

# RCT og Register-RCT

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## Læringsmål

Studentene skal kunne redegjøre for:

- Hva er en RCT?
- Hvilke begrensninger har RCT-en?
- Alternativer til tradisjonell RCT:
  - Registerbasert RCT
  - Registerbasert – Propensity score(PS) matchet observasjonsstudie
  - RCT med extra PS-kontroller fra register

slido



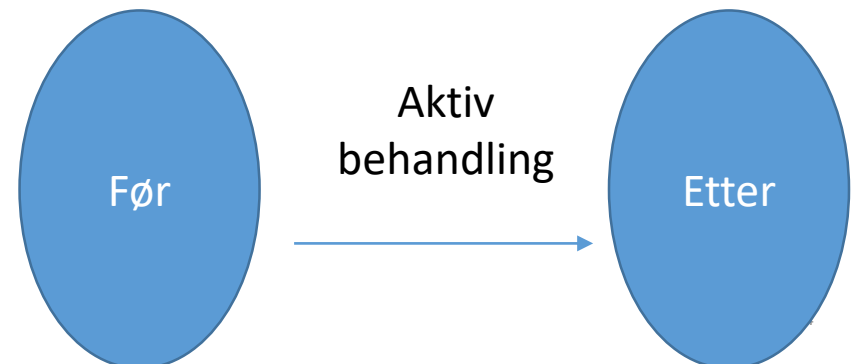
**Hva slags studier skal til for at  
noe blir noe sant i medisinen?**

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

# Fra erfaringsbasert til systematisk kunnskapsoppbygging



- **Avicenna**
- Persisk lege
- 980 - 1037 e. Kr
- *Den medisinske kanon*
- *Introduserte:*
  - *systematiske eksperiment*
  - *måling av effekt av behandling*

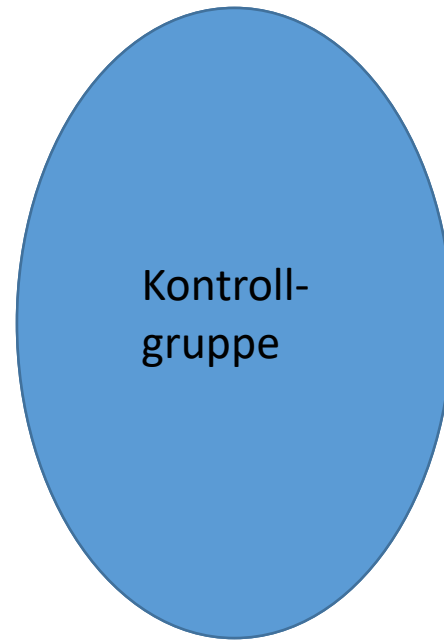


# Seruminjeksjoner ved difteri

- 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

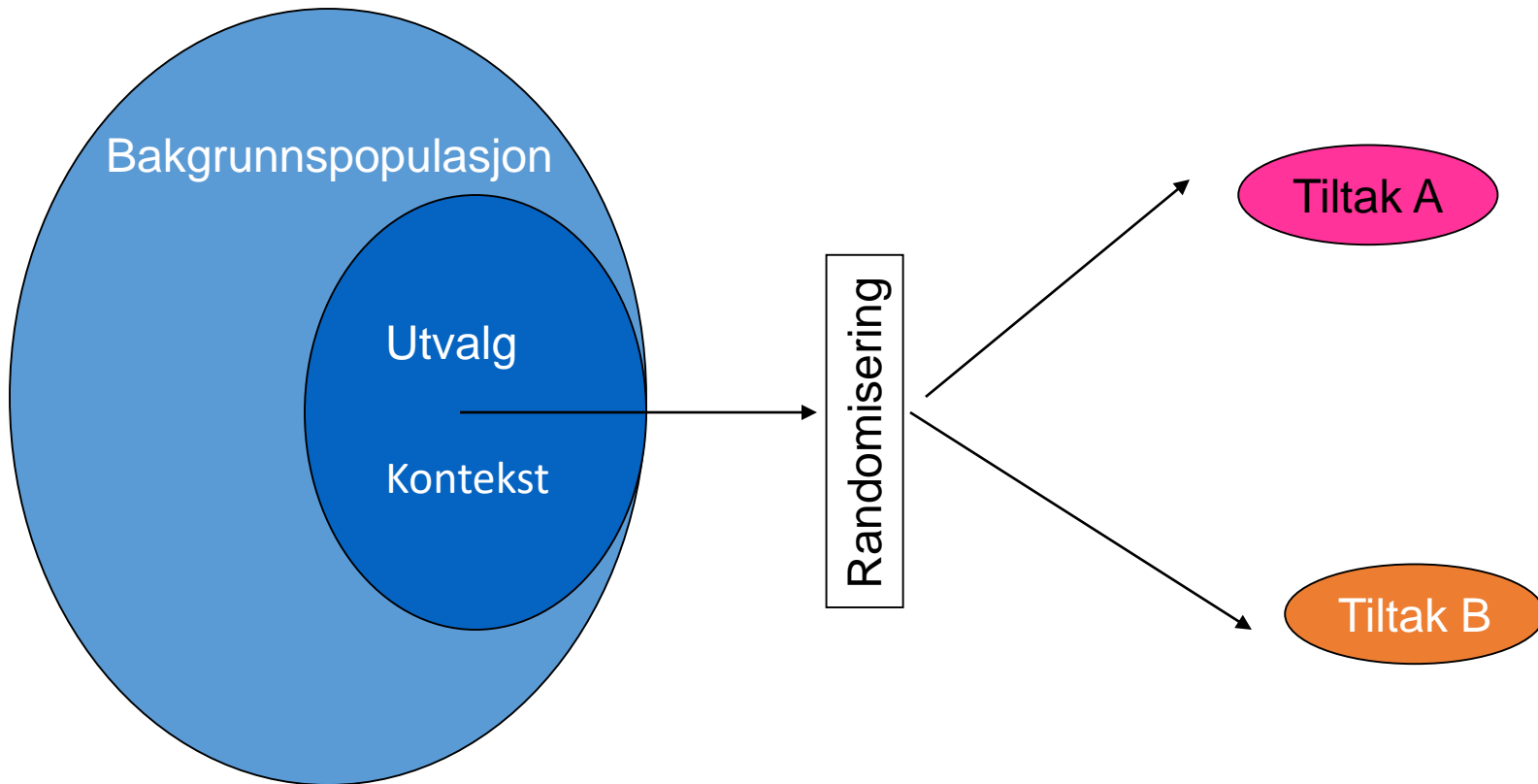
## Bradford Hill – tilfeldig tilordning 1937

- Gruppetilordning skal skje tilfeldig
  - Randomisering
- Verken behandler eller pasient skal vite om de får aktiv behandling
  - Dobbelt blindet
- RCT - det randomiserte kontrollerte eksperiment



Bradford Hill

RCT'n fordeler både kjente og ukjente faktorer slik at gruppene blir sammenliknbare



RCT => gjennomsnittlig forskjell mellom gruppene



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	27%	14	27%
Total .. ..	55	100%	52	100%

