agriculture experiments discussed in the GLM course
    - Clinical trials
    - A/B tests in marketing

- Observational designs
  - The researcher has no active role. Only observes exposure.
  - Examples
    - Analysis of insurance claim data
    - The Framingham study

PART 1
Experimental design

Can we estimate an individual causal contrast?

Hardly ever possible to estimate $Y(1)$ - $Y(0)$ for an individual

Some possibilities:

- Find two identical individuals, assign X=1 to one , X=0 to the other.
  - Examples: genetically identical mice; identical twins
- Give both X=1 and X=0 to the same individual
  - Examples: Left and right eye; n-of-1 trial

If individual contrast cannot be estimated, then:

- Consider $\mathrm{E}(Y(1))$ and $\mathrm{E}(Y(0))$ and define contrast of average potential outcomes in a certain population

Randomized studies

- The exposure (cause) of interest is randomly assigned.

In an *ideal* randomized study, we obtain:

- Exchangeability ✓
  - The group with X=1 and X=0, are identical except from random variation
- Positivity ✓
- Consistency: well defined exposure levels ✓
- Consistency: No interference . ?
  - Usually we can assume no interference, but not always: Example: vaccination trials

A realistic example from 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Clinical trial

- Experiment to study the effect of an intervention in human beings.
- Starts with a protocol. (a detailed plan)

- Protocol needs to be approved by medical ethical committee (law of medical research)

- Protocol is published in a trial registry

- What should be in the protocol?

Key elements in protocol (as defined by Hernán and Robins (2016)):

1. Eligibility criteria
2. Exposure definition (Intervention and control)
3. Assignment procedures
4. Follow-up period
5. Outcome definition
6. Causal contrast of interest
7. Analysis plan

Protocols for clinical trials

COVID-19 paper:

Protocol with its statistical analysis plan is available at NEJM.org and on the trial website at www.recoverytrial.net.

https://www.nejm.org/doi/suppl/10.1056/NEJMoa2021436/suppl_file/nejmoa2021436_protocol.pdf

Dutch standard template

https://www.ccmo.nl/onderzoekers/standaardonderzoeksdossier/c-protocol/c1-onderzoeksprotocol

Protocol elements and causal assumptions

Assumption	Eligibility Criteria	Exposure Definition	Assignment Procedures	Follow-up Period	Outcome Definition	Causal contrast	Analysis Plan
Consistency (Well defined exposure)	✓	✓					
Consistency (No interference)		✓	✓		✓		✓
Positivity	✓		✓				✓
Exchangeability	✓		✓	✓			✓

Table 4.2: Mapping assumptions to elements of a study protocol

ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

METHODS

In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.

Key protocol elements of the COVID-19 study

1. Eligibility criteria

   Patients, in hospital, with clinically suspected or laboratory confirmed SARS-CoV-2 infection (all ages), in the United Kingdom.

2. Exposure definition (Intervention and control)

   Intervention: usual standard of care plus oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days.

   Control: usual care alone

3. Assignment procedures

   Random assignment at start, controlled open label

Randomization

Why?

- To create exchangeable groups

Ethical?

- Yes, if it is truly unknown if one treatment is better than another ("equipoise")

Practical issues

To obtain two groups of similar sizes

- Randomization is often done in "blocks" in which the same number of people receive X=1 and X=0.

To reduce risk of imbalance with respect to prognostic variables

- Randomization can be done separately in different groups ('strata')

Covid-19 example

the trial site. Randomization was performed with the use of a Web-based system with concealment of the trial-group assignment. Eligible and consenting patients were assigned in a 2:1 ratio to receive either the usual standard of care alone or the usual standard of care plus oral or intravenous dexamethasone (at a dose of 6 mg once

Controlled open label study

- Controlled: intervention is compared to a control group.

- Open label: both the researchers and participants know after randomization which treatment is being administered
- In this study treatment assignment is concealed at randomisation

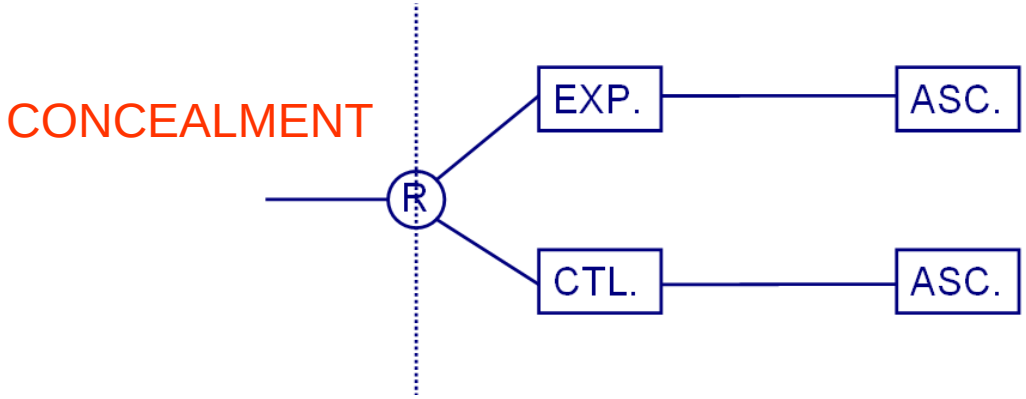
- Problem?
- Alternative?

