RCT og Register-RCT

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Enhet for allmennmedisin, institutt for samfunnsmedisin, UiT

slido

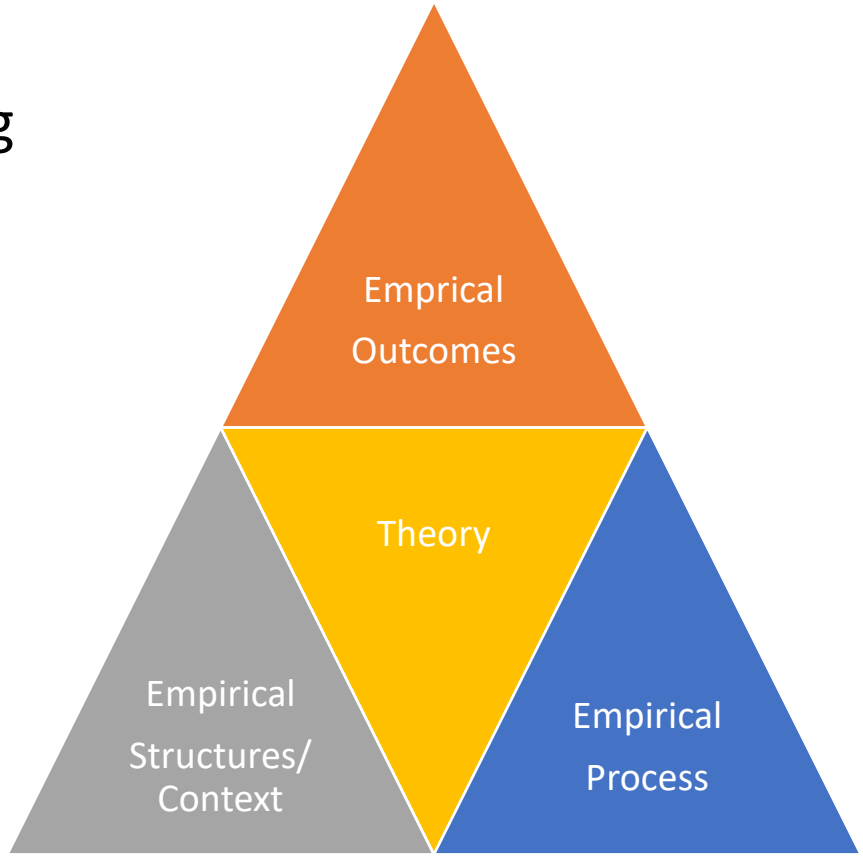
Hva slags studier skal til for at noe blir noe sant i medisinen?

ⓘ Start presenting to display the poll results on this slide.

Hva er effekten av X

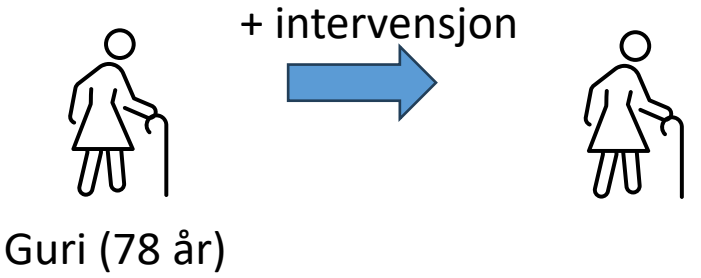
- Er digital hjemmeoppfølging bra for pasientene?

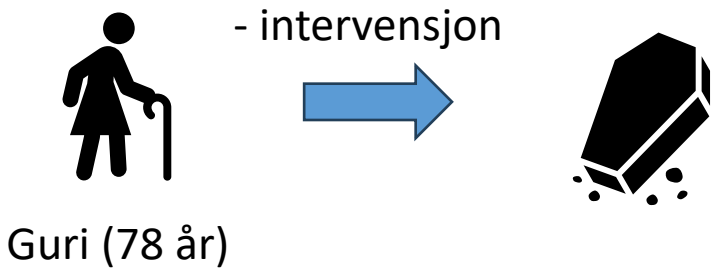
- Studiet av kausale sammenhenger:
  - Teori – fundamentet
  - Struktur/ kontekst virker sammen med prosess / intervensjon
  - Empiri=> vise at det virker i virkeligheten



The fundamental problem of causal inference

Alltid en sammenlikning mot en kontrollsituasjon





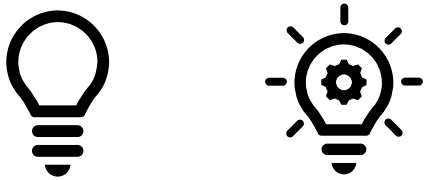
Det er umulig å studere Guri 78 I begge situasjoner!

Holland PW. Statistics and causal inference. Journal of the American statistical Association. 1986;81(396):945-60.

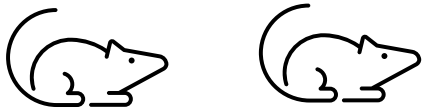
Kausal sammenheng ?

- Alltid en sammenlikning mot en kontrollsituasjon
- Intervensjon og kontroll enhetene må være sammenliknbare

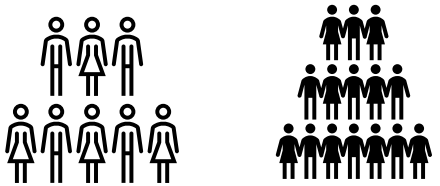
Homogen over tid



Homogene enheter



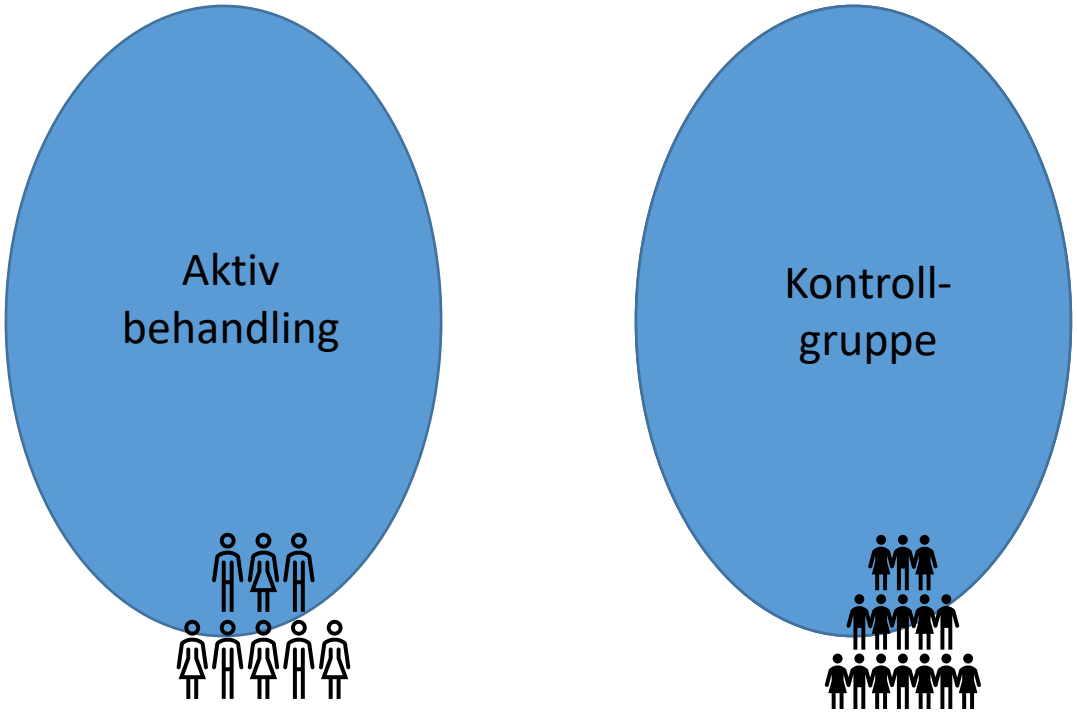
Homogene grupper



Seruminjeksjoner ved difteri

- 1898 – Johannes Fibiger - Sammenliknet to grupper
- Aktiv behandling / ingen behandling (kontroll) på alternerende dager
- 3% vs 12% døde i favør av aktiv behandling