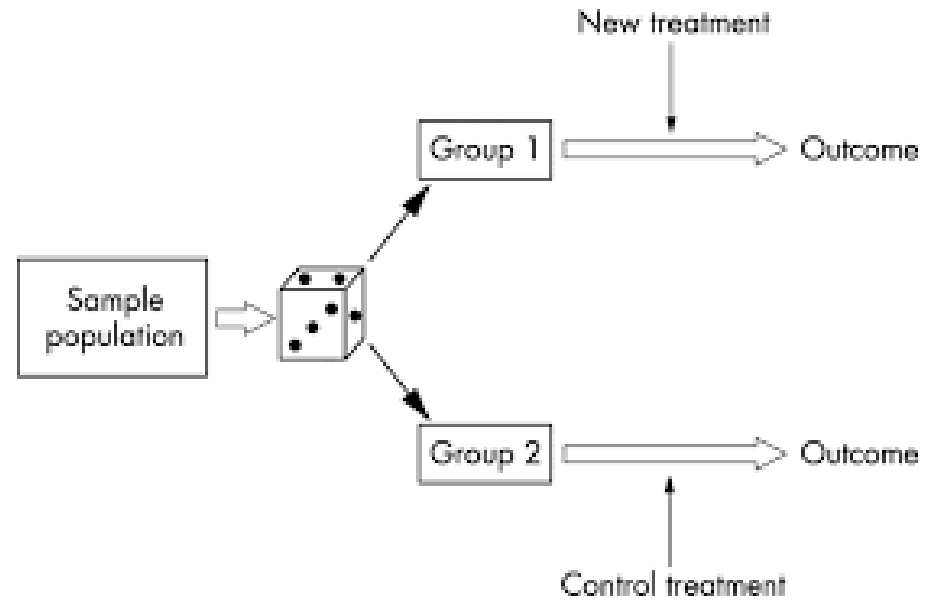
# Typisk RCT design

## Hypotese testende

- Kontekst => Inklusjons- og Eksklusjonskriterier
- Virkningsmekanisme
  - Forventet resultat i aktiv gruppe
  - Forventning i Kontrollgruppe

## Bare nyttig dersom:

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



# Hjelper antibiotika X for bronkitt?

**Kontekst =>**

**Inklusjon:**

Pasienter med symptomer på bakteriell bronkitt

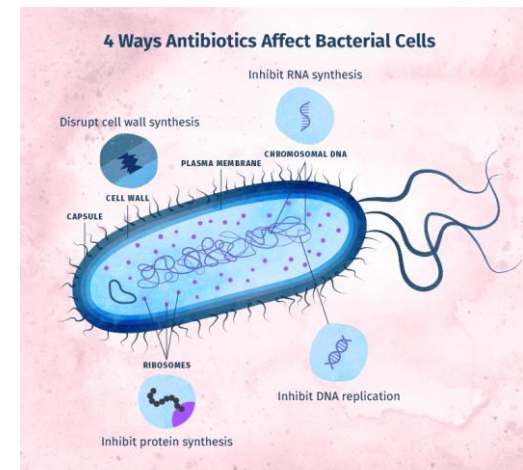
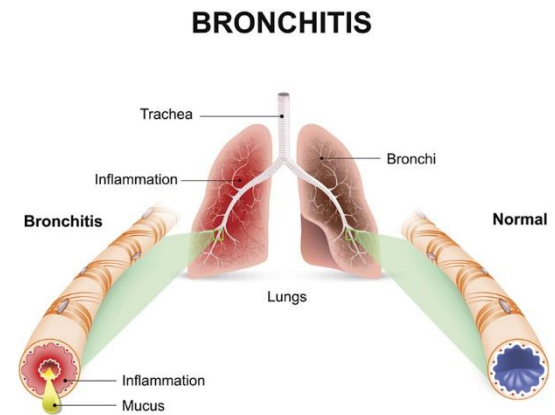
**Eksklusjon:**

Pasienter med symptomer på ikke-bakteriell bronkitt

Pasienter som ikke har bronkitt

**Mekanisme =>** Penicillin bryter ned celleveggen

Mulige «sidespor»





# RCT i Evidence Based Medicine (EBM)

slido



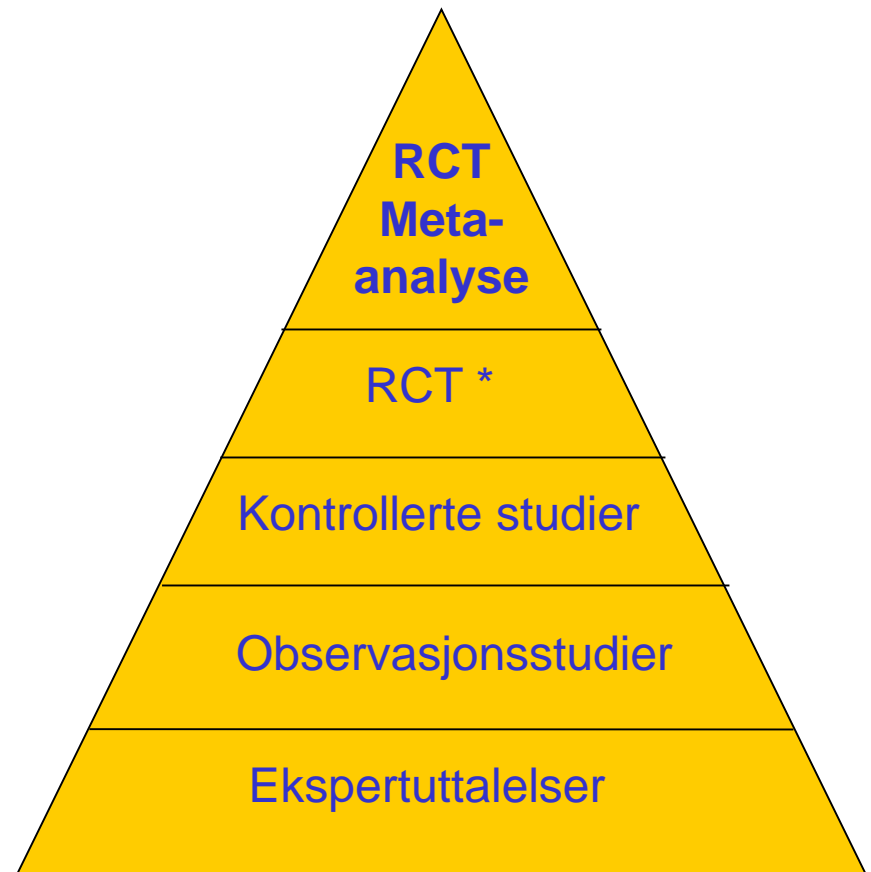
**Ranger styrken på "evidens"**

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## 1980 - Evidence Based Medicine

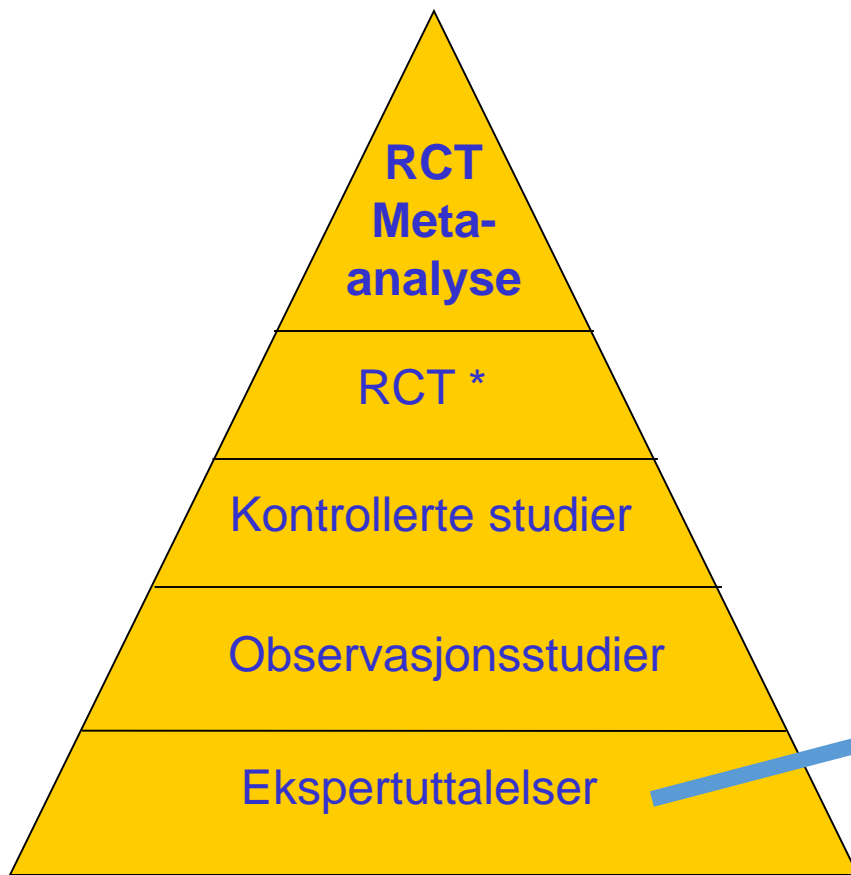
Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

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>.