- Blinding

Why blinding (1)

Prevention of selection bias

- Blinding to conceal treatment allocation
- To hide who get what

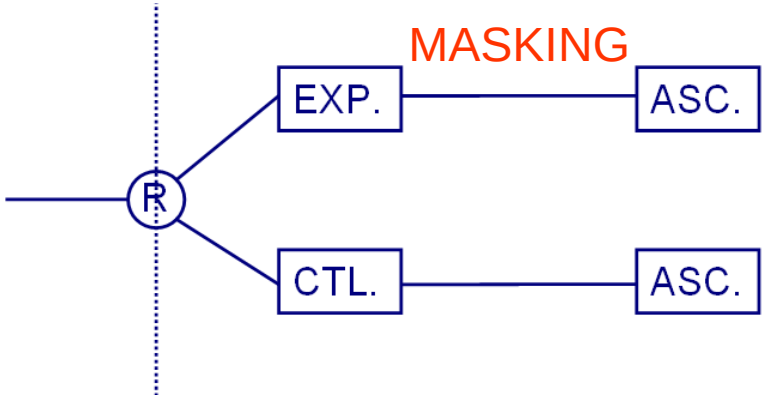


Why blinding (2)

Prevention of information bias

- during the study
  - co-medication
  - co-interventions
  - change of life style

- at end of study
  - outcome assessment



Blinding

Blinding → exchangeability

Double blinded: neither the participants nor the doctors/researchers know which study group the participants are in.

What could be the reason that the Covid study is not double blinded?

Advantage of open label study

- The doctors know which treatment a patient gets
- It is easier to carry out
- Sometimes blinding is not possible (e.g. surgery versus no surgery)

Placebo

Sometimes “placebo” in control group

Placebo: A fake substance resembling treatment being investigated .
Used as a control treatment.

Design may be

- 1) treatment vs placebo or
- 2) Best standard of care plus either experimental treatment or a matching placebo

Placebo in our Covid example?

Key elements in protocol (as defined by Hernán and Robins (2016)):

4. Follow-up period

    28 days after randomization (it should be clear what time zero is)

5. Outcome definition

    28 day mortality

6. Causal contrast of interest

Define causal contrast

Notation:

X: for treatment. *X*=1 is dexamethasone, *X*=0 usual care

Potential outcomes

Y(1): potential 28 day mortality if receiving *X*=1

Y(0): potential 28 day mortality if receiving *X*=0

Causal difference in mean potential outcomes:

$$E(Y(1)) - E(Y(0))$$

Average treatment effect in the population (ATE)