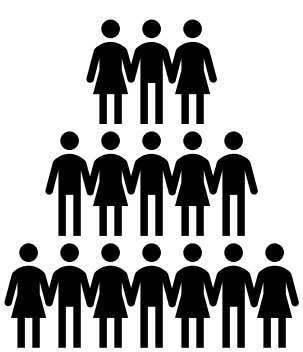
BMJ 1998;317:1243-1245 (31 October)



Pasienter i kontrollgruppen dør lettere enn de som får aktiv behandling

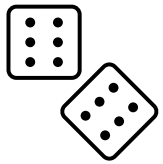
1. Behandling beskytter?
2. Pasientene i kontrollgruppen er mer utsatt

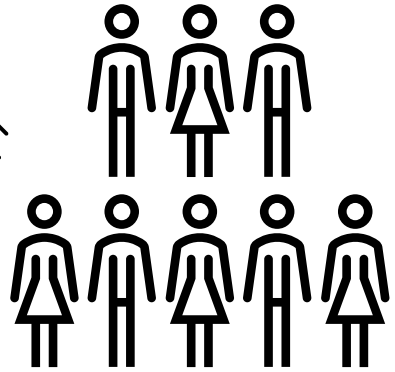
Uavhengighets prinsippet



Intervensjon

Tilordning til intervensjonen er UAVHENGIG av dine egenskaper (alder, kjønn, diagnose etc)





Kontroll

First randomiserte kontrollerte forsøk – RCT 1948

- **Streptomycin mot tuberkulose**

Table II.–*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

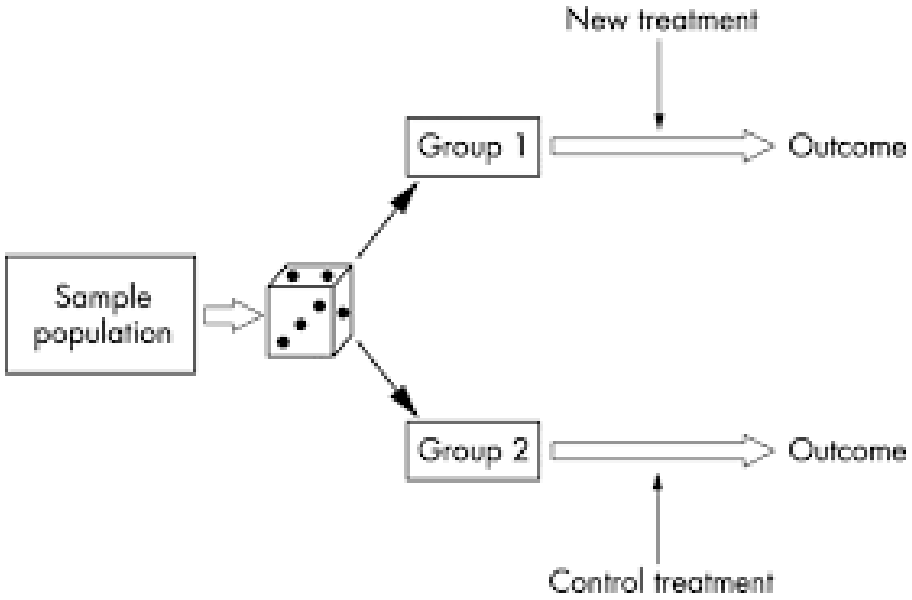
Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement . .	28	*51%*	4	*8%*
Moderate or slight improvement	10	*18%*	13	*25%*
No material change	2	*4%*	3	*6%*
Moderate or slight deterioration	5	*9%*	12	*23%*
Considerable deterioration . .	6	*11%*	6	*11%*
Deaths	4	*7%*	14	*27%*
Total	55	*100%*	52	*100%*

Bradford Hill

Forklarende - RCT design

Hypotese testende

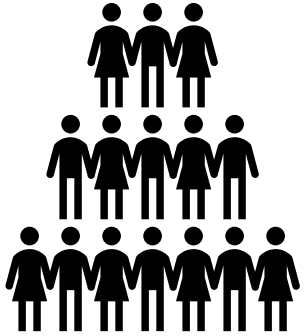
- Kontekst => Inklusjons- og Eksklusjonskriterier
- Virkningsmekanisme
  - Hvilken kontekst må være tilstede for effekt å oppstå
  - Forventet resultat i aktiv gruppe
  - Forventning i Kontrollgruppe



Bare nyttig (etisk) dersom:

- Vi ikke kjenner svaret på forhånd
- Kan beskrive intervensjonen tydelig
- Vi vet hvilken kontekst som er nødvendig for at intervensjonen skal virke

Formelt språk for Kausalitet - 1986



Gitt at enhetene er sammenliknbare, dvs at forutsetningen om uavhengighet er oppfylt:

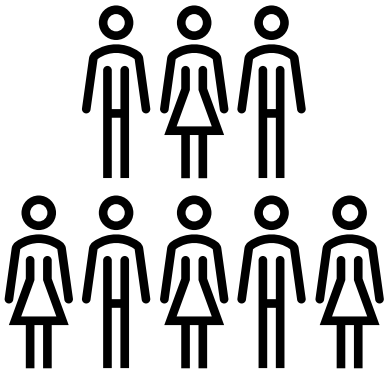
Treatment - effekt

$$T = Y_t(u) - Y_c(u), \quad \text{for all } u \text{ in } U.$$

Effekt Y for Treat

Effekt Y for control

Missing data problem
Propensity Score



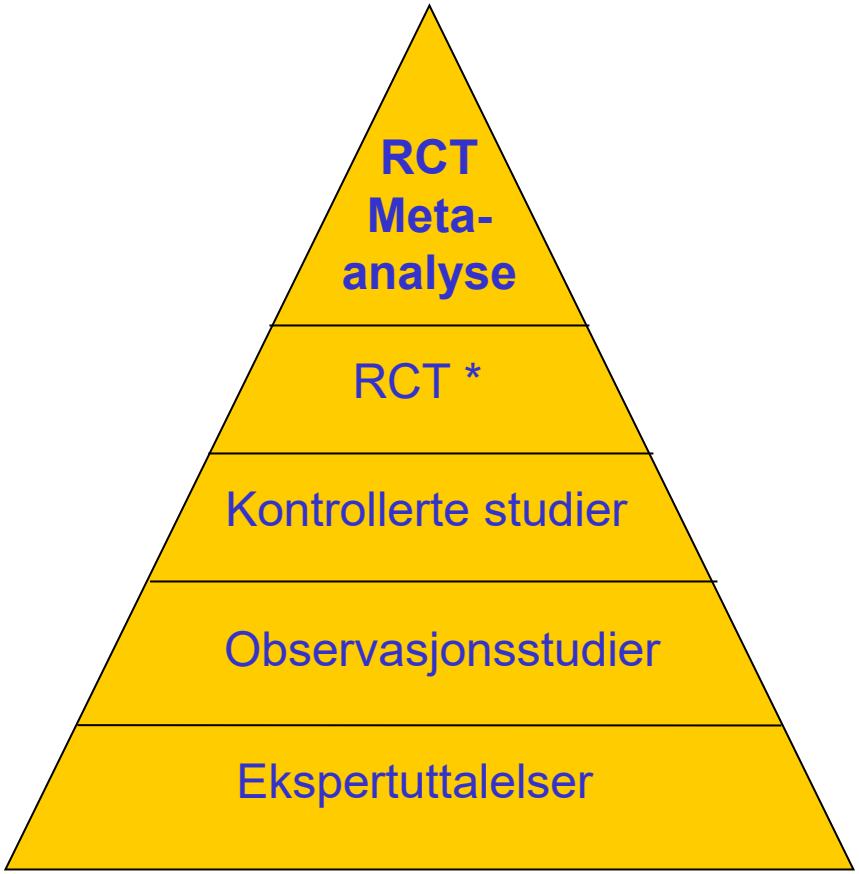
Holland PW. Statistics and causal inference. Journal of the American statistical Association. 1986;81(396):945-60.

Evidence Based Medicine (EBM)

1980 - Evidence Based Medicine

Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

1. individual clinical expertise
2. systematic research.
3. patients' predicaments, rights, and preferences



* Randomised Controlled Trial

Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS (1996). "Evidence based medicine: what it is and what it isn't". *BMJ* **312** (7023): 71–2. PMID 8555924. http://www.bmj.com/cgi/content/full/312/7023/71.

Østrogenbehandling
Premarin fra Ayerst I 1942

Husbands, too, like "Premarin"®

THE physician who puts a woman on "Premarin" when she is suffering in the menopause usually makes her pleasant to live with once again. It is no easy thing for a man to take the stings and barbs of business life, then to come home to the turmoil of a woman "going through the change of life." If she is not on "Premarin," that is.

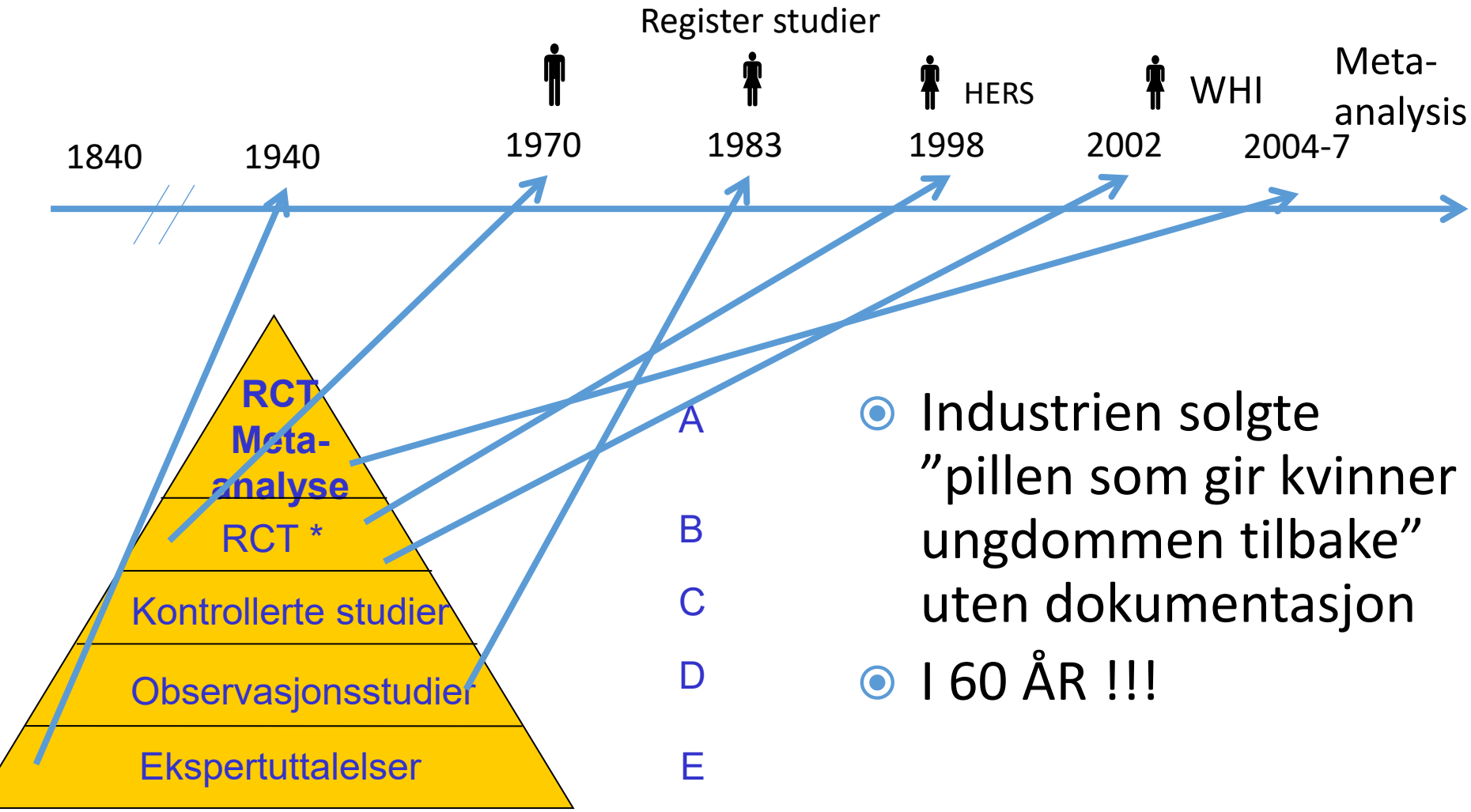
But have her begin estrogen replacement therapy with "Premarin" and it makes all the difference in the world. She experiences relief of physical distress and also that very real thing called a "sense of well-being" returns. She is a happy woman again — something for which husbands are grateful.

"Premarin," conjugated estrogens (equine), a complete natural estrogen complex, is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N. Y. • Montreal, Canada

- Annonsekampanje – 1960-tallet:
- *"Premarin when she is suffering from the menopause usually makes her pleasant to live with once again.*
- *It is no easy thing for a man to take the stings and barbs of business life, then to come home to the turmoil of a woman "going through the change of life".*
- *If she is not on "Premarin", that is."*

Østrogen for menopausale plager



- Industrien solgte "pillen som gir kvinner ungdommen tilbake" uten dokumentasjon
- I 60 ÅR !!!

