Bien conduire en urgence la recherche clinique en situation d'émergence pandémique

Bruno Hoen

Disclosure of potential conflicts of interest

- I have no COI to disclose

Agenda

- Why randomized controlled trials still are the gold standard
- Why randomized controlled trials have limitations in a major public health crisis such as a high death toll emerging pandemic
- How to optimize randomized controlled trials in public health emergency situations
  - Adaptive platform RCT
  - Contactless (remote) RCT
- Using "big data" to conduct controlled (low-bias) clinical trials
  - Registry-based RCT
  - Cohort-embedded trials
  - Emulated trials
- Other possible options when a RCT is not "immediately" feasible
  - Monitored Emergency Use of Unregistered Interventions (MEURI)
  - Almost experimental observational studies

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ELSEVIER

Journal of Clinical Epidemiology

Volume 42, Issue 6, 1989, Pages 481-489

Two special commentary

Epidemiologic analyses of causation: the

SPECIAL ARTICLE

A Comparison of Observational Studies and Randomized, Controlled Trials

SPECIAL ARTICLE

Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs

Article Figures/Media

EDITORIAL

Randomized Trials or Observational Tribulations?

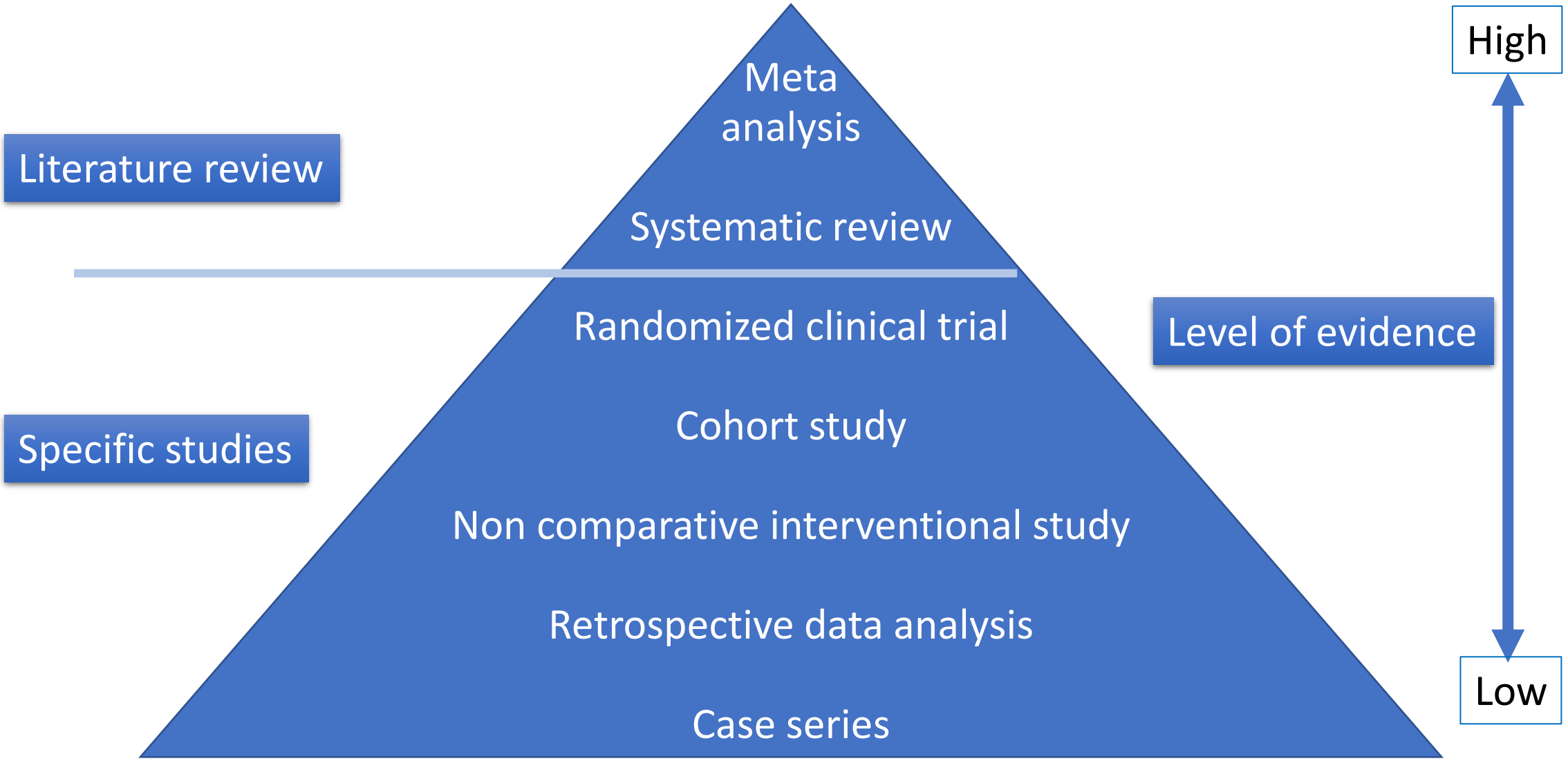
Stuart J. Pocock, Ph.D., and Diana R. Elbourne, Ph.D.