Y is binary, therefore this is equal to the risk difference in the population

Alternative causal contrasts

Binary outcome: $\mathrm{E}(Y(1)) = \mathrm{P}(Y(1) = 1)$

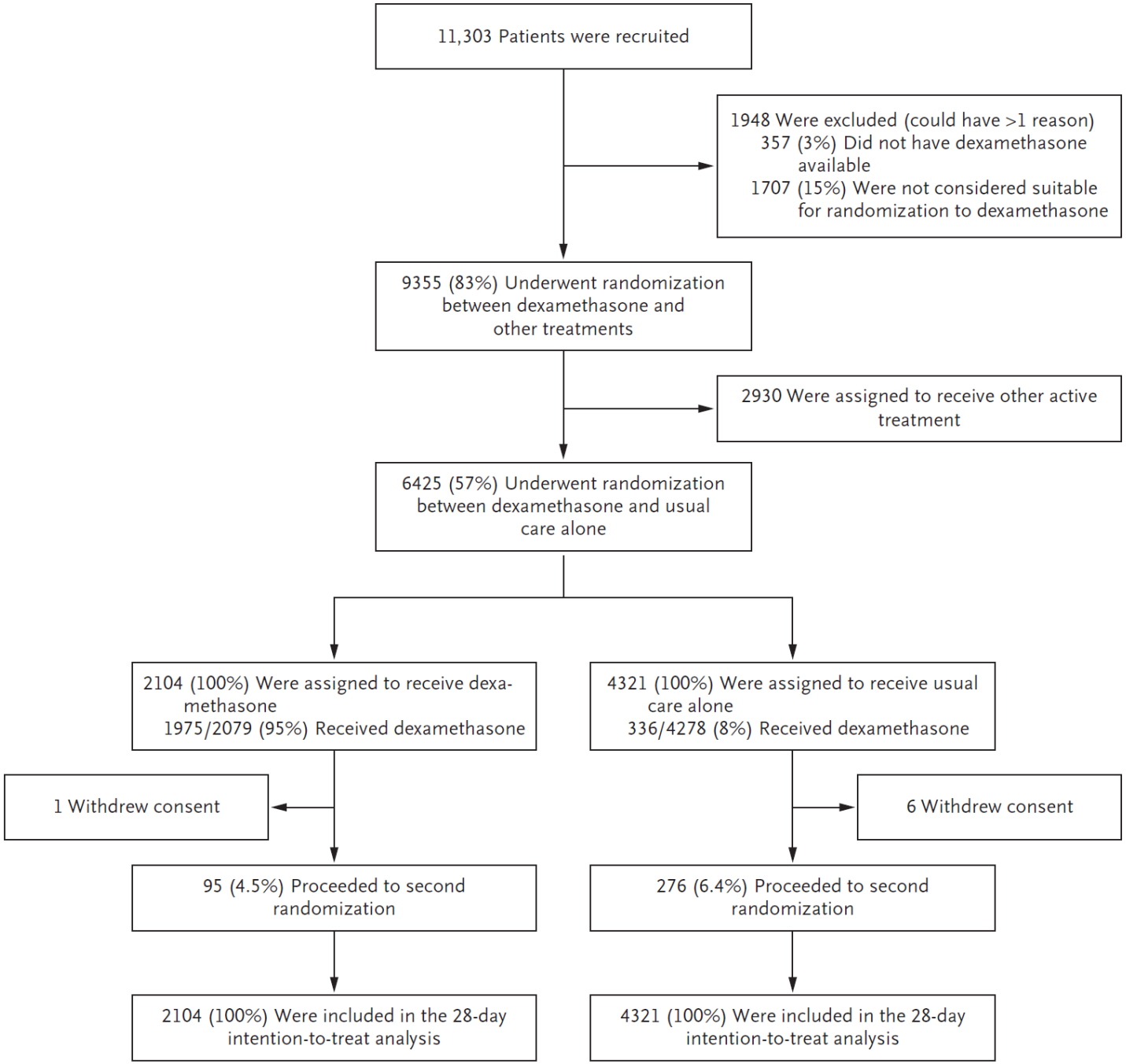
$$\mathrm{E}\big(Y(0)\big) = \mathrm{P}(Y(0) = 1)$$

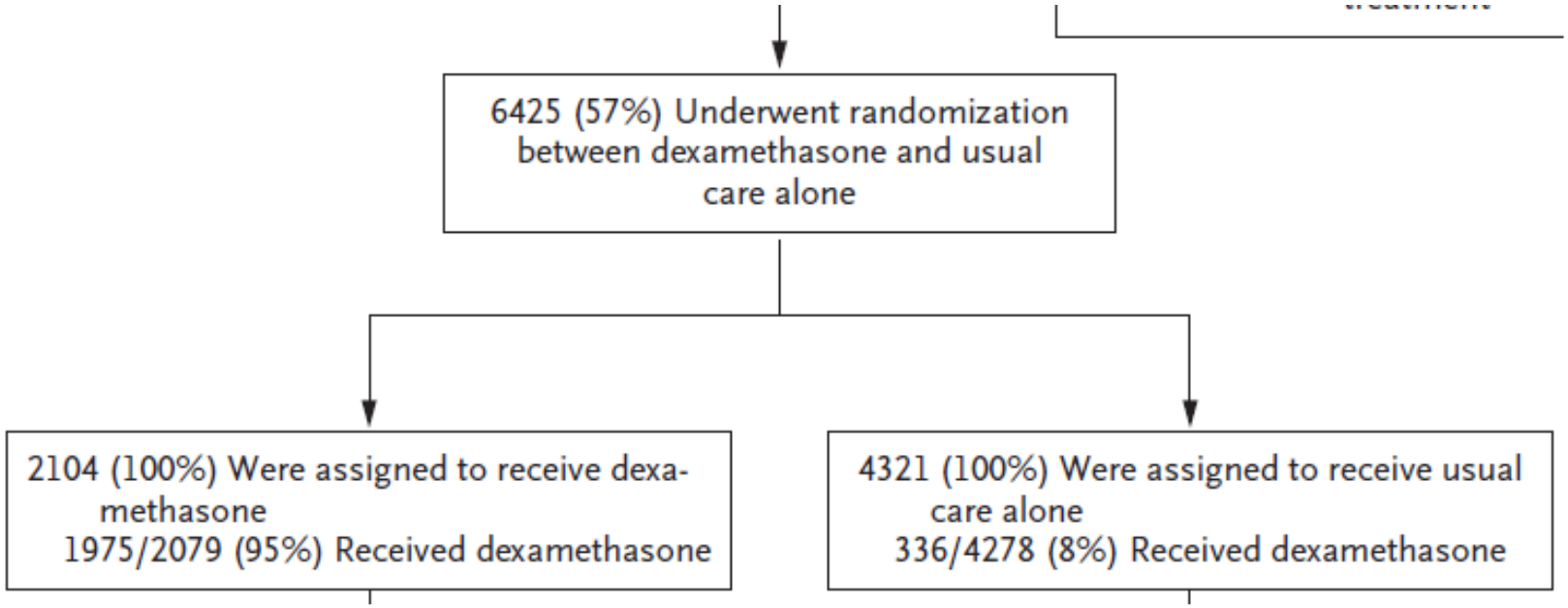
Common used causal contrasts for binary outcomes:

Risk difference: $\mathrm{RD} = \mathrm{E}\big(Y(1)\big) - \mathrm{E}(Y(0))$

Risk ratio: $\mathrm{RR} = \mathrm{E}(Y(1)) \,/\, \mathrm{E}(Y(0))$

Odds ratio: $\mathrm{OR} = \dfrac{\mathrm{E}(Y(1))/(1-\mathrm{E}(Y(1))}{\mathrm{E}(Y(0))/(1-\mathrm{E}(Y(0))}$


11,303 Patients were recruited
1948 Were excluded (could have >1 reason)
357 (3%) Did not have dexamethasone available
1707 (15%) Were not considered suitable for randomization to dexamethasone
9355 (83%) Underwent randomization between dexamethasone and other treatments
2930 Were assigned to receive other active treatment
6425 (57%) Underwent randomization between dexamethasone and usual care alone
2104 (100%) Were assigned to receive dexamethasone
1975/2079 (95%) Received dexamethasone
4321 (100%) Were assigned to receive usual care alone
336/4278 (8%) Received dexamethasone
1 Withdrew consent
6 Withdrew consent
95 (4.5%) Proceeded to second randomization
276 (6.4%) Proceeded to second randomization
2104 (100%) Were included in the 28-day intention-to-treat analysis
4321 (100%) Were included in the 28-day intention-to-treat analysis



What to do with
(a) patients randomised for dexamethason, but did not receive it?
(b) patients randomised for usual care alone, who received dexamethason?

Intention to treat analysis

Patients are analyzed according to the group to which they were assigned

Even if they

- Did not receive the treatment
- Did not adhere to the treatment (dropped out or did not comply).

“If randomized, then analyze”

Covid-19 trial:

- patients randomized for dexamethasone remain in this group, even if they did not receive dexamethasone.
- And patients randomized for control treatment, but who received dexamethasone (or another treatment) remain in the control group

Why not make two groups: actual taking dexamethasone yes/no?