* Randomised Controlled Trial

Cagnacci A, Venier M. The Controversial History of Hormone Replacement Therapy. Medicina (Kaunas). 2019;55(9).

RCT begrensninger

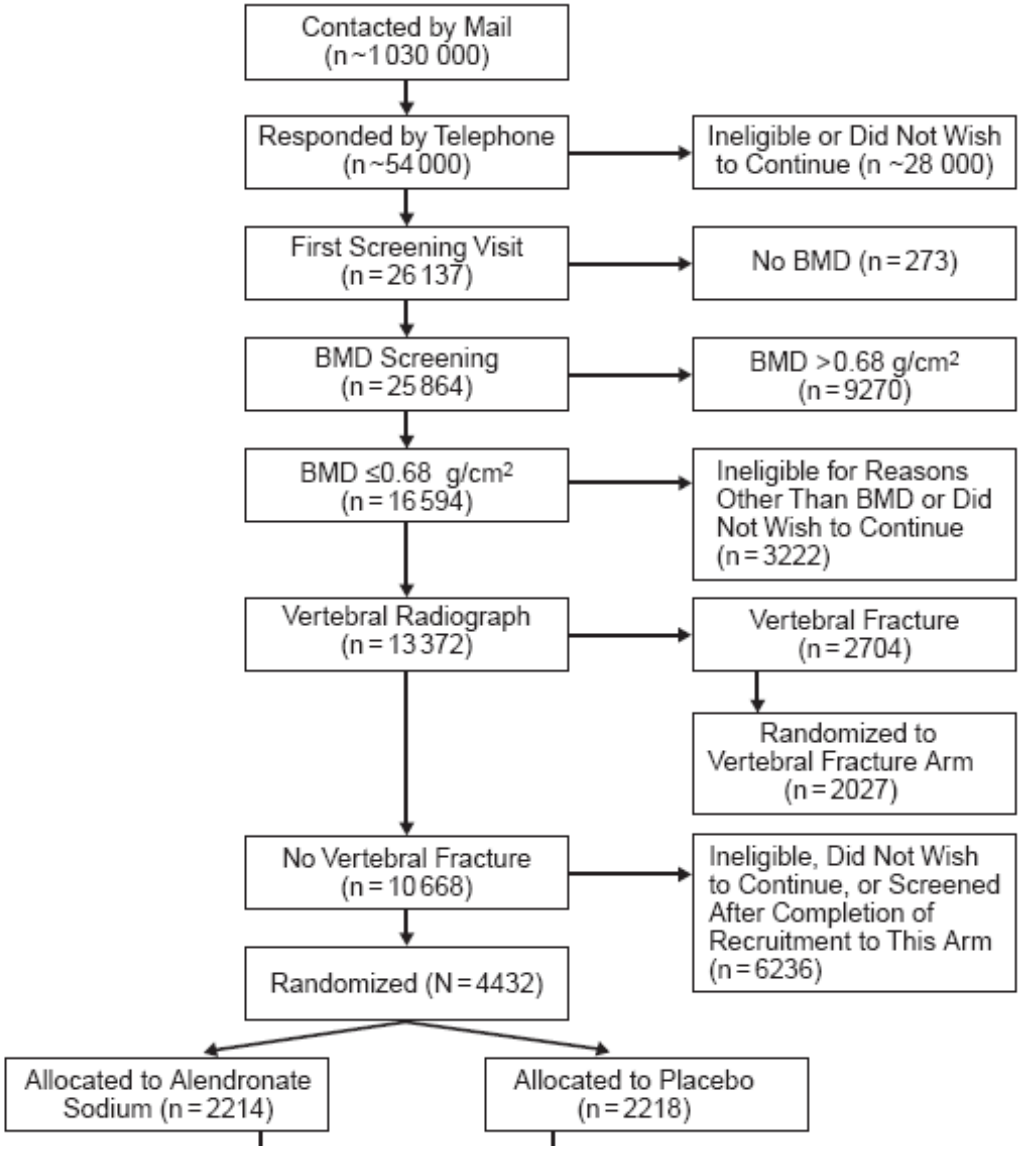
slido

Diskuter to og to:

Hvilke begrensninger har RCT-studier?

ⓘ Start presenting to display the poll results on this slide.

The FIT trial : Effect of Alendronate on Risk of Fracture

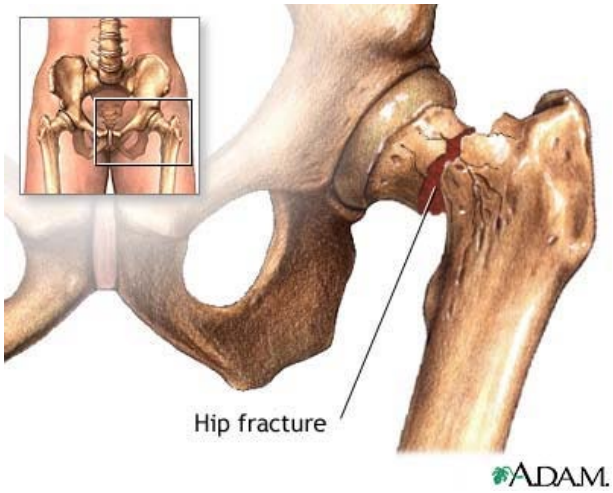


We excluded women who had Recent peptic ulcers or ulcers that required hospitalization, dyspepsia requiring daily treatment, significant renal or hepatic dysfunction, medical problems that precluded participation, severe malabsorption, blood pressure exceeding 210 mm Hg systolic or 105 mm Hg diastolic, myocardial infarction within 6 months, unstable angina, hypothyroidism, hyperthyroidism, or hyperparathyroidism. We also excluded women who had taken estrogen or calcitonin within the preceding 6 months or bisphosphonates or sodium fluoride (.1 mg/d) at any time. Althoughwomentaking estrogen were excluded from entry into the trial, 246 (11.1%) in the placebo group and 204 (9.2%) in the alendronate group took estrogen at some time during the study.

JAMA. 1998;280:2077-2082

92% av potensielt valgbare deltakere blir ekskuldert

Fru Hansen – 72 år



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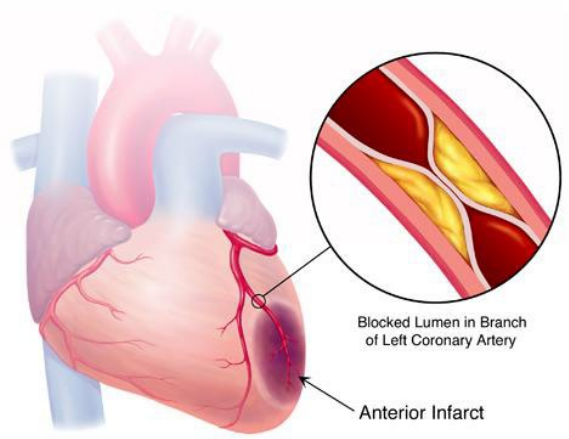


?