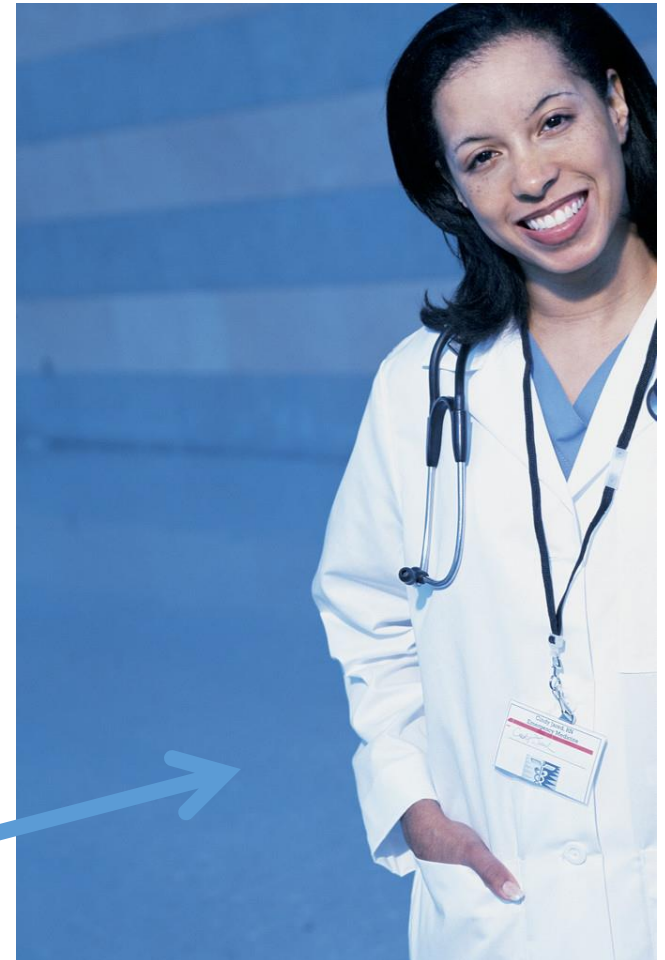
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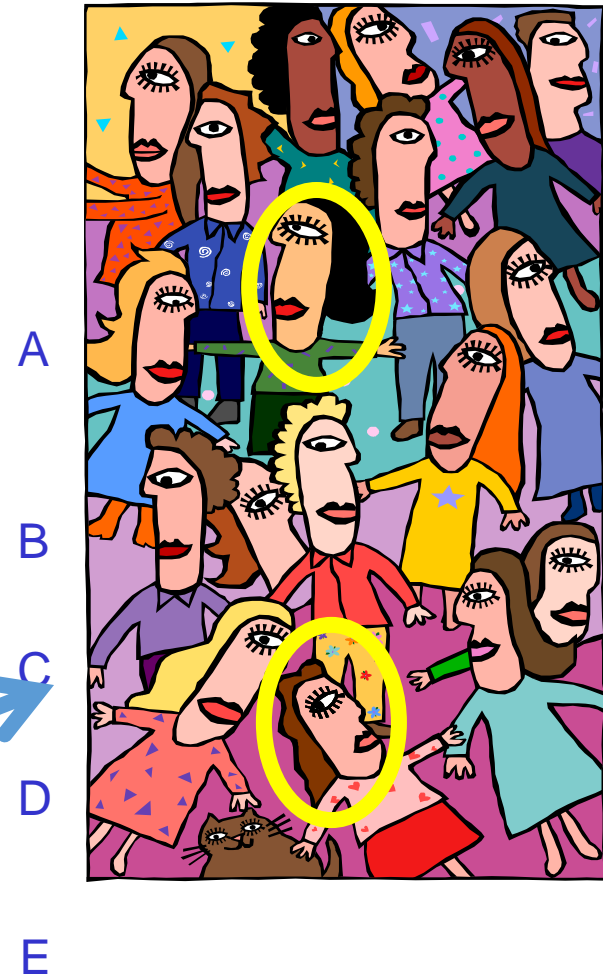
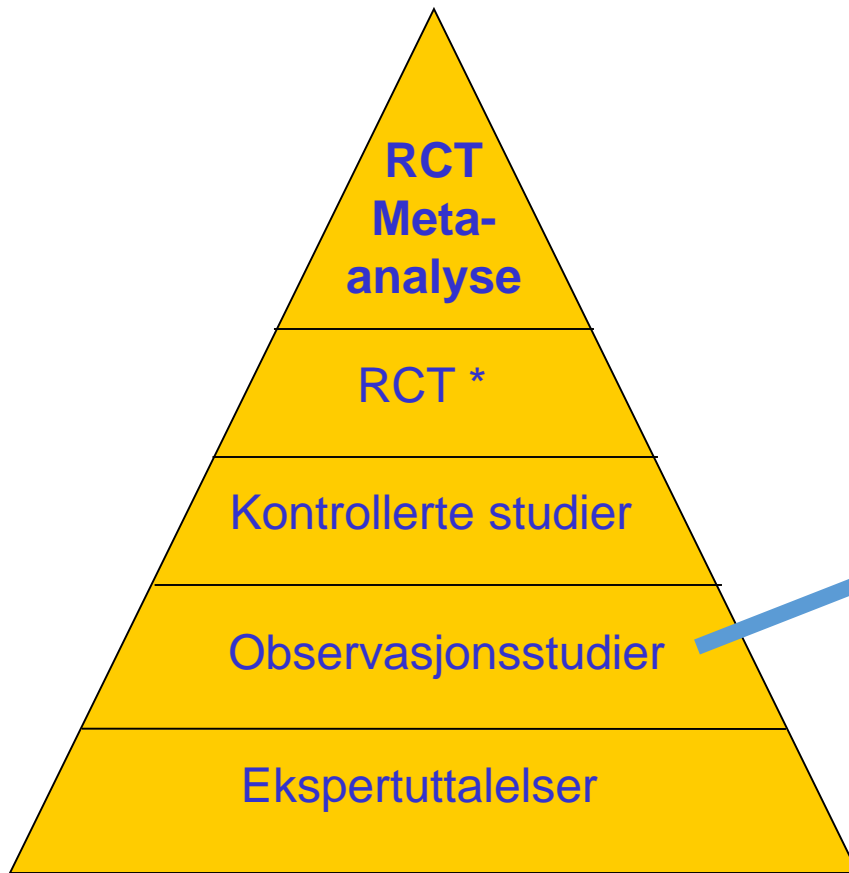
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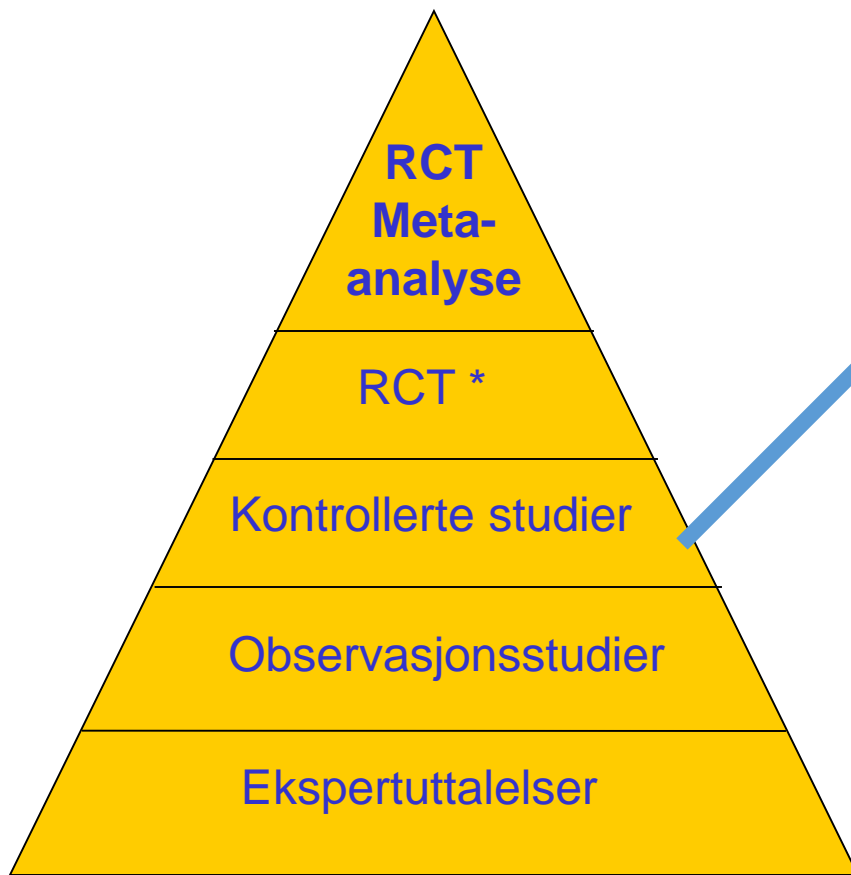