Article

June 22, 2000

N Engl J Med 2000; 342:1907-1909

Evidence-based medicine



Key topics in evidence-based medicine, Levi & McGovern, 2001

Limitations of non randomized studies

- In a noncomparative evaluation, the investigator's judgment is predictably biased (confusion bias)
  - When the outcome is favorable, it is thanks to the intervention
  - When the outcome is not favorable, it is due to the disease severity
- In a non randomized comparative study, il is virtually impossible to get rid of the numerous biases that distort the evaluation of the relationship between the observed outcome and the performed intervention
  - Selection bias
  - Attrition bias
  - Follow-up bias
  - Evaluation bias

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Ethical conditions for a randomized clinical trial

- There is a **true uncertainty** regarding the efficacy and safety of a treatment versus another (or no) treatment: CLINICAL EQUIPOISE (Freedman, NEJM 1987)
- The effect of the assessed treatment is not big enough to be observed with the naked eye (the parachute paradigm)
- The clinical trial must be feasible
- The clinical trial must lead to a conclusion
- Patients' safety must be guaranteed
- The clinical trial must lead to a significant breakthrough in knowledge, allowing the community to proceed towards a consensus on the efficacy and safety of a treatment
- The community must be ready to accept to wait for the results of robust controlled trials before pronouncing in favor or against the use of a given treatment

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What is an adaptive platform RCT?

- A master protocol defines objectives, endpoints, eligibility criteria, and rules of randomization
- It establishes prospective decision criteria for
  - discontinuing interventions for futility
  - stopping because of superiority against placebo
  - adding new interventions
- It is adaptive in the way it applies sample size reassessment approaches, with the help of a reactive IDMC

The achievements of the major platform adaptive COVID-19 trials (SOLIDARITY, RECOVERY, PRINCIPLE, REMAP-CAP, DISCOVERY) of repurposed drugs

- Treatments that proved ineffective (at any stage of the disease)
  - Hydroxychloroquine, Azithromycin, alone or in combination
  - Lopinavir/ritonavir, Interferon β-1a, alone or in combination
  - Remdesivir
  - Convalescent plasma
  - Colchicine
  - Ivermectin
  - Aspirin
- Treatments that proved effective (in severe forms of the disease)
  - Corticosteroids (Dexamethasone)
  - Anti-IL-6 agents (Tocilizumab)

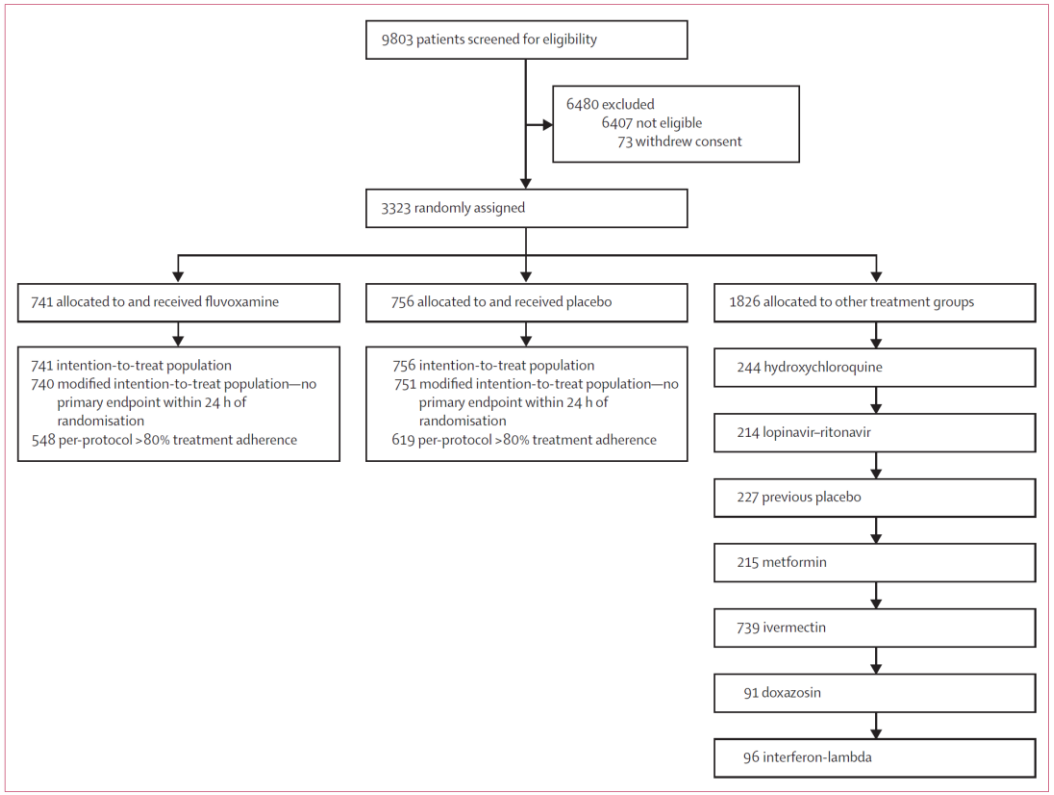
Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial

*Gilmar Reis, Eduardo Augusto dos Santos Moreira-Silva, Daniela Carla Medeiros Silva, Lehana Thabane, Aline Cruz Milagres, Thiago Santiago Ferreira, Castilho Vitor Quirino dos Santos, Vitoria Helena de Souza Campos, Ana Maria Ribeiro Nogueira, Ana Paula Figueiredo Guimaraes de Almeida, Eduardo Diniz Callegari, Adhemar Dias de Figueiredo Neto, Leonardo Cançado Monteiro Savassi, Maria Izabel Campos Simplicio, Luciene Barra Ribeiro, Rosemary Oliveira, Ofir Harari, Jamie I Forrest, Hinda Ruton, Sheila Sprague, Paula McKay, Alla V Glushchenko, Craig R Rayner, Eric J Lenze, Angela M Reiersen, Gordon H Guyatt, Edward J Mills, for the TOGETHER investigators**

Lancet Glob Health 2021

Published Online
October 27, 2021
https://doi.org/10.1016/
S2214-109X(21)00448-4

- The TOGETHER trial is a randomised, adaptive platform trial to investigate the efficacy of repurposed treatments for COVID-19 disease among high-risk adult outpatients
- A master protocol defines prospective decision criteria for discontinuing interventions for futility, stopping because of superiority against placebo, or adding new interventions
- Interventions evaluated in the TOGETHER trial, thus far, include, hydroxychloroquine, lopinavir–ritonavir metformin, ivermectin, fluvoxamine, doxasozin, and pegylated interferon lambda versus matching placebos



Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial

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- This trial is adaptive and applies sample size reassessment approaches. To plan for each arm, we assumed a minimum clinical utility of 37·5% (relative risk reduction) to achieve 80% power with 0·05 two-sided type 1 error for a pairwise comparison against the placebo assuming a control event rate of 15%. This resulted in an initial plan to recruit 681 participants per arm
- The statistical team did planned interim analyses
  - Stopping thresholds for futility were established if the posterior probability of superiority was less than 40% at interim analysis
  - An arm could be stopped for superiority if the posterior probability of superiority met the threshold of 97·6%.

- Primary outcome: a composite endpoint of
  - medical admission to a hospital setting due to COVID-19-related illness defined as COVID-19 emergency setting visits with participants remaining under observation for more than 6 h

  or
  - referral to further hospitalisation due to the progression of COVID-19 within 28 days of randomisation

	Intention-to-treat analysis			Modified intention-to-treat analysis		
	N	n (%)	Relative risk (95% BCI)	N	n (%)	Relative risk (95% BCI)
Fluvoxamine	741	79 (11%)	0·68 (0·52–0·88)	740	78 (11%)	0·69 (0·53–0·90)
Placebo	756	119 (16%)	1 (ref)	752	115 (15%)	1 (ref)

BCI=Bayesian credible interval.

Table 2: **Proportion of primary outcome events and relative risk of hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 for patients allocated fluvoxamine versus placebo**

The European clinical research response to optimise treatment of patients with COVID-19: lessons learned, future perspective, and recommendations

Herman Goossens, Lennie Derde, Peter Horby, Marc Bonten

Lancet Infect Dis 2021

Published Online
December 21, 2021
https://doi.org/10.1016/
S1473-3099(21)00705-2

- Create structures/partnerships that facilitate prioritisation of clinical research
  - a European pandemic clinical research authority should be created to oversee pandemic preparation, clinical research response, and to prioritise clinical studies
  - A partnership should be developed between the EU Member States and the European Commission to agree on aligned goals of clinical research in response to pandemics
- Simplify clinical trial delivery
- Develop digital models and procedures for data collection and sharing
- Invest in clinical trial networks, platform trials, and master protocols
- Embed the EU pandemic clinical research response in the global response

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Conducting clinical trials at the time of COVID-19

Fully remote (contactless) clinical trial:

An urgent need for a revolution
in clinical research

What is a fully remote (contactless) clinical trial

- Recruitment: innovative study advertising (as appropriate and non exclusive)
  - via electronic health records and/or a study website
  - through physician and other health professional referrals,
  - study advertisements near COVID-19 testing centers and in emergency departments,
  - communication in local television and newspapers
- Enrollment
  - Screening by email, phone or interactive webpages
  - Informed consent provided and signed electronically
- Shipment of study material
  - Study medication shipped (and received) the same day as consent is signed
  - Monitoring tools: pulse oxymeter, automated blood pressure monitor, thermometer
- Participants' follow-up
  - REDCap formularies filled by participants themselves
  - phone-based data collection as backup to ensure that individuals without internet access are able to participate