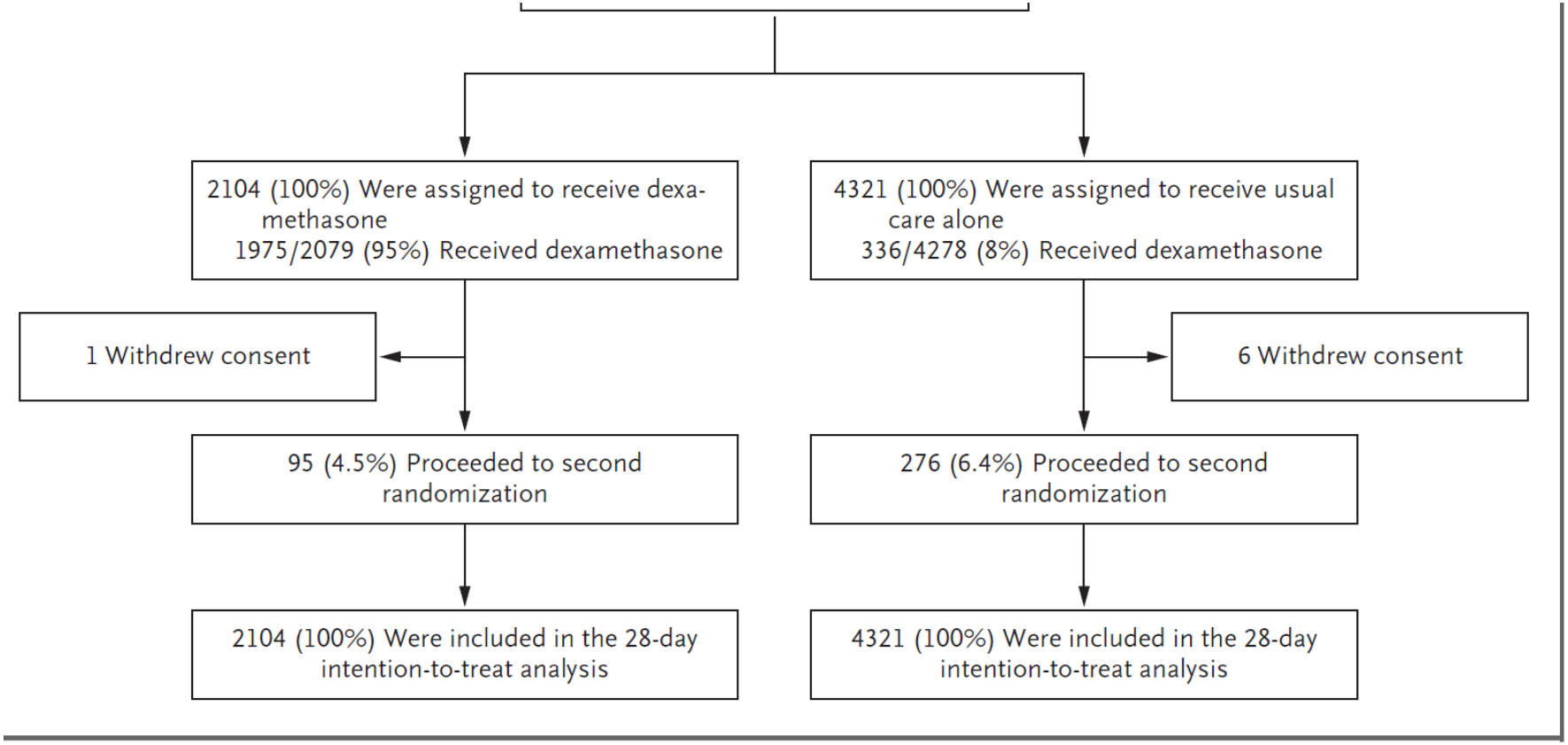
Groups are no longer exchangeable
No longer the advantage of randomization

ITT considers the effect of treatment policy, not the effect of the treatment received

In fact we consider:

Y(1): potential 28 days mortality outcome when intention is to give X=1

Y(0): potential 28 days mortality outcome when intention is to give X=0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Assumption	Ideal Randomized Trial	Realistic Randomized Trial
Consistency (Well defined exposure)	😄	😄
Consistency (No interference)	🤷	🤷
Positivity	😄	😄
Exchangeability	😄	🤷

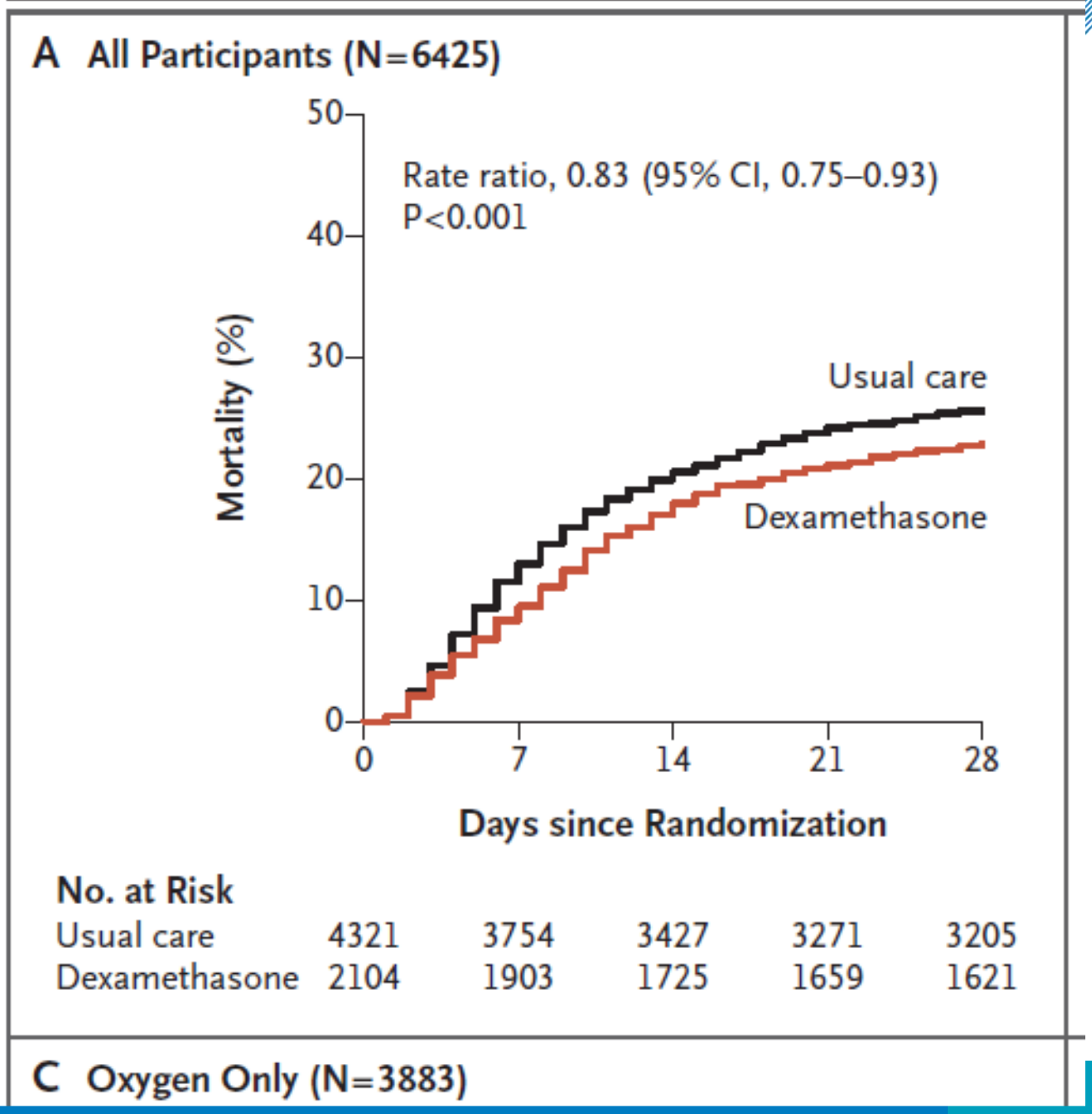
Table 4.1: Assumptions solved by study design. 😄 indicates it is solved by default, 🤷 indicates that it is *solvable* but not solved by default.