\* Randomised Controlled Trial



\* Randomised Controlled Trial





A

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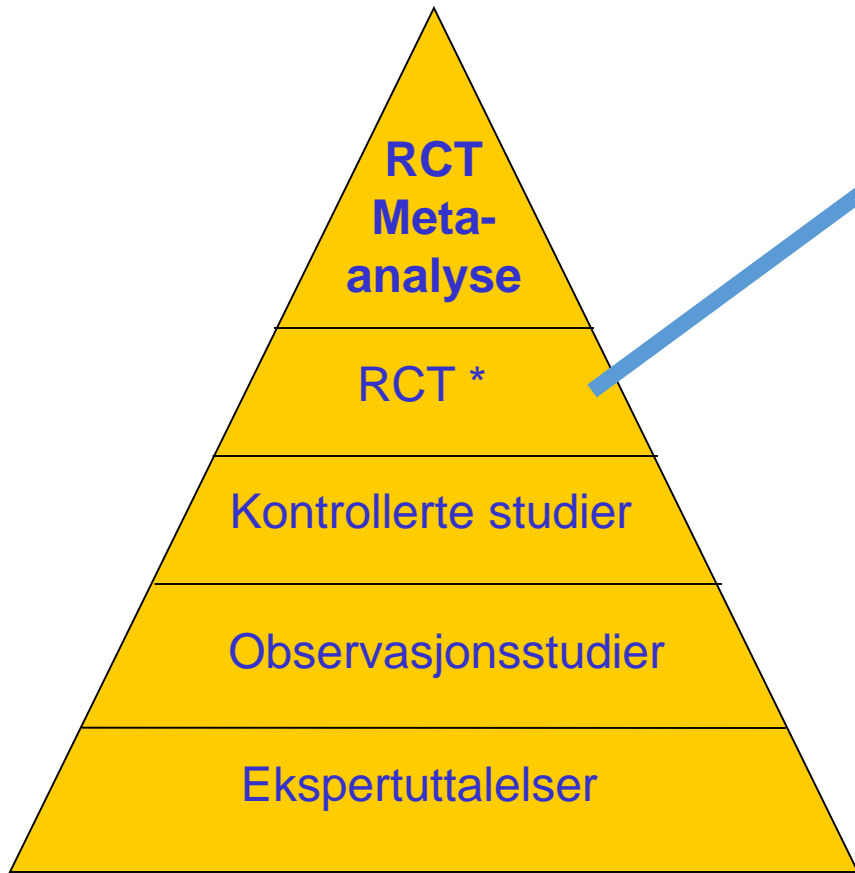
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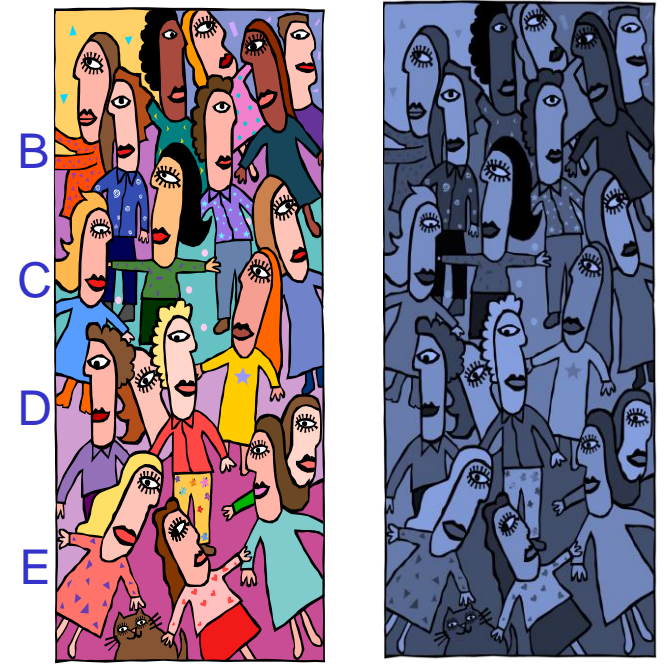
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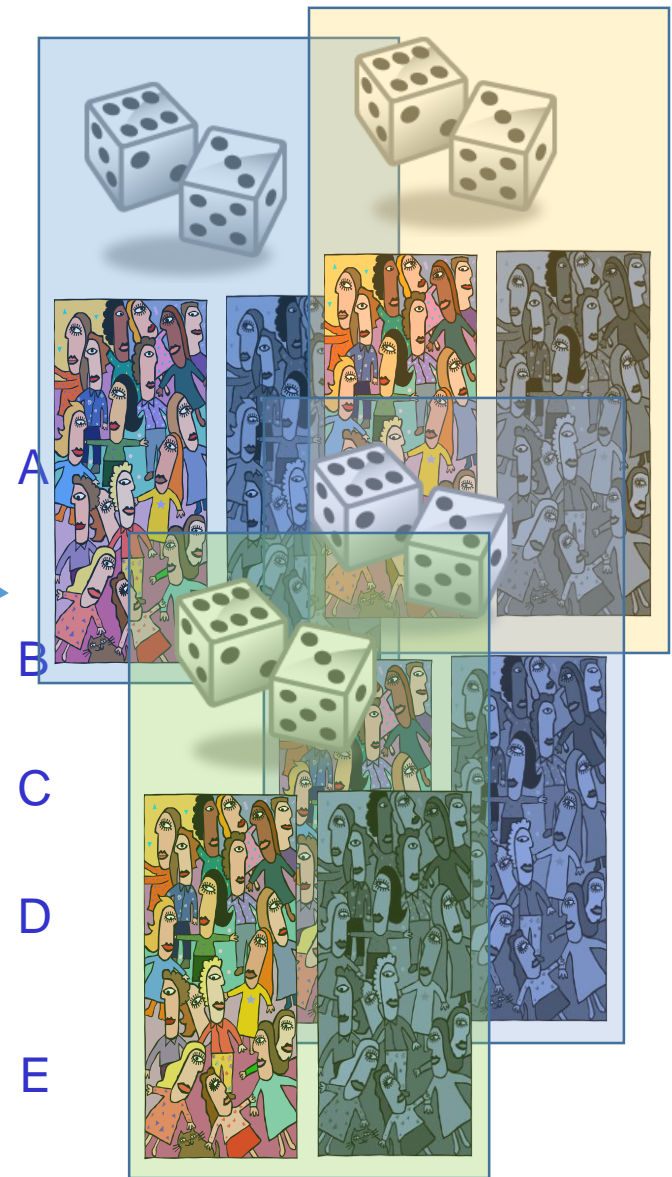
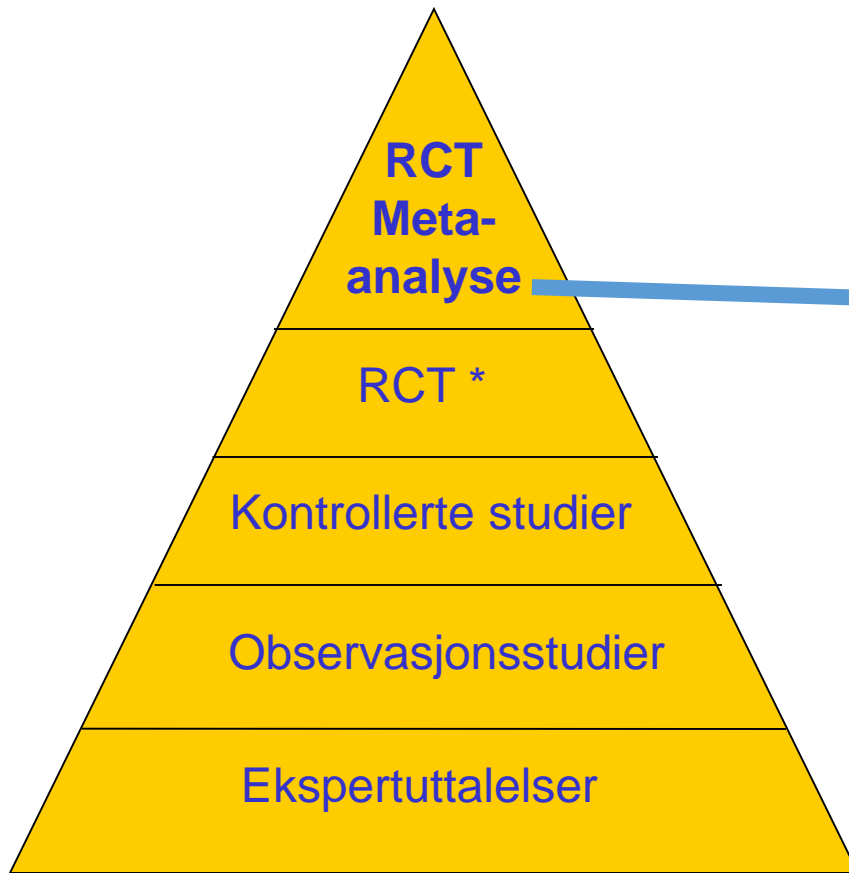
\* Randomised Controlled Trial



