Kliiniset kokeet

Jouko Miettunen, dosentti
Psykiatrian klinikka, OY
Oulu 23.9.2013

Esityksen sisältö

- Kliinisten kokeiden taustaa
- Kliinisten kokeiden alatyypit
- Tilastomenetelmät
  - voimalaskelmat
- Interventiot
- CONSORT statement

Kokeellinen vs. epäkokeellinen tutkimus

Kokeellinen tutkimus *(experimental study)*

- tutkija päättää käsittelyn eli altistuksen, järjestää koetilanteen
- vertaillaan tuloksia altistuksen saaneessa ryhmässä ja muissa ryhmissä

Epäkokeellinen tutkimus *(non-experimental study, observational study)*

- tutkijalla ei ole päätäntävaltaa altistukseen, eli eri altistusryhmät muodostuvat tutkijasta riippumatta, eikä altistusryhmien vertailukelpoisuutta ole
- ei aktiivisesti vaikuteta altistumisen jakautumiseen tutkittavien kesken, eli ei sisällä interventiota tai koetta
- tutkija toimii vain havainnoijana

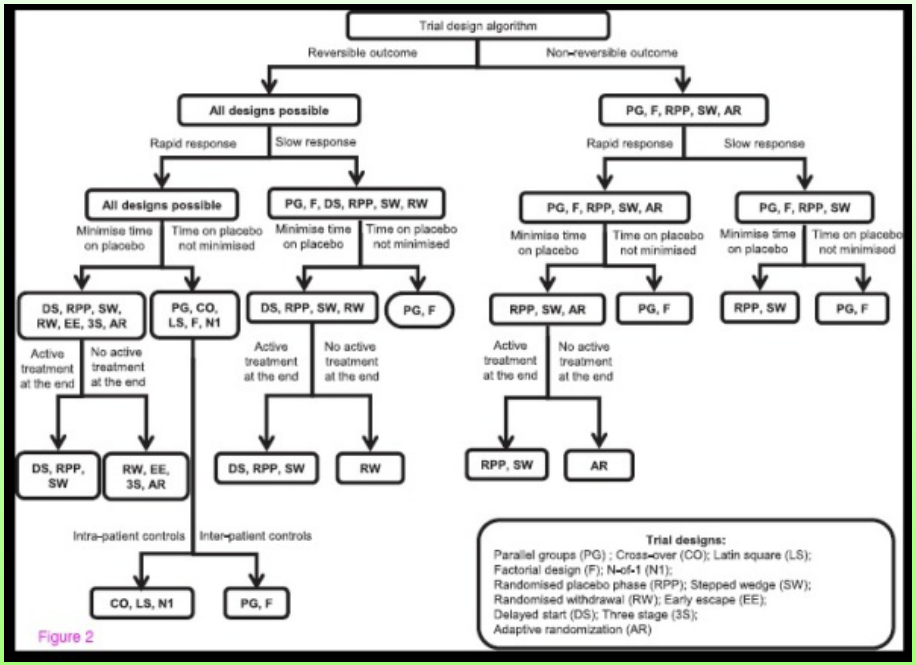
Taustaa kliinisille kokeille

- Kokeelliset (*experimental*) tutkimukset
- Randomized Controlled Trial (RCT)
  - verrataan uutta hoitoa (lääke, terapia tms.) joko lume- eli plasebohoitoon tai aiempaan vallitsevaan lääkkeeseen
- Interventiot