The Minneapolis group

- The Minneapolis group conducted simultaneoulsy three contactless placebo-controlled, randomized trials to asssess the efficacy of OHCLQ in pre-exposure, post-exposure, or early treatment of COVID-19
  - In total 2900 subjects were enrolled in these 3 trials within 6 weeks
- Key facts for the PEP trial
  - Protocol writing March 1-10, 2020
  - IRB and FDA files submitted March 10, 2020
  - IRB approval March 15 and FDA approval March 17
  - First subject enrolled March 17, 2020
  - Targetted number of subjects (adapted after 1st interim analysis): 950
  - Enrollment stopped May 6, 2020 (after 821 subjects have been enrolled, upon recommendation of DMSB for futility at the 3rd interim analysis)
  - Paper published online in NEJM on June 3, 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

D.R. Boulware, M.F. Pullen, A.S. Bangdiwala, K.A. Pastick, S.M. Lofgren, E.C. Okafor, C.P. Skipper, A.A. Nascene, M.R. Nicol, M. Abassi, N.W. Engen, M.P. Cheng, D. LaBar, S.A. Lother, L.J
R. Zarychanski, L.E. Kelly, I.S. Schwart
T.C. Lee, and K

This article was published on June 3, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2016638

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

- Recruitment was performed primarily with the use of social media outreach as well as traditional media platforms
- Participants were enrolled nationwide in the United States and in the Canadian provinces of Quebec, Manitoba, and Alberta
- Participants enrolled themselves through a secure Internet-based survey using the Research Electronic Data Capture (REDCap) system
- After participants read the consent form, their comprehension of its contents was assessed; participants provided a digitally captured signature to indicate informed consent
- Hydroxychloroquine sulfate or placebo was dispensed and shipped overnight to participants by commercial courier
- Follow-up e-mail surveys on days 1, 5, 10, and 14. A survey at 4 to 6 weeks asked about any follow-up testing, illness, or hospitalizations
- Participants who did not respond to follow-up surveys received text messages, e-mails, telephone calls, or a combination of these to ascertain their outcomes

Pullen et al, OFID 2021

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DOI: 10.1056/NEJMoa2016638, June 3, 2020

- Randomized, double-blind, placebo-controlled trial (USA and Canada)
- Adults who had household or occupational exposure to someone with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while
  - wearing neither a face mask nor an eye shield (high-risk exposure)
  - wearing a face mask but no eye shield (moderate-risk exposure)
- Within 4 days after exposure, participants were randomly assigned to receive either placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days)
- Primary outcome: incidence of laboratory-confirmed Covid-19 or illness compatible with Covid-19 within 14 days

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DOI: 10.1056/NEJMoa2016638, June 3, 2020

- 821 asymptomatic participants were enrolled (overall, 87.6% had high-risk exposure)
- incidence of new illness compatible with Covid-19
  - participants receiving hydroxychloroquine (49 of 414 [11.8%])
  - Participants receiving placebo (58 of 407 [14.3%])
- Absolute difference −2.4 percentage points (95% CI, −7.0 to 2.2; P = 0.35)
- Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported

CONCLUSIONS

After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure.

COVID-OUT: Outpatient Treatment for SARS-CoV-2 Infection, a Factorial Randomized Trial

Are you 30 - 85 years old and just tested positive? You may be eligible, no matter where you live!

REQUEST A CALLBACK **or SIGN-UP ONLINE**

or Call (651) 661-9560 to speak to someone now

Mobile clinical research is part of mobile Health (mHealth)

- Clinical research needs to be pragmatic, resilient, and flexible
- Clinical researchers have an obligation to implement and measure the feasibility and scalability of new approaches (as well as the impact of these new approaches on participants and communities)
- Clinical research studies should have the ability to adapt to such disruptions as COVID-19 pandemic
- COVID-19 is not the last disruption that will affect our day-to-day life
  - we need to learn to be better prepared
  - WE NEED TO ADAPT QUICKLY

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The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

N ENGL J MED 369;17 NEJM.ORG OCTOBER 24, 2013

What is a randomized registry-based trial?

- A registry-based trial is a RCT conducted within or with the help of a registry or multiple registries, the registries being used to
  - identify patients
  - replace the CRF
  - carry out patients' follow-up
- R-B RCTs have already been conducted
  - TASTE (Thrombus Aspiration during ST-segment Elevation
    - One single registry, 3 countries (Sweden, Denmark, Iceland)
    - PCI + TA vs PCI alone in Patients with ST-segment elevation AM
    - Outcome 30-day mortality
  - CHAP (Cardiovascular Health Awareness Program)
    - 9 registries in a single country (Canada)
    - CHAP vs SOC in community residents aged ≥65 years old
    - Outcome: admission to hospital for AMI, stroke or CHF
  - REDUCE MRSA (Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA)
    - The corporate data warehouses in the USA (74,256 patients in
    - Universal or targeted decolonization vs isolation in patients ac ons
    - Outcome: rates of MRSA clinical isolates and bloodstream infections