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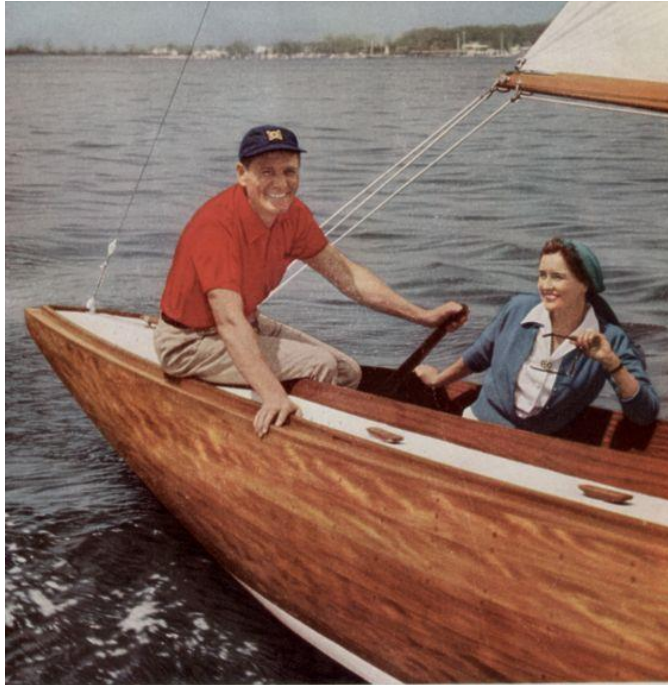


\* Randomised Controlled Trial



\* Randomised Controlled Trial

# 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 strings 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 estrogen complex, is available as tablets and liquid, and also in combination with norethandrolone or methyltestosterone.

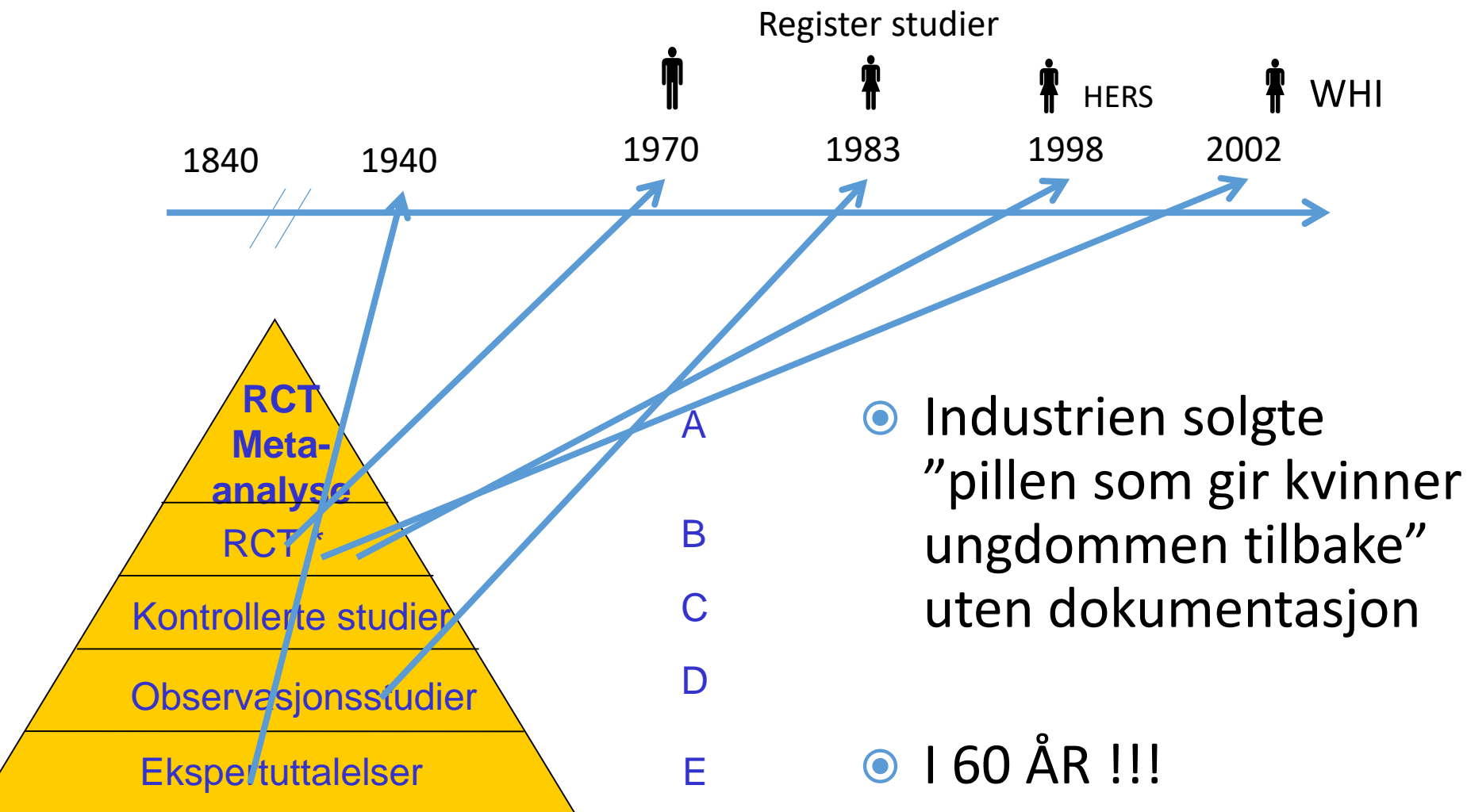
Ayerst Laboratories • New York 16, N. Y. • Montreal, Canada



- Annonsekampanje – 1960-tallet:
- “Det er ikke lett for en mann å ta utfordringer og tunge tak i arbeidslivet for så komme hjem til kaoset rundt en kvinne i overgangsalderen.

Hvis hun ikke bruker Premarin da.”