Inkluderte pasienter ikke representative for de pasientgruppene som faktisk får behandling

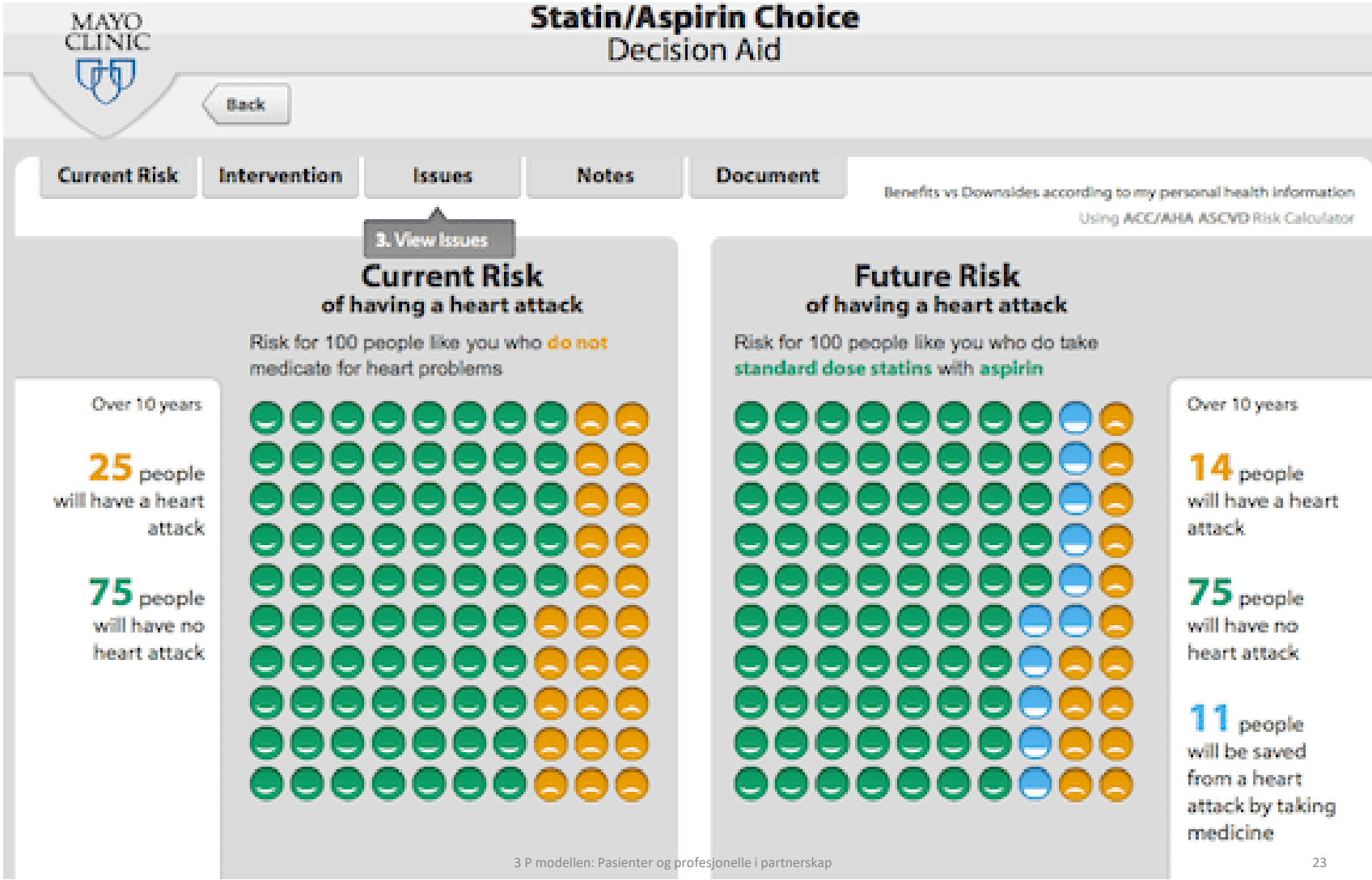
The controlled clinical trial

- *The main technical limitation of clinical trial methodology is that it assumes the homogeneity of the research populations which it studies.*
- *The assumption of homogeneity is enshrined in the use of averages and the statistics based on their comparison....*

- *For the individuals in the trial a comparison of means may hide much more than it reveals."*

John Heron(1986)

For 100 personer med din tilstand



Ikke etisk korrekt å lage en RCT

- Eksperimentet bare der det gagner intervensjonsgruppen
- ikke er dårligere en «vanlig behandling»

- Penicillin => kontrollgruppen skadelidende
- Røyking => Intervensjonsgruppen skadelidende

Kostnadskrevende

- Bare finansiellt sterke aktører har råd til å lage RCT-er
- Ikke-patenterbare produkter blir ofte ikke etterprøvd med RCT
- Eksempel: Østrogen

Ressursbruk - Tid

- Strenge formalia knyttet til godkjenninger av eksperimentell behandling – koster tid og penger
- Ofte for kort oppfølgingstid til å evaluere langtidseffekter av behandling

Komplekse intervensjoner

- Element x virker ikke uten element Y
- Det er umulig å identifisere hva X og Y er og sammenhengen mellom de
- Eksempel:
  - Barneoppdragelse

RCT i komplekse intervensjoner

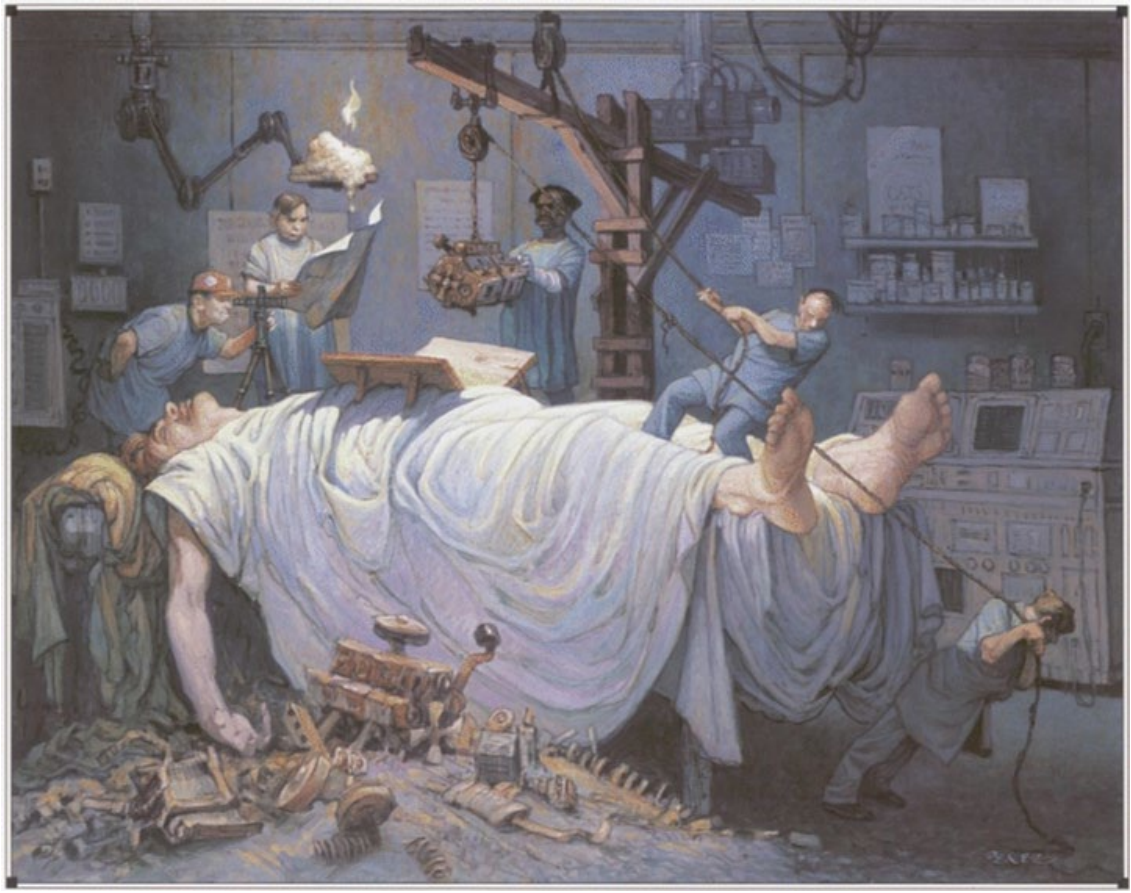
- Effekt avhengig av en kjede med hendelser