Covid trial- baseline characteristics, table 1

Table 1. Characteristics of the Patients at Baseline, According to Treatment Assignme

Characteristic	Treatment Assignment	
	Dexamethasone (N=2104)	Usual Care (N=4321)
Age†		
Mean — yr	66.9±15.4	65.8±15.8
Distribution — no. (%)		
<70 yr	1141 (54)	2504 (58)
70 to 79 yr	469 (22)	859 (20)
≥80 yr	494 (23)	958 (22)
Sex — no. (%)		
Male	1338 (64)	2749 (64)
Female‡	766 (36)	1572 (36)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)
Respiratory support received — no. (%)		
No oxygen	501 (24)	1034 (24)
Oxygen only	1279 (61)	2604 (60)
Invasive mechanical ventilation	324 (15)	683 (16)
Previous coexisting disease		
Any	1174 (56)	2417 (56)

No p-values in Table 1


A All Participants (N=6425)
Rate ratio, 0.83 (95% CI, 0.75–0.93)
P<0.001
Mortality (%)
50
40
30
20
10
0
Usual care
Dexamethasone
0
7
14
21
28
Days since Randomization
No. at Risk
Usual care 4321 3754 3427 3271 3205
Dexamethasone 2104 1903 1725 1659 1621
C Oxygen Only (N=3883)

After 28 days

$\hat{p}_1$ = estimated probability to die in dexametason group 0.177

$\hat{p}_0$ = estimated probability to die for usual care 0.246

Risk difference : 0.177- 0.246 = -0.069

Relative risk: 0.177/ 0.246 = 0.72

Odds ratio (0.177/ (1- 0.177)) / (0.246 /(1-0.246))=0.66

PART 2
Observational designs

Experimental versus observational

Experimental/Intervention studies: the investigator has an active role, performs an intervention

But: randomization is not always feasible, ethical

Observational studies: the investigator only observes.

Observational studies

Different sampling schemes (see course GLM)

- Cohort studies. Prospective sampling. Sample from Y|X.
- Outcome based sampling (case-control studies). Retrospective sampling. Sample from X|Y
- In this course we focus on Cohort studies

Types of cohort studies

Concurrent/Prospective study: first sample data on X and subsequently follow individuals over time while recording outcome(s) of interest

- These studies often take years to conduct
- You determine what data to collect and when to collect data

The Framingham study is an example (started in 1948)

Non concurrent/ historical/retrospective cohort study. Population is assembled from available data records

- Can be conducted in quite a short time
- But not all information of interest may have been recorded

Editor's Note: This article was published on May 7, 2020, at NEJM.org.

ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleris, M.D., Yifei Sun, Ph.D., Jonathan Platt, Ph.D., Jason Zucker, M.D., Matthew Baldwin, M.D., George Hripcsak, M.D., Angelena Labella, M.D., Daniel K. Manson, M.D., Christine Kubin, Pharm.D., R. Graham Barr, M.D., Dr.P.H., Magdalena E. Sobieszczyk, M.D., M.P.H., and Neil W. Schluger, M.D.