The NEW ENGLAND JOURNAL of MEDICINE

BMJ

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Advantages of a R-B RCT? 1. Lower costs

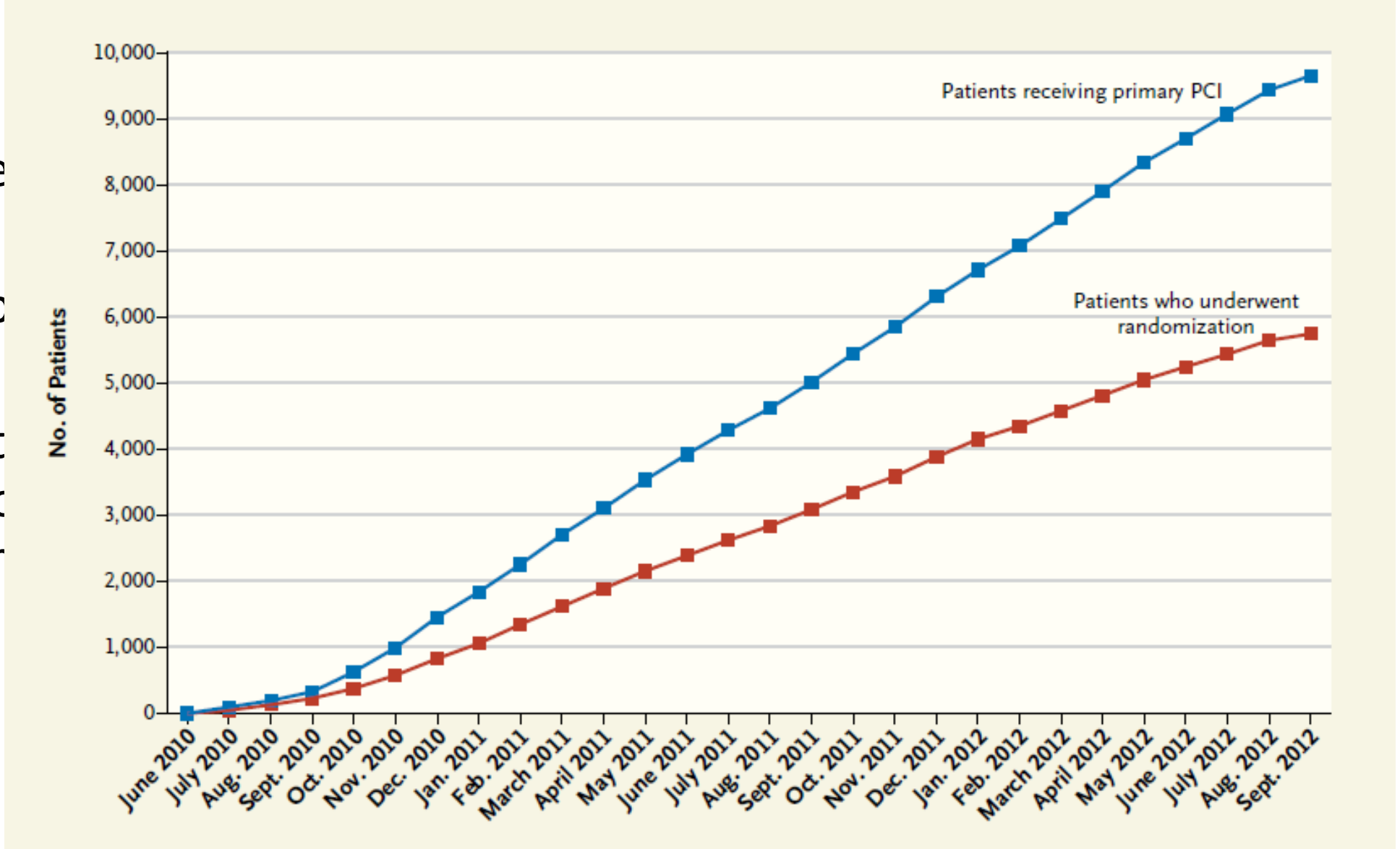
- Examples
  - TASTE 50 USD/patient (300,000 USD for 7,200 pts, 2% of a conventional RCT)
  - CHAP 16 USD/resident (most explanatory trials in CVD cost 5,000 USD /patient)
  - REDUCE MRSA 40 USD/patient
- How can this be achieved?
  - use of existing registries to
    - identify participants
    - collect baseline and study data
    - detect outcomes
  - (Costs that would normally be incurred in a more traditional randomized controlled trial are indirectly transferred onto the health system where electronic registries are maintained)
  - Reduced or even no cost of follow-up study visits
  - Minimization of extra administrative costs
  - Cost saving in training site staff and research coordinators
  - For example, in the TASTE trial, the trial did not
    - create any additional case report forms for data collection
    - require any additional patient visits
    - organize training sessions for trialists and staff