Vi kjører en RCT:

- En «black box» intervensjon
- A får Black-box - B får ikke

- Hvis vi får et negativt resultat
  - Var det fordi A ikke virket?
  - Eller var det fordi vi ikke hadde skapt de forholdene som var nødvendige for at A skulle virke?

- Hvis vi får et positivt resultat:
  - Kan vi reprodusere Forholdene som gjør at A virker?



Intervensjoner på organisasjonsnivå

- Randomisering og resultater rapporteres på organisasjonsnivå
- Umulig å randomisere store organisasjoner

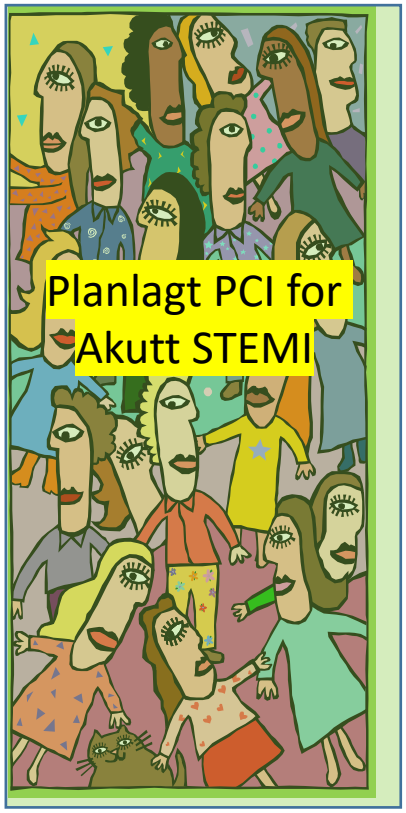
- Eksempler:
  - Gir Elektroniske pasient journaler (EPJ) bedre pasientbehandling?

Alternativer til den tradisjonelle RCT-en

Register basert RCT

TASTE – studien thrombus Aspiration in ST-Elevation MyocardialInfarction in Scandinavia

Valgbar ?
Baseline data



SCAAR

RCT

Effektmål

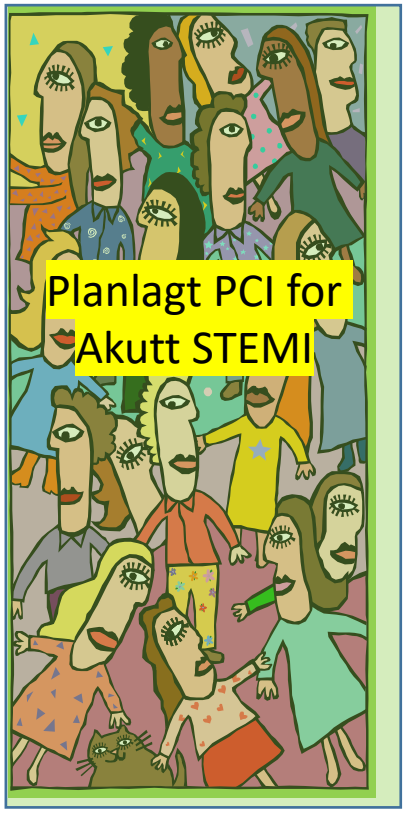
SCAAR

- Swedish Coronary Angiography and Angioplasty Registry (SCAAR), part of SWEDEHEART.
- Lagerqvist B, Fröbert O, Olivecrona GK, Gudnason T, Maeng M, Alström P, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. New England Journal of Medicine. 2014;371(12):1111-20.

Register basert RCT - styrker

TASTE – studien thrombus Aspiration in ST-Elevation MyocardialInfarction in Scandinavia

Valgbar ?
Baseline data



SCAAR

- Lavere kostnader => kostnader er overført til registeret
- Kan bruke kliniske kriterier til inklusjons screening.
- God kunnskap om hvem som ikke er med i studien
- Fortløpende rullering
- Komplett oppfølging
- Kan gjøre studier av «seleksjon» i alle ledd av studien

- Swedish Coronary Angiography and Angioplasty Registry (SCAAR), part of SWEDEHEART.
- Lagerqvist B, Fröbert O, Olivecrona GK, Gudnason T, Maeng M, Alström P, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. New England Journal of Medicine. 2014;371(12):1111-20.

Redusert tid og ressurser til:

- Formelle godkjenninger til datafangst
- Baseline datafangst allerede gjennomført
- Oppfølging av hendelser allerede rutine

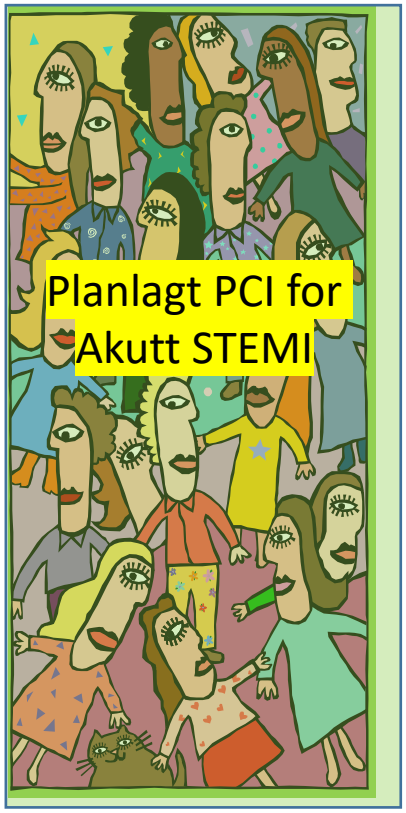
TASTE: N=7400
90% ↓ kostnader
Sammenliknet med en vanlig RCT

James S, Rao SV, Granger CB. Registry-based randomized clinical trials--a new clinical trial paradigm. Nat Rev Cardiol. 2015;12(5):312-6.