METHODS

We examined the association between hydroxychloroquine use and intubation or death at a large medical center in New York City. Data were obtained regarding consecutive patients hospitalized with Covid-19, excluding those who were intubated, died, or discharged within 24 hours after presentation to the emergency department (study baseline). The primary end point was a composite of intubation or death in a time-to-event analysis. We compared outcomes in patients who received hydroxychloroquine with those in patients who did not, using a multivariable Cox model with inverse probability weighting according to the propensity score.

Target trial emulation

For observational data, ask:

- What experiment would you design if you could?

Then

- Write down the protocol of this “target trial”
- Use the observed data to estimate the causal estimand of interest

Key elements of protocol of target trial(1-2)

1. Eligibility criteria

   Consecutive patients hospitalized in a medical center in NY with COVID-19, excluding those who died, where ventilated or discharged within 24 hours

2. Exposure definition

   Exposed in study: Receiving hydroxychloroquine: if patient receive it at study baseline (24 hours after arrival hospital) or during the follow-up period before intubation or death.

   Non exposed: no hydroxychloroquine

   How to define exposure in target trial ?

How to define exposure in our target trial?

1. Start HCQ at baseline vs never give it?

2. Start HCQ at baseline vs give it later if needed

3. Give HCQ when needed vs never give it.

There should be a clear definition to achieve consistency.

Different definitions require different analyses

Key elements of protocol of target trial(3-7)

3. Assignment procedures

In study: The decision to prescribe medications was left to the discretion of the treating team for each individual patient.

In target trial: assignment at baseline?

4. Follow-up period

28 days after 24 hours in hospital (baseline)

5. Outcome definition

a composite of intubation or death

6. Causal contrast of interest

$E(Y(1)) - E(Y(0))$

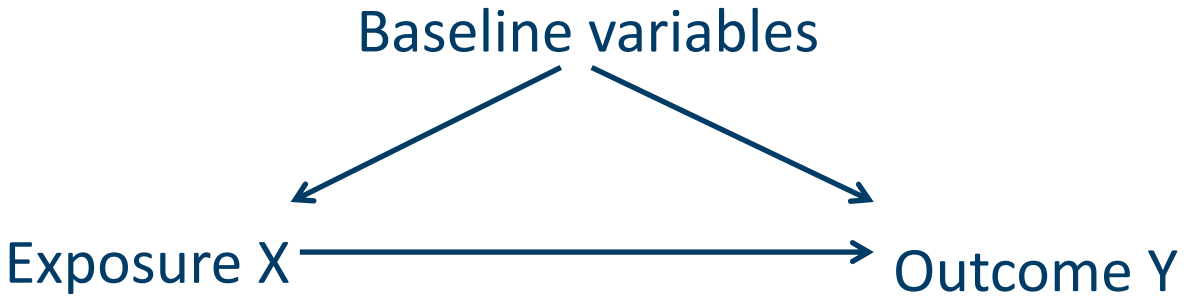
7. Analysis plan

Results: 1376 patients

	Hydroxychloroquine (N=811)	No Hydroxychloroquine (N=565)
Age — no. (%)		
<40 yr	80 (9.9)	105 (18.6)
40–59 yr	217 (26.8)	142 (25.1)
60–79 yr	367 (45.3)	220 (38.9)
≥80 yr	147 (18.1)	98 (17.3)
Female sex — no. (%)	337 (41.6)	258 (45.7)
Past diagnoses — no. (%)		
Chronic lung disease¶	146 (18.0)	105 (18.6)
Diabetes	301 (37.1)	190 (33.6)
Hypertension	398 (49.1)	38 (6.7)
Cancer	109 (13.4)	67 (11.9)
Chronic kidney disease	133 (16.4)	105 (18.6)
Transplantation, HIV infection, or immune-suppressive medications	40 (4.9)	18 (3.2)

No exchangeability in this study

- Patients receiving HCQ are older and more severily ill
- Age and severity of illness are also related to bad outcomes
- **Confounding**: there are common causes of the exposure and outcome



Exposed and unexposed patients are not comparable/not exchangeable

In the coming weeks:

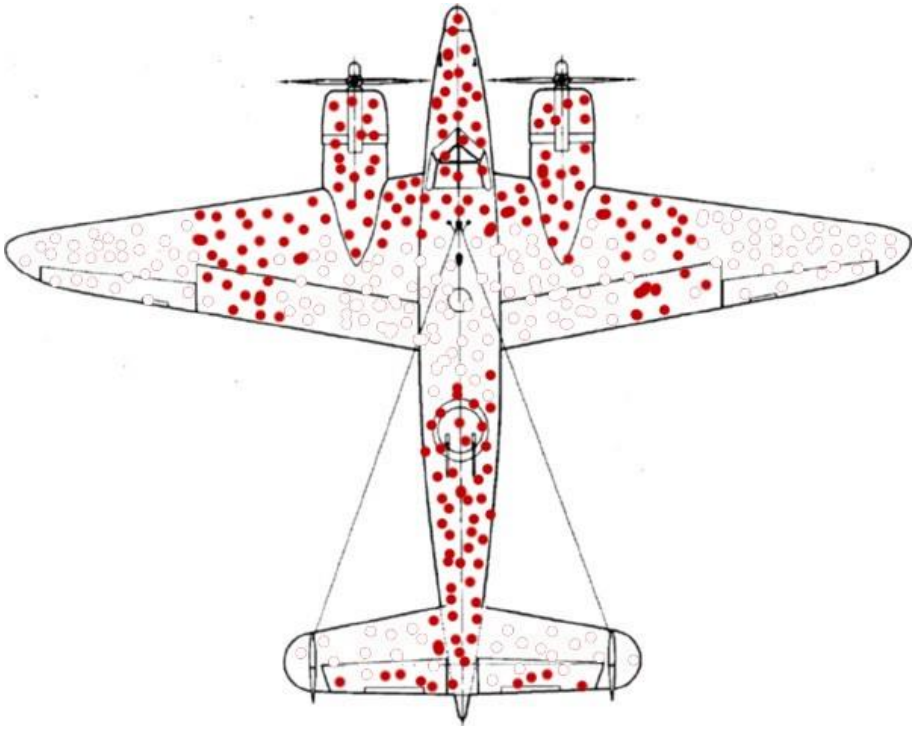
- Extend causal assumptions: conditional exchangeability
- Methods to handle confounding in the analysis

Assumption	Ideal Randomized Trial	Realistic Randomized Trial	Observational Study
Consistency (Well defined exposure)	😄	😄	🤷
Consistency (No interference)	🤷	🤷	🤷
Positivity	😄	😄	🤷
Exchangeability	😄	🤷	🤷

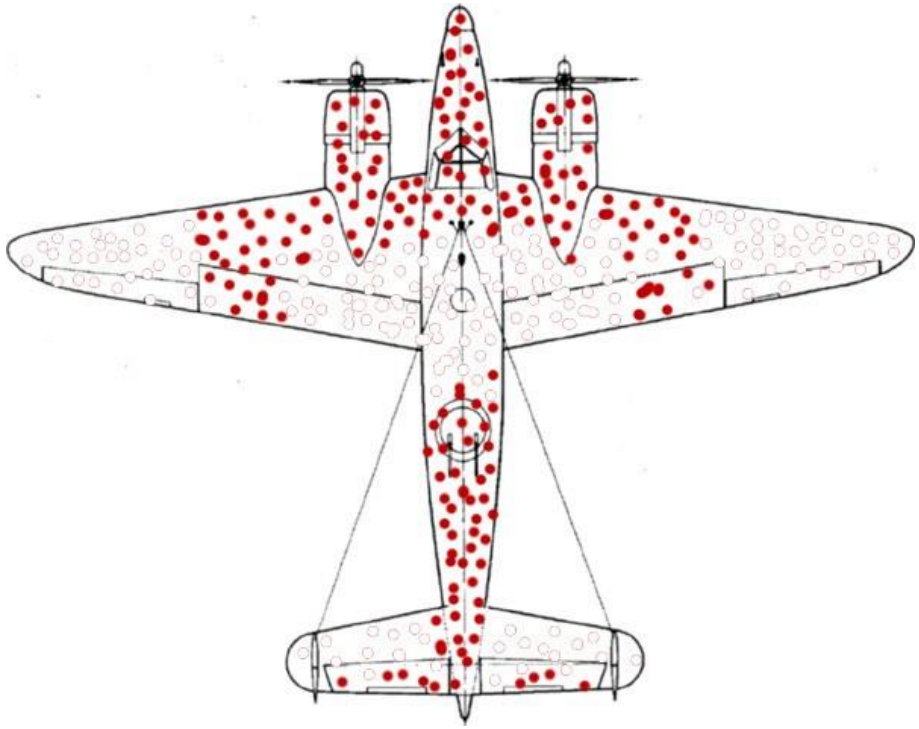
Table 4.1: Assumptions solved by study design. 😄 indicates it is solved by default, 🤷 indicates that it is *solvable* but not solved by default.

Another source of bias in observational studies

World war II. The damaged areas of returning English planes



Selection bias



A selected sample, airplanes which were shot down are missing

THE END