Advantages of a R-B RCT?
2. Enhanced generalizability of findings

- Generally, in R-B RCTs
  - Inclusion and/or exclusion criteria are less stringent
  - Patient monitoring and follow-up are more akin to real world than the more intensive monitoring in explanatory trials, which enhances the generalizability of their findings
- The cost and recruitment efficiencies of R-B RCTs are most times fully realized with trial designs that allow recruitment of less-selected populations in real-world settings, where blinding or crossover prohibitions are not required, and where follow-up end points can be abstracted from other registries or health care administrative data
- Consequently, findings from well designed registry-based randomized controlled trials may be broadly generalizable while answering a comparative effectiveness research question

Advantages of a R-B RCT?
3. Rapid consecutive enrollment

- In R-B RCTs, inve
  rapidly identify e
- They may no lon
  participant eligib
  registry, thereby
- For instance, in t
  segment elevatic
  within 2 years ar



Advantages of a R-B RCT?
4. Potential completeness of follow-up

- In countries where unique patient identification numbers in registries are available (Nordic European countries, Canada, France, India), these allow for an almost complete tracking of patients across registries
- Because of the linkage to registries such as interconnected health records, it is possible to retrieve extensive clinical information of participants using their unique identification number in the tracking system
- R-B RCTs have the potential to describe and follow up the complete reference population for
  - eligible but nonrandomized participants
  - noneligible participants

R-B RCTs: limitations and challenges
1. Registry data quality

- Definition, collection, and accuracy of baseline data gathered in registries may be various and questionable in terms of quality
- Outcome data documented in registries may be subject to uncertainty
- Registries may have many missing data or fail to capture important prognostic factors

R-B RCTs: limitations and challenges
2. Ethical issues

- Screening registry participants for trial inclusion if they have not previously consented to records review
- The potential need for formal informed consent for a treatment that is already being used in routine practice
- Protecting the data and participant privacy
- How to handle participant withdrawal from the trial or registry
- How to coordinate the overlapping role of Data and Safety Monitoring Board in the trial with the role of registry executives

R-B RCTs: limitations and challenges
3. Methodological issues

- Common confusion and controversies about the research question being addressed by the study design
- Ensuring the representativeness of study participants in recruitment
- Research questions, study designs, and types of outcomes limited by quality and features of registries to be used
- Guidelines for reporting study results are still to be written
- Criteria analogous to those of GRADE system for R-B RCTs are still lacking

Title: Effectiveness of antibiotic prophylaxis of infective endocarditis before invasive dental procedures in patients with prosthetic heart valves: a registry-based, cluster-randomized trial in primary care

Co-investigators

François Alla, Xavier Duval, Bruno Hoen

Funding
French MoH (DGOS)
PHRC 2021

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American Journal of Epidemiology

Vol. 183, No. 8
DOI: 10.1093/aje/kwv254
Advance Access publication:
March 18, 2016

Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

Miguel A. Hernán* and James M. Robins

* Correspondence to Dr. Miguel A. Hernán, Department of Epidemiology, 677 Huntington Avenue, Boston, MA 02115 (e-mail: miguel_hernan@post.harvard.edu).

- When one cannot conduct a randomized experiment, we still can analyze observational data
- Causal inference from large observational databases (big data) can be viewed as an attempt to emulate a randomized experiment (the target experiment or the target trial) that would answer the question of interest

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

Noa Dagan, M.D., Noam Barda, M.D., Eldad Kepten, Ph.D., Oren Miron, M.A., Shay Perchik, M.A., Mark A. Katz, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Reis, Ph.D., and Ran D. Balicer, M.D.

This article was published on February 24, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2101765

- Observational study to emulate a target trial of the causal effect of the BNT162b2 vaccine on Covid-19 outcomes.
- Data in this study comes from the electronic medical records of Clalit Health Services (CHS), the largest of the four Israel's health funds, insuring 53% of Israel’s population
- CHS pools data from its many operational systems into a unified analytic data warehouse that is used for policy and research

- This data repository includes detailed information on
  - Primary care
  - Secondary care
  - Hospitalizations
  - Medications
  - Laboratory results
  - Imaging data

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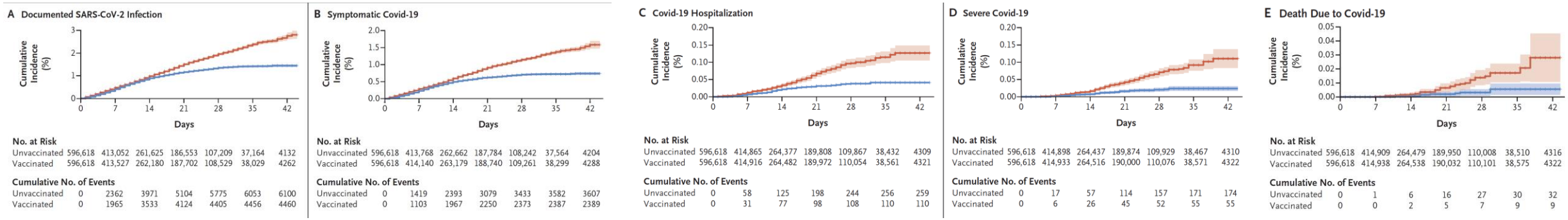

Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study

Eleftheria Vasileiou, Colin R Simpson*, Ting Shi*, Steven Kerr*, Utkarsh Agrawal, Ashley Akbari, Stuart Bedston, Jillian Beggs, Declan Bradley, Antony Chuter, Simon de Lusignan, Annemarie B Docherty, David Ford, F D Richard Hobbs, Mark Joy, Srinivasa Vittal Katikireddi, James Marple, Colin McCowan, Dylan McGagh, Jim McMenamin, Emily Moore, Josephine L K Murray, Jiafeng Pan, Lewis Ritchie, Syed Ahmar Shah, Sarah Stock, Fatemeh Torabi, Ruby S M Tsang, Rachael Wood, Mark Woolhouse, Chris Robertson†, Aziz Sheikh†*

Lancet 2021; 397: 1646–57

Published Online
April 23, 2021
https://doi.org/10.1016/
S0140-6736(21)00677-2

- Open, real-time prospective observational cohort study with national-level coverage in Scotland using a unique dataset
- The Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) database linked vaccination, primary care (940 general practices), laboratory testing, hospital admission, and mortality data for 5·4 million people in Scotland (99% of the population)
- Data were linked using the Community Health Index number, which is the unique identifier used for all health-care contact across Scotland
- Ethical approval was obtained from the
  - National Research Ethics Service Committee
  - Public Benefit and Privacy Panel for Health and Social Care

Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study

Eleftheria Vasileiou, Colin R Simpson*, Ting Shi*, Steven Kerr*, Utkarsh Agrawal, Ashley Akbari, Stuart Bedston, Jillian Beggs, Declan Bradley, Antony Chuter, Simon de Lusignan, Annemarie B Docherty, David Ford, F D Richard Hobbs, Mark Joy, Srinivasa Vittal Katikireddi, James Marple, Colin McCowan, Dylan McGagh, Jim McMenamin, Emily Moore, Josephine L K Murray, Jiafeng Pan, Lewis Ritchie, Syed Ahmar Shah, Sarah Stock, Fatemeh Torabi, Ruby S M Tsang, Rachael Wood, Mark Woolhouse, Chris Robertson†, Aziz Sheikh†*

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- First study of COVID-19 vaccine effect against hospital admissions for an entire nation after a single dose of vaccine
  - A single dose of the BNT162b2 vaccine was associated with a vaccine effect of 91% (95% CI 85–94) for hospital admissions due to COVID-19 28–34 days after vaccination
  - A single dose of the ChAdOx1 vaccine was associated with a vaccine effect of 88% (95% CI 75–94) for hospital admissions due to COVID-19 at 28–34 days post-vaccination
- Implications of the evidence
  - We provide national evidence that the mass roll-out of first doses of the COVID-19 vaccines currently being used in the UK vaccination programme was associated with substantial reductions in risk of COVID-19 hospital admissions in the populations at highest risk for severe COVID-19 outcomes
  - However, we note that some of the observed effects might have been due to residual confounding

ORIGINAL ARTICLE

Waning Immunity after the BNT162b2 Vaccine in Israel

Yair Goldberg, Ph.D., Micha Mandel, Ph.D., Yinon M. Bar-On, M.Sc., Omri Bodenheimer, M.Sc., Laurence Freedman, Ph.D., Eric J. Haas, M.D., Ron Milo, Ph.D., Sharon Alroy-Preis, M.D., Nachman Ash, M.D., and Amit Huppert, Ph.D.

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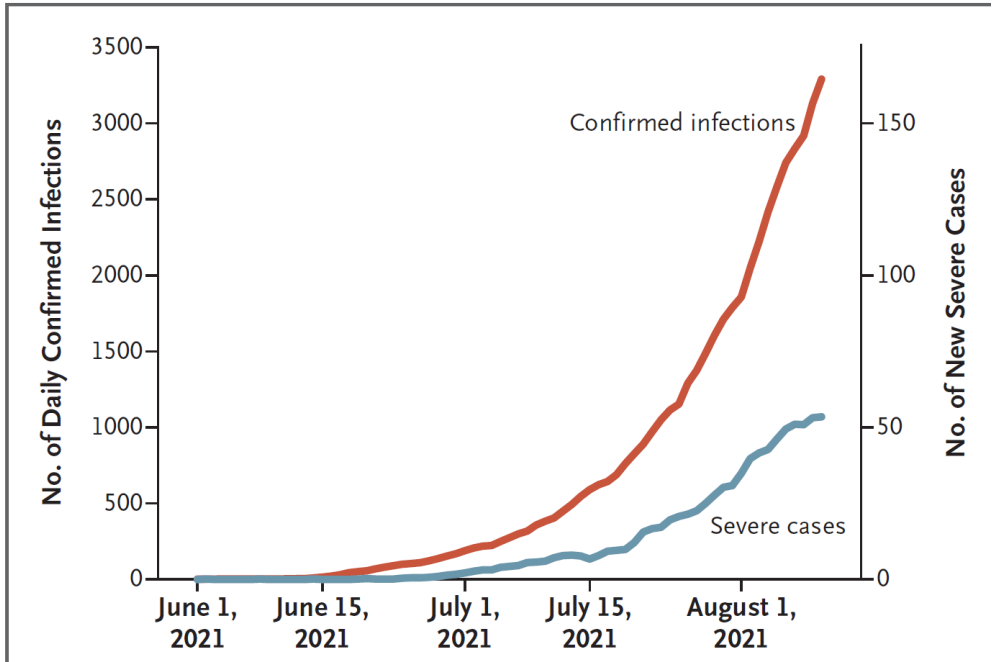