# Østrogen behandlingens historie



Randomised Controlled Trial



# RCT begrensninger

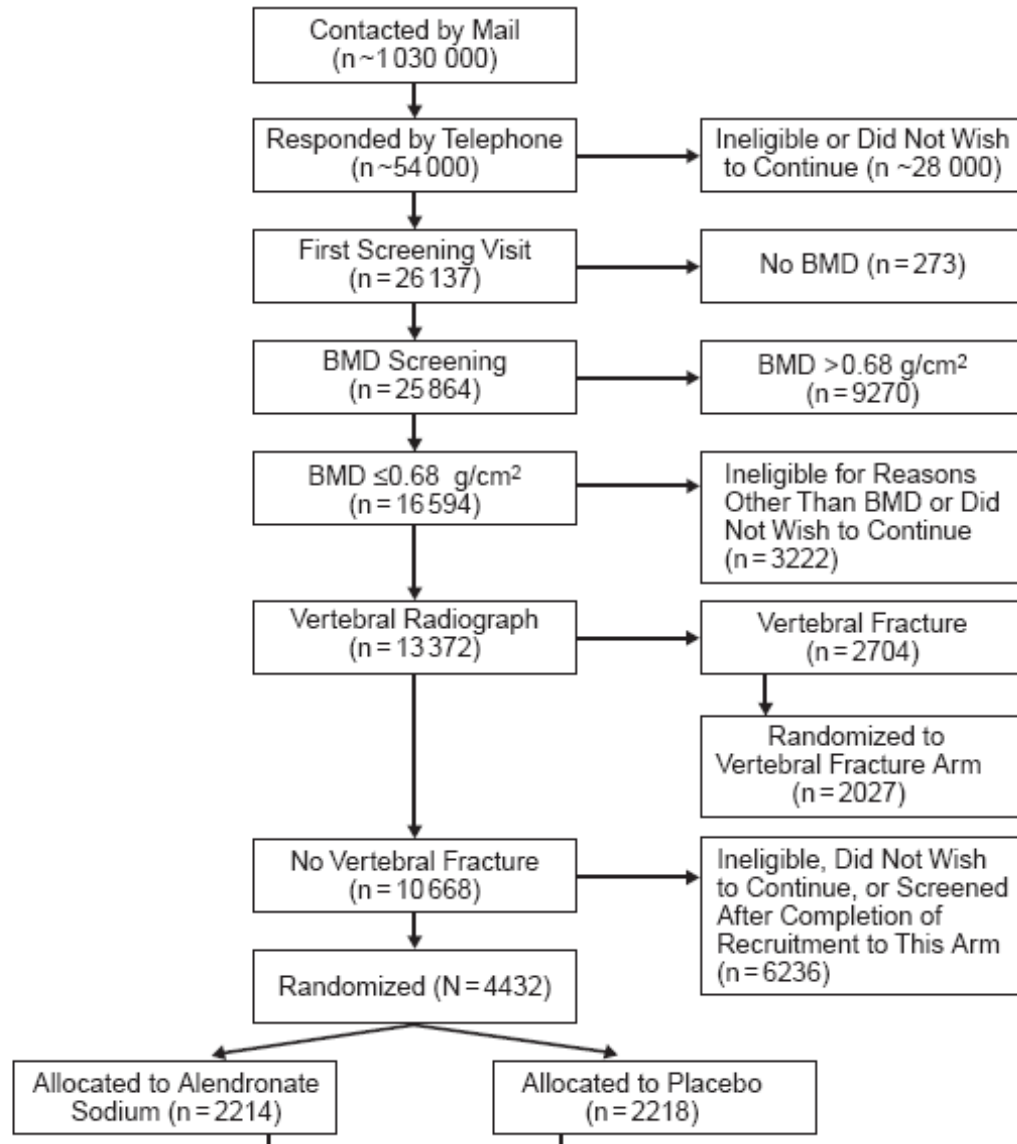
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**Hvilke begrensninger har RCT-studier?**

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## The FIT trial : Effect of Alendronate on Risk of Fracture



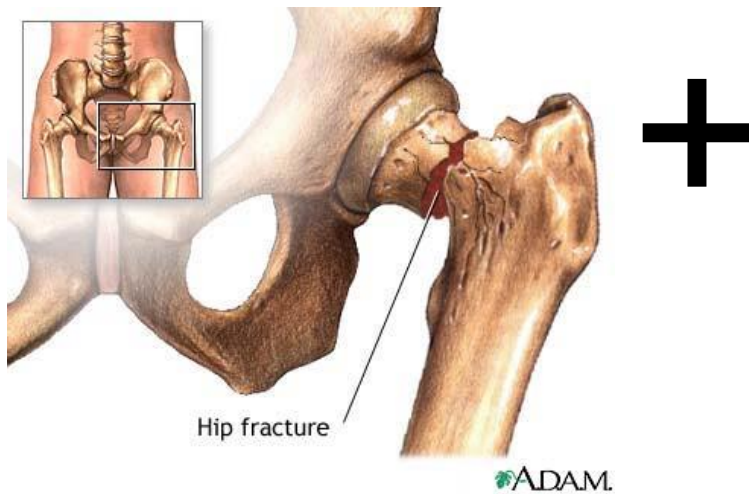
We excluded women who had Recent peptic ulcers or ulcers that required hospitalization, dyspepsia requiring daily treatment, significant renal or hepatic dysfunction, medical problems that precluded participation, severe malabsorption, blood pressure exceeding 210 mm Hg systolic or 105 mm Hg diastolic, 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. Although women taking 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

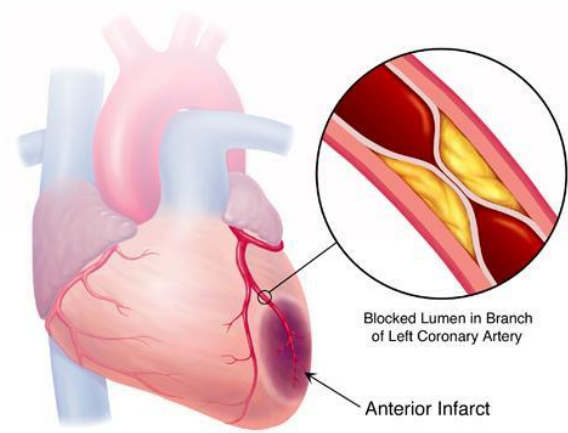
92% av potensielt valgbare deltakere blir ekskludert



Fru Hansen – 72 år



+



?

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.”*

For 100 personer med din tilstand

**MAYO CLINIC**

## Statin/Aspirin Choice Decision Aid

Back

Current Risk Intervention Issues Notes Document

Benefits vs Downsides according to my personal health information  
Using ACC/AHA ASCVD Risk Calculator

3. View Issues

### Current Risk of having a heart attack

Risk for 100 people like you who **do not** medicate for heart problems

Over 10 years

**25** people will have a heart attack

**75** people will have no heart attack

Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
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### Future Risk of having a heart attack

Risk for 100 people like you who do take **standard dose statins with aspirin**

Over 10 years

**14** people will have a heart attack

**75** people will have no heart attack

**11** people will be saved from a heart attack by taking medicine

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3 P modellen: Pasienter og profesjonelle i partnerskap

27



Ikke etisk  
korrekt å lage  
en RCT

- Eksperimentet bare der det etter teorien gagner intervensjonsgruppen
- ikke er dårligere en «vanlig behandling»
- Penicillin => kontrollgruppen skadelidende
- Røyking => Intervensjonsgruppen skadelidende

## Kostnadskrevende



- Bare finansielt 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:

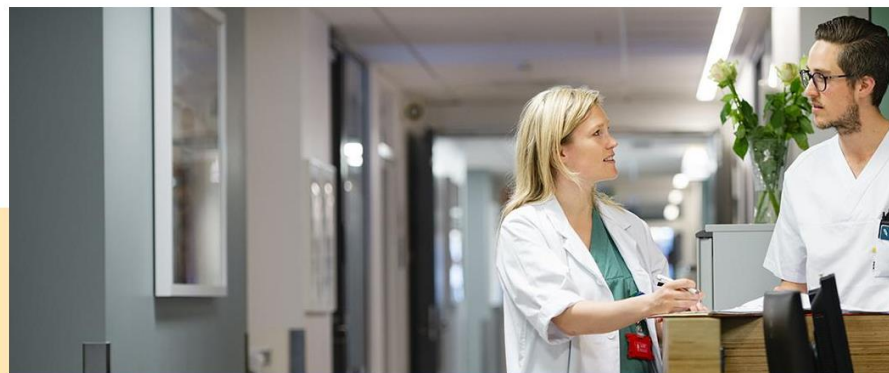
- En «black box» intervensjon
- A får Black-box - B får ikke
- Hvis vi får et negativt resultat
  - Var det fordi A ikke virket?
  - Eller var det fordi vi ikke hadde skapt de forholdene som var nødvendige for at A skulle virke?
- Hvis vi får et positivt resultat:
  - Kan vi reprodusere Forholdene som 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?