Register basert RCT - Utfordringer

TASTE – studien thrombus Aspiration in ST-Elevation MyocardialInfarction in Scandinavia

Valgbar ?
Baseline data



SCAAR

- Må skaffe lovlig og praktisk tilgang til registeret
- Etablere en randomisering utenfor eller i registeret
- Datakvalitet:
  - Data innhentet til et annet formål Validering av datakvalitet og data kompletthet
- Samtykke ?
  - Før screening for inklusjon?
  - Etter inklusjon - Før randomisering
  - Etter randomisering ?
  - Søke om fritak fra samtykke
  - Deltakere trekker seg
- Praktisk - Sikkerhets og monitorerings analyser

- Swedish Coronary Angiography and Angioplasty Registry (SCAAR), part of SWEDEHEART.
- Lagerqvist B, Fröbert O, Olivecrona GK, Gudnason T, Maeng M, Alström P, et al. Outcomes 1 year after thrombus aspiration for myocardial infarction. New England Journal of Medicine. 2014;371(12):1111-20.

Register basert RCT => Eller Register definert RCT?

- Hvor relevante er de tilgjengelige inklusjonsvariable og effektmål?

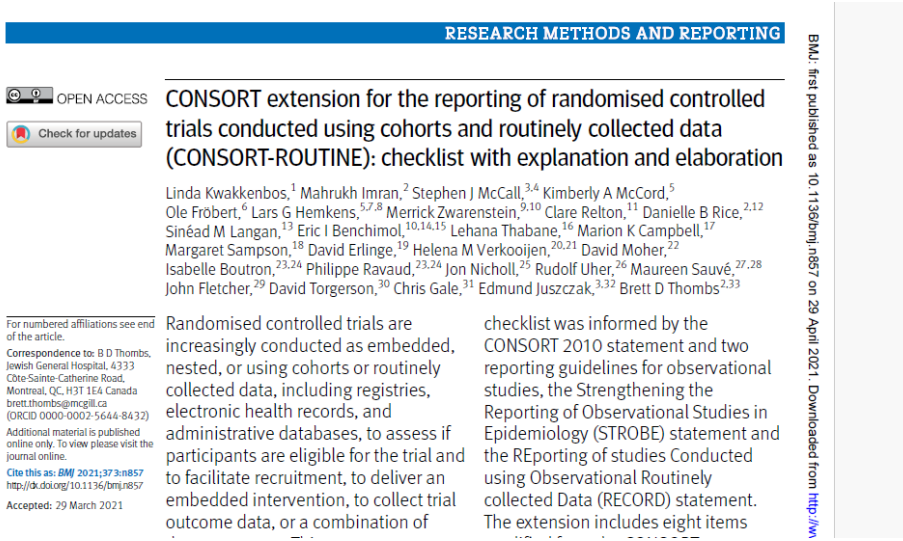
De fleste R – RCT-er kan kalles pragmatiske studier

- Real world context
- Gir det nytte?

Thabane L, Kaczorowski J, Dolovich L, Chambers LW, Mbuagbaw L, investigators C. Reducing the confusion and controversies around pragmatic trials: using the Cardiovascular Health Awareness Program (CHAP) trial as an illustrative example. Trials. 2015;16:1-8.

Steg for å gjennomføre en Register RCT

- Identifisere relevante inklusjonskriterier, evt justeringsvariable, og endepunktsvariable i registeret(ene)
- Sjekke – data-kvalitet – prosedyrer/ ekstra studier?
- Etablere en randomiseringsrutine
- Etablere rutiner for å beskytte data og pasientens personvern i forbindelse med gjennomføring
- Etiske og juridisk tillatelser: REK, PVO
- Praktisk tilgang til data og registerets interne personell
- Etablere rutine for informert samtykke
- Etablere randomiseringsrutine
- Utvikle prosedyrer og etablere kontakt med kliniske utøvere implementere intervensjonen
- Søke tillatelse fra deltakere for å la dem bli kontaktet for fremtidige forskningsstudier.



RESEARCH METHODS AND REPORTING

OPEN ACCESS

Check for updates

CONSORT extension for the reporting of randomised controlled trials conducted using cohorts and routinely collected data (CONSORT-ROUTINE): checklist with explanation and elaboration

Linda Kwakkenbos,[1] Mahrukh Imran,[2] Stephen J McCall,[3,4] Kimberly A McCord,[5] Ole Fröbert,[6] Lars G Hemkens,[5,7,8] Merrick Zwarenstein,[9,10] Clare Relton,[11] Danielle B Rice,[2,12] Sinéad M Langan,[13] Eric I Benchimol,[10,14,15] Lehana Thabane,[16] Marion K Campbell,[17] Margaret Sampson,[18] David Erlinge,[19] Helena M Verkooijen,[20,21] David Moher,[22] Isabelle Boutron,[23,24] Philippe Ravaud,[23,24] Jon Nicholl,[25] Rudolf Uher,[26] Maureen Sauvé,[27,28] John Fletcher,[29] David Torgerson,[30] Chris Gale,[31] Edmund Juszczak,[3,32] Brett D Thombs[2,33]

For numbered affiliations see end of the article.

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;373:n857 http://dx.doi.org/10.1136/bmj.n857

Accepted: 29 March 2021

Randomised controlled trials are increasingly conducted as embedded, nested, or using cohorts or routinely collected data, including registries, electronic health records, and administrative databases, to assess if participants are eligible for the trial and to facilitate recruitment, to deliver an embedded intervention, to collect trial outcome data, or a combination of

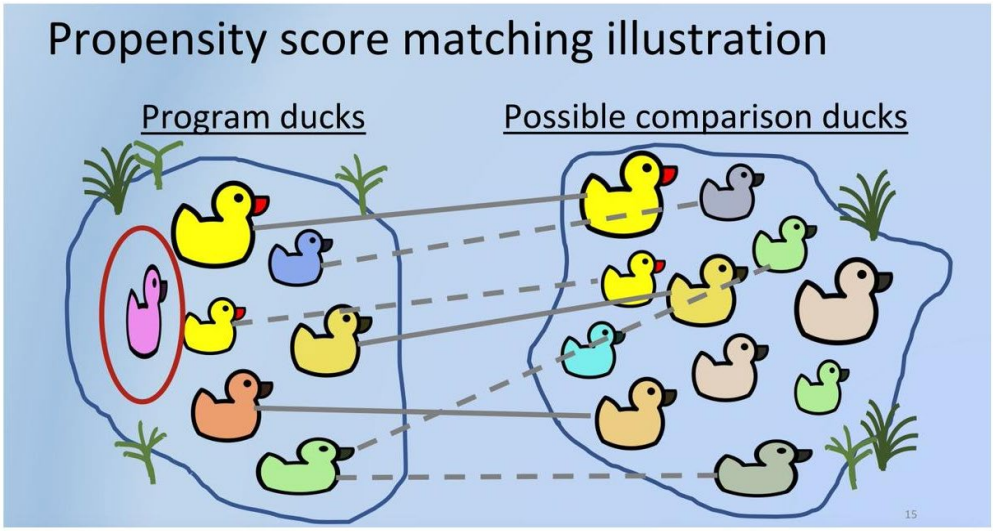
checklist was informed by the CONSORT 2010 statement and two reporting guidelines for observational studies, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and the REporting of studies Conducted using Observational Routinely collected Data (RECORD) statement. The extension includes eight items