Figure 1. Daily Confirmed SARS-CoV-2 Infections and New Cases of Severe Covid-19 among Fully Vaccinated Persons in Israel, June through Early August 2021.

- Question: do breakthrough infections result from reduced vaccine effectiveness against the delta variant or waning immunity?
- Data: Israel MoH central database
  - PCR tests and results
  - vaccination dates and type
  - daily clinical status of all COVID-19 hospitalized patients
  - COVID-19 related deaths
- Answer: immunity against the delta variant of SARS-CoV-2 waned in all age groups a few months after receipt of the second dose of vaccine

Big data and the risk to trade off quality against quantity

Hydroxychloroquine or chloroquin… …ot a macrolide for treatment of CO… …ational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka

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RETRACTED

Interpretation We were … …t of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-h… …VID-19. Each of these drug regimens was associated with decreased in-hospital survival a… …ency of ventricular arrhythmias when used for treatment of COVID-19.

Agenda

- Why randomized controlled trials still are the gold standard
- Why randomized controlled trials have limitations in a major public health crisis such as a high death toll emerging pandemic
- How to optimize randomized controlled trials in public health emergency situations
  - Adaptive platform RCT
  - Contactless (remote) RCT
- Using "big data" to conduct controlled (low-bias) clinical trials
  - Registry-based RCT
  - Cohort-embedded trials
  - Emulated target trials
- Other possible options when a RCT is not "immediately" feasible
  - Monitored Emergency Use of Unregistered Interventions (MEURI)
  - Almost experimental observational studies

Monitored Emergency Use of Unregistered and Investigational Interventions

- An ethically-approved protocol developed by the World Health Organization to evaluate the potential use of experimental drugs in the event of public health emergencies
- Created by the WHO Ebola Ethics Working Group in 2014 in the context of the 2014 West Africa Ebola outbreak
- The WHO recommends that the term be preferred to the term "compassionate use" or "expanded access" for the controlled use of unregistered treatments in public health emergency measures

“Do the best you can, with what you have, where you are” Theodore Roosevelt

- Randomized controlled trials should remain the gold satandard
- Randomized registry trials and cohort embedded trials are disruptively transforming existing standards, procedures, and cost structures
- They should be given serious consideration as a way to resolve the recognized limitations of conventional clinical trial design
- Today we can no longer afford to undertake randomized effectiveness trials that cost tens or hundreds of millions of euros
- But today we have registries and other powerful digital platforms
- Today we must design and conduct megatrials with what we have: bigger data and smaller budgets

Back-up slides

Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial

Robert W Yeh,[1] Linda R Valsdottir,[1] Michael W Yeh,[2] Changyu Shen,[1] Daniel B Kramer,[1] Jordan B Strom,[1] Eric A Secemsky,[1] Joanne L Healy,[1] Robert M Domeier,[3] Dhruv S Kazi,[1] Brahmajee K Nallamothu[4] On behalf of the PARACHUTE Investigators

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- **Objective**: To determine if using a parachute prevents death or major traumatic injury when jumping from an aircraft
- **Design** Randomized controlled trial
- **Setting** Private or commercial aircraft between September 2017 and August 2018.
- **Participants** 92 aircraft passengers aged 18 and over were screened for participation. 23 agreed to be enrolled and were randomized
- **Intervention** Jumping from an aircraft (airplane or helicopter) with a parachute versus an empty backpack (unblinded)
- **Main outcome measures** Composite of death or major traumatic injury (defined by an Injury Severity Score over 15) upon impact with the ground measured immediately after landing
- **Results** Parachute use did not significantly reduce death or major injury (0% for parachute *v* 0% for control; P>0.9). This finding was consistent across multiple subgroups. Compared with individuals screened but not enrolled, participants included in the study were on aircraft at significantly lower altitude (mean of 0.6 m for participants *v* mean of 9146 m for nonparticipants; P<0.001) and lower velocity (mean of 0 km/h *v* mean of 800 km/h; P<0.001).
- **Conclusions** Parachute use did not reduce death or major traumatic injury when jumping from aircraft in the first randomized evaluation of this intervention. However, the trial was only able to enroll participants on small stationary aircraft on the ground, suggesting cautious extrapolation to high altitude jumps