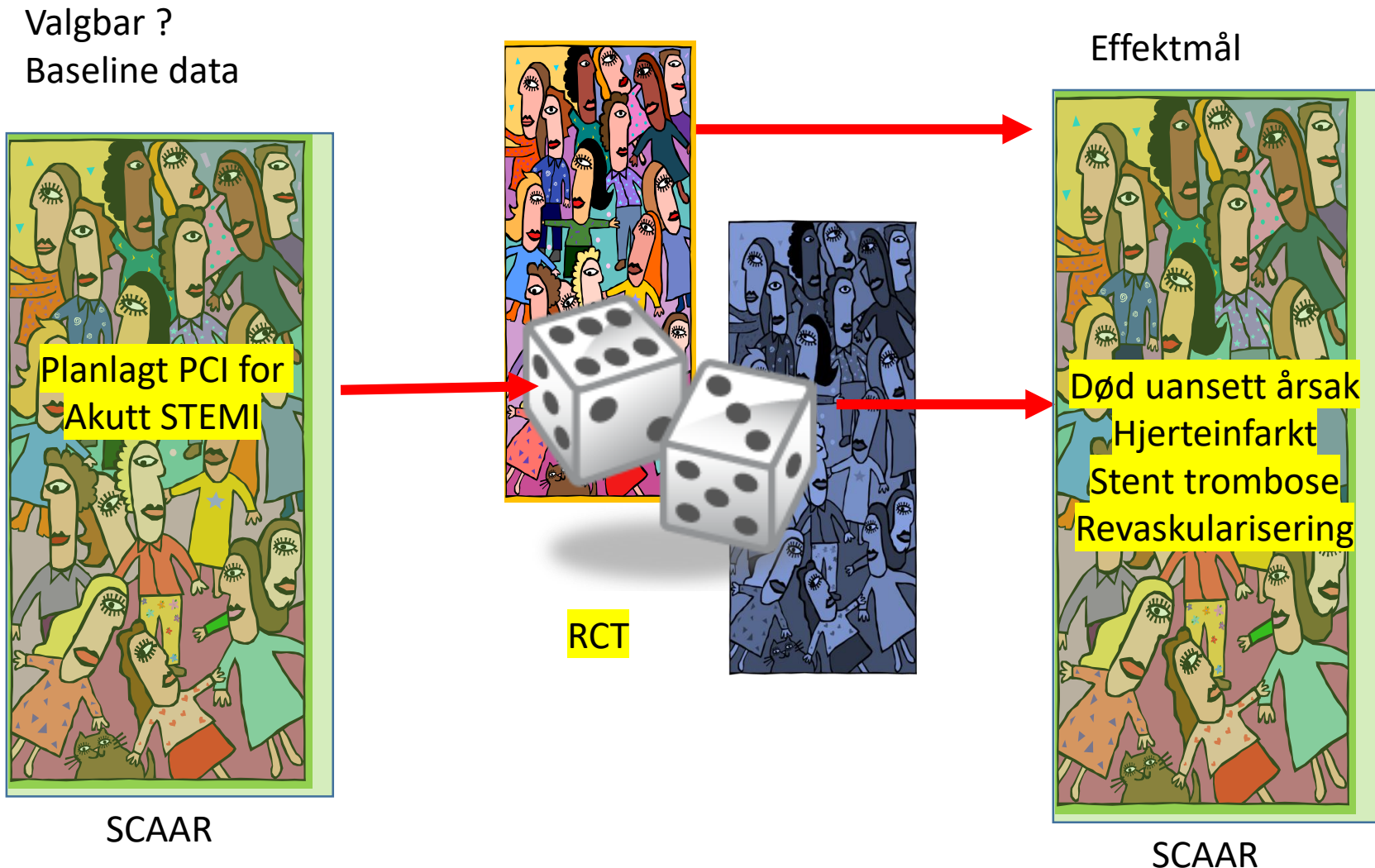
Felles pasientjournal i Midt-Norge



# Alternativer til den tradisjonelle RCT-en

# Register basert RCT

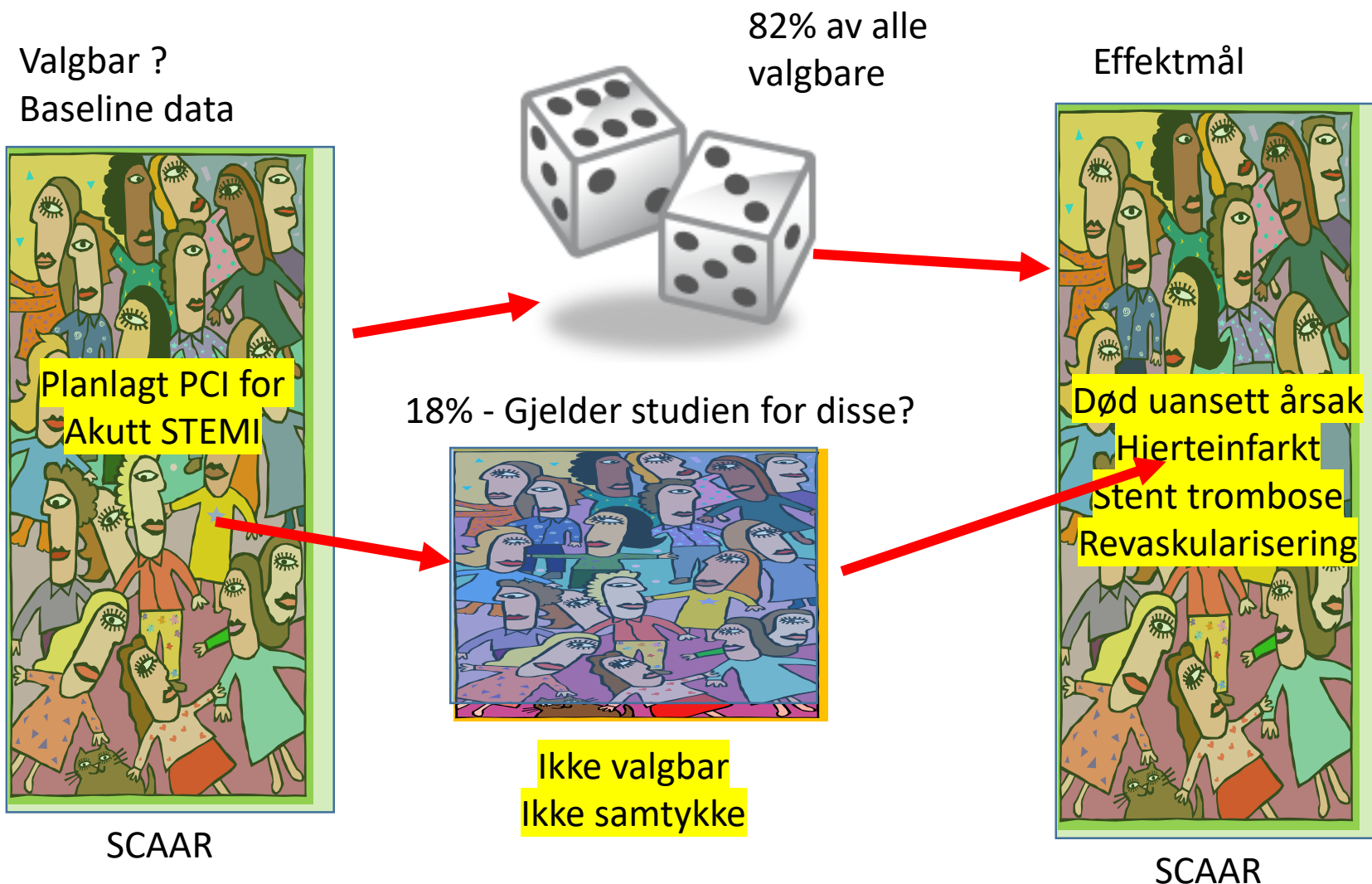
TASTE – studien thrombus Aspiration in ST-Elevation MyocardialInfarction in Scandinavia