Observasjonsstudier - Propensity Score matching

- Relevant der det er
- Etisk vanskelig
- Sjeldne tilstander – vanskelig å finne kontroller
- Intervensjoner på systemnivå

- En skår lages av alle målte variable som kan tenkes å forutsi effekt
- Matche på skår
- Blir sammenliknbare på gruppenivå for de variablene som vi har målt

- Det er gjort flere studier som sammenlikner RCT og Propensity score resultater fra observasjonsstudier
- De gir i hovedsak samme resultat



Design - Emulated RCT

The Annals of Applied Statistics
2008, Vol. 2, No. 3, 808–840
DOI: 10.1214/08-AOAS187
© Institute of Mathematical Statistics, 2008

FOR OBJECTIVE CAUSAL INFERENCE, DESIGN TRUMPS ANALYSIS[1]

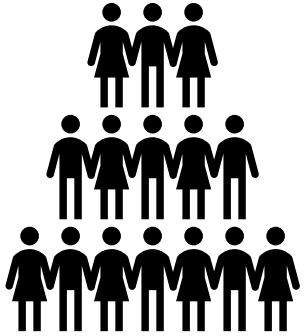
BY DONALD B. RUBIN
Harvard University

Table 1. A Summary of the Protocol of a Target Trial to Estimate the Effect of Postmenopausal Hormone Therapy on the 5-Year Risk of Breast Cancer

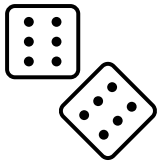
Protocol Component	Description
Eligibility criteria	Postmenopausal women within 5 years of menopause between the years 2005 and 2010 and with no history of cancer and no use of hormone therapy in the past 2 years.
Treatment strategies	Refrain from taking hormone therapy during the follow-up. Initiate estrogen plus progestin hormone therapy at baseline and remain on it during the follow-up unless you are diagnosed with deep vein thrombosis, pulmonary embolism, myocardial infarction, or cancer.
Assignment procedures	Participants will be randomly assigned to either strategy at baseline and will be aware of the strategy to which they have been assigned.
Follow-up period	Starts at randomization and ends at diagnosis of breast cancer, death, loss to follow-up, or 5 years after baseline, whichever occurs first.
Outcome	Breast cancer diagnosed by an oncologist within 5 years of baseline.
Causal contrasts of interest	Intention-to-treat effect, per-protocol effect
Analysis plan	Intention-to-treat effect estimated via comparison of 5-year cancer risks among individuals assigned to each treatment strategy. Per-protocol effect estimation requires adjustments for pre- and postbaseline prognostic factors associated with adherence to the strategies of interest. All analyses will be adjusted for pre- and postbaseline prognostic factors associated with loss to follow-up (57). This analysis plan implies that the investigators prespecify and collect data on the adjustment factors.

Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. American journal of epidemiology. 2016;183(8):758-64.

Maskin læring og Kausalitet



Gitt at enhetene er sammenliknbare, dvs at forutsetningen om uavhengighet er oppfylt:



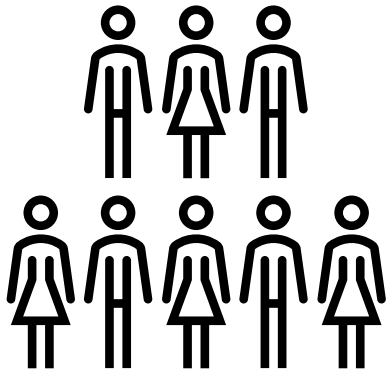
Treatment - effekt

$$T = Y_t(u) - Y_c(u), \qquad \text{for all } u \text{ in } U.$$

Prediksjon 1

Prediksjon 2

(Prediksjon 1 – Prediksjon 2) – vektet for forskjeller i gruppene med Propensity Score



1. Nie X, Wager S. Quasi-oracle estimation of heterogeneous treatment effects. Biometrika. 2021;108(2):299-319.
2. Salditt M, Eckes T, Nestler S. A Tutorial Introduction to Heterogeneous Treatment Effect Estimation with Meta-learners. Adm Policy Ment Health. 2023:1-24.

Kvalitative og kvantitative studier – mixed methods

- Menneskeskapte system
- Ekstrapolere fra tall til å se på det som skjer mellom mennesker
- Samle data kan også være tekst, bilder, notater, video, intervju

Registre => En lærende helsetjeneste

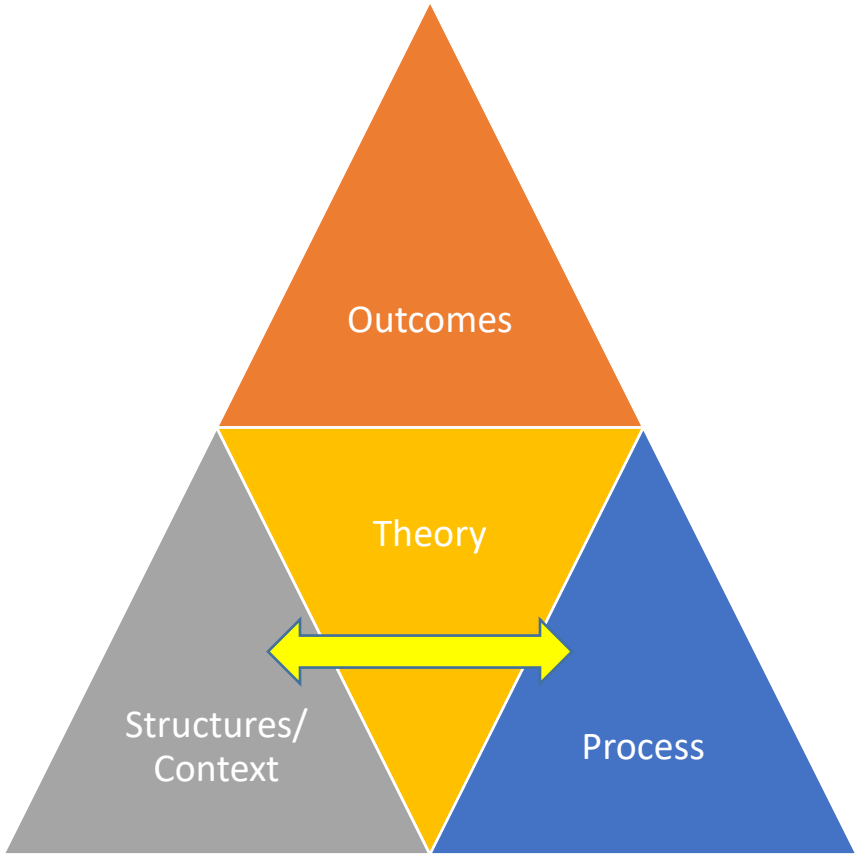
- Data om eksposisjon og endepunkt
- Analysekompetanse
- Kunnskap tilbake til praksisfeltet

- OBS – registrering av data er en ekstra kostnad

Kunnskap – et helhetlig puslespill

- En helhetlig vurdering av alle trekanter

- Teori – fundamentet
- Struktur/ kontekst virker sammen med prosess / intervensjon
- Empiri=> vise at det virker i virkeligheten



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