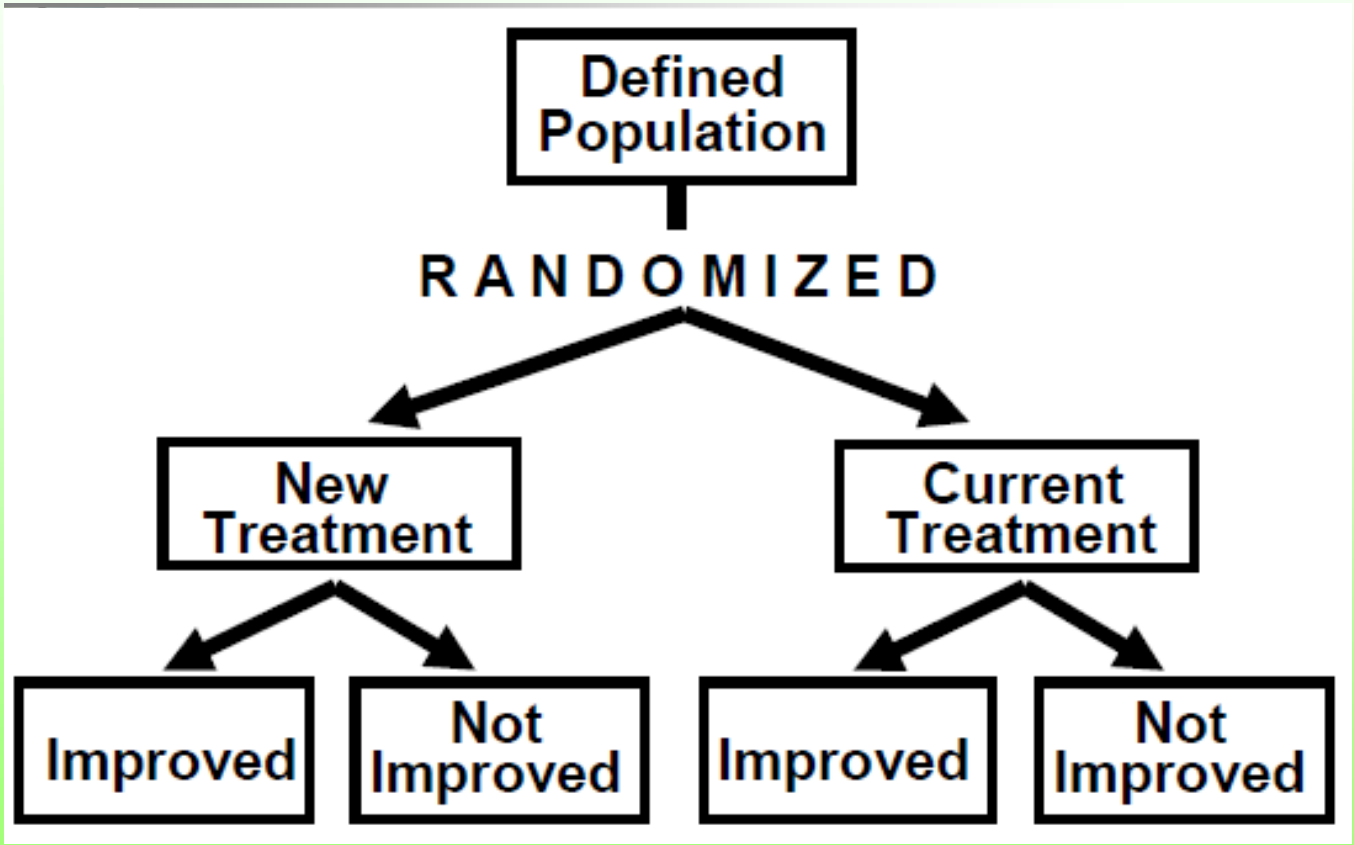
Clinical Trial Phases

	Phase 1	Phase 2	Phase 3	Phase 4
Number of participants	15-30 people	Less than 100 people	Generally, from 100 to thousands of people	Several hundred to several to thousand people
Purpose	• To find a safe dosage • To decide how the agent should be given • To observe how the agent affects the human body	• To determine if the agent or intervention has an affect on a particular cancer • To see how the agent or intervention affects the human body	• To compare the new agent or intervention (or new use of a treatment) with the current standard	• To further evaluate the long- term safety and effectiveness of a new treatment

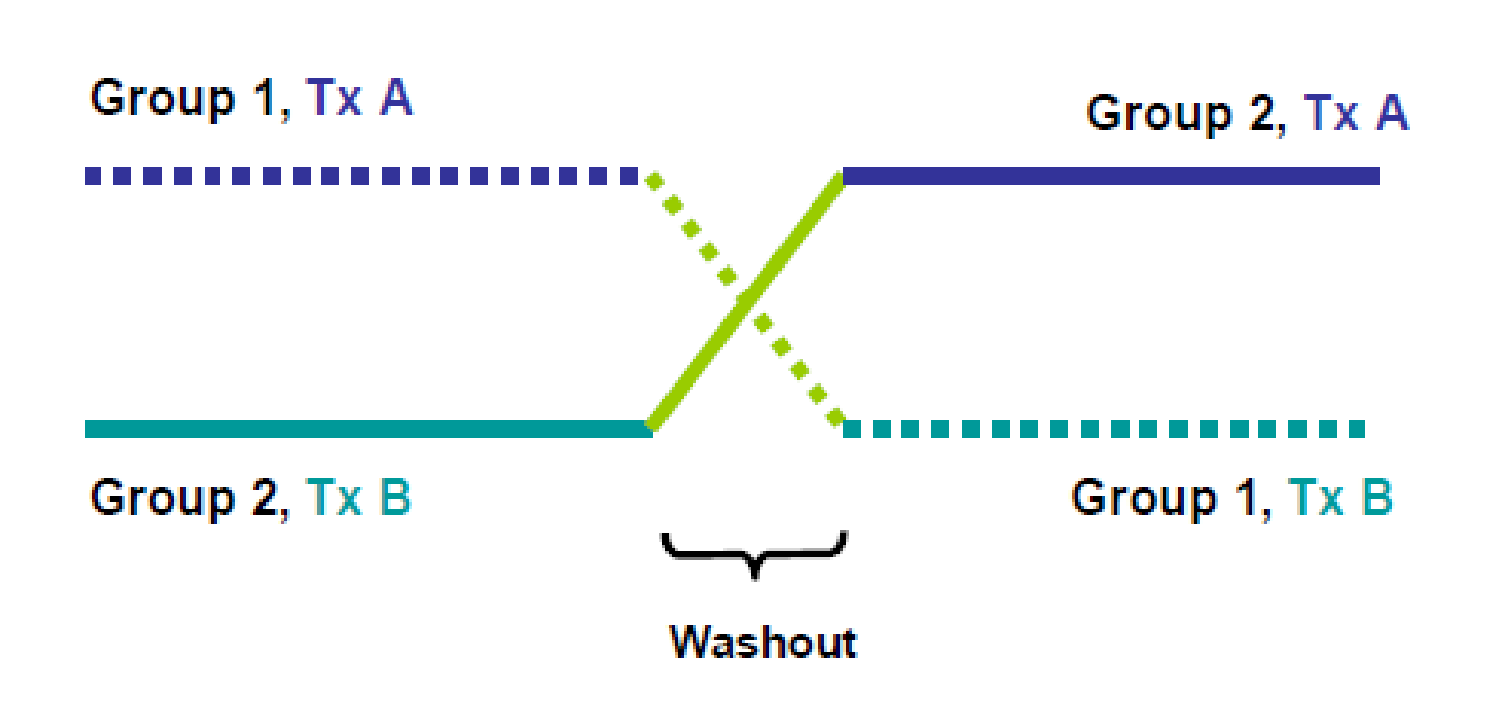
Asetelmat


Trial design algorithm
Reversible outcome
Non-reversible outcome
All designs possible
PG, F, RPP, SW, AR
Rapid response
Slow response
Rapid response
Slow response
All designs possible
PG, F, DS, RPP, SW, RW
PG, F, RPP, SW, AR
PG, F, RPP, SW
Minimise time on placebo
Time on placebo not minimised
Minimise time on placebo
Time on placebo not minimised
Minimise time on placebo
Time on placebo not minimised
Minimise time on placebo
Time on placebo not minimised
DS, RPP, SW, RW, EE, 3S, AR
PG, CO, LS, F, N1
DS, RPP, SW, RW
PG, F
RPP, SW, AR
PG, F
RPP, SW
PG, F
Active treatment at the end
No active treatment at the end
Active treatment at the end
No active treatment at the end
Active treatment at the end
No active treatment at the end
DS, RPP, SW
RW, EE, 3S, AR
DS, RPP, SW
RW
RPP, SW
AR
Intra-patient controls
Inter-patient controls
CO, LS, N1
PG, F
Trial designs:
Parallel groups (PG) ; Cross-over (CO); Latin square (LS);
Factorial design (F); N-of-1 (N1);
Randomised placebo phase (RPP); Stepped wedge (SW);
Randomised withdrawal (RW); Early escape (EE);
Delayed start (DS); Three stage (3S);
Adaptive randomization (AR)
Figure 2

parallel design