- Swedish Coronary Angiography and Angioplasty Registry (SCAAR), part of SWEDHEART.
- 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 –

## TASTE – studien thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia



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### Redusert tid og ressurser til:

- Formelle godkjenninger til datafangst
- Baseline datafangst allerede gjennomført
- Oppfølging av hendelser allerede rutine
- Kan si noe om de som ikke ble inkludert

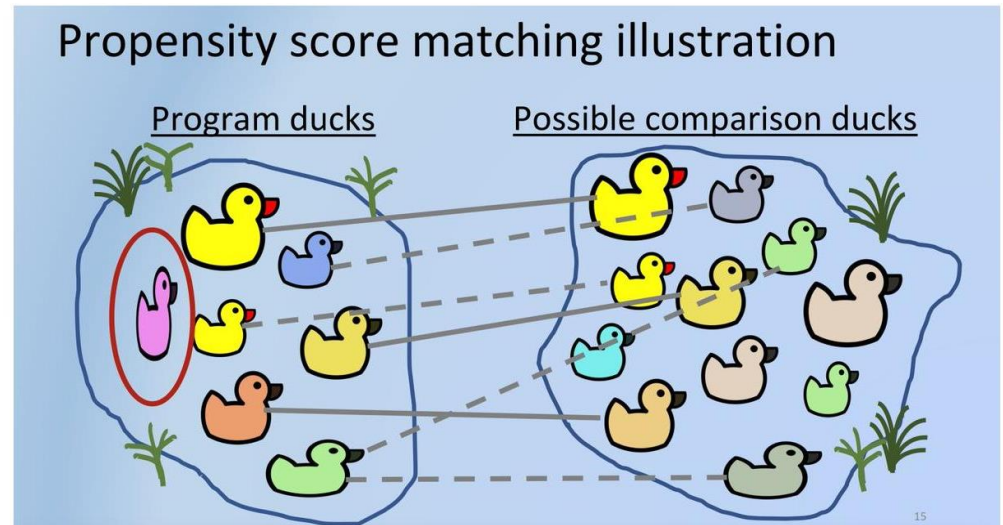
Unngår re-insamling og re-organisering av datafangst for hver ny studie



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

# Observasjonsstudier - Propensity Score matching

- 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



# Oppslag i registeret

13-year-old girl with systemic lupus erythematosus(SLE). Our patient's presentation was complicated by nephroticrange proteinuria, antiphospholipid antibodies, and pancreatitis.

Results of Electronic Search of Patient Medical Records (for a Cohort of 98 Pediatric Patients with Lupus) Focused on Risk Factors for Thrombosis Relevant to Our 13-Year-Old Patient with Systemic Lupus Erythematosus.*			
Outcome or Risk Factor	Keywords Used to Conduct Expedited Electronic Search	Prevalence of Thrombosis <i>no./total no (%)</i>	Relative Risk (95% CI)
Outcome — thrombosis	"Thrombus," "Thrombosis," "Blood clot"	10/98 (10)	Not applicable
Thrombosis risk factor			
Heavy proteinuria (>2.5 g per deciliter)			
Present at any time	"Nephrosis," "Nephrotic," "Proteinuria"	8/36 (22)	7.8 (1.7–50)
Present >60 days	"Urine protein"	7/23 (30)	14.7 (3.3–96)
Pancreatitis	"Pancreatitis," "Lipase"	5/8 (63)	11.8 (3.8–27)
Antiphospholipid antibodies	"Aspirin"	6/51 (12)	1.0 (0.3–3.7)

Frankovich J, Longhurst CA, Sutherland SM. Evidence-based medicine in the EMR era. *New England Journal of Medicine*. 2011.

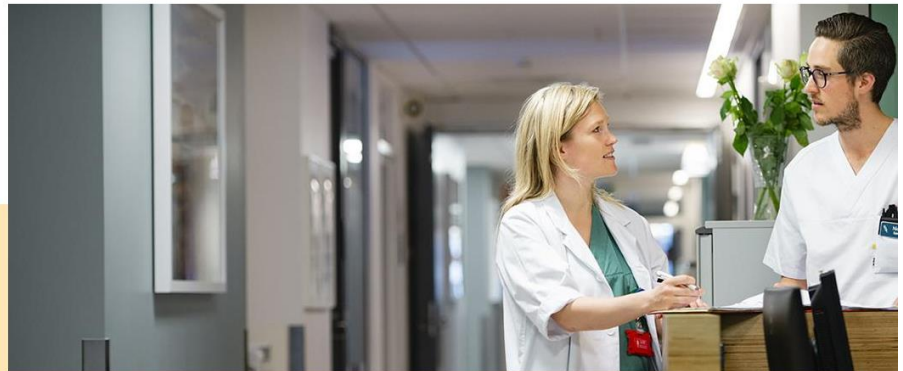
# Kvalitative og kvantitative studier – mixed methods

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



LOGG INN  
HelsaMi

SØK 🔍



Felles pasientjournal i Midt-Norge

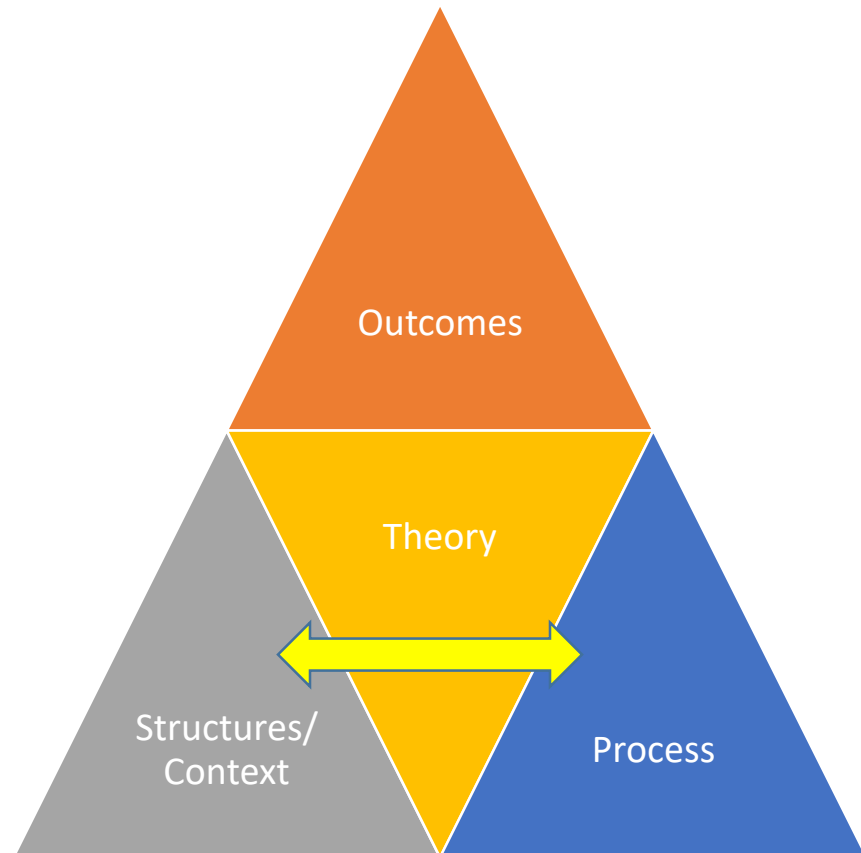


# Registre => En lærende helsetjeneste

- Data om eksponisjon 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





Spørsmål eller kommentarer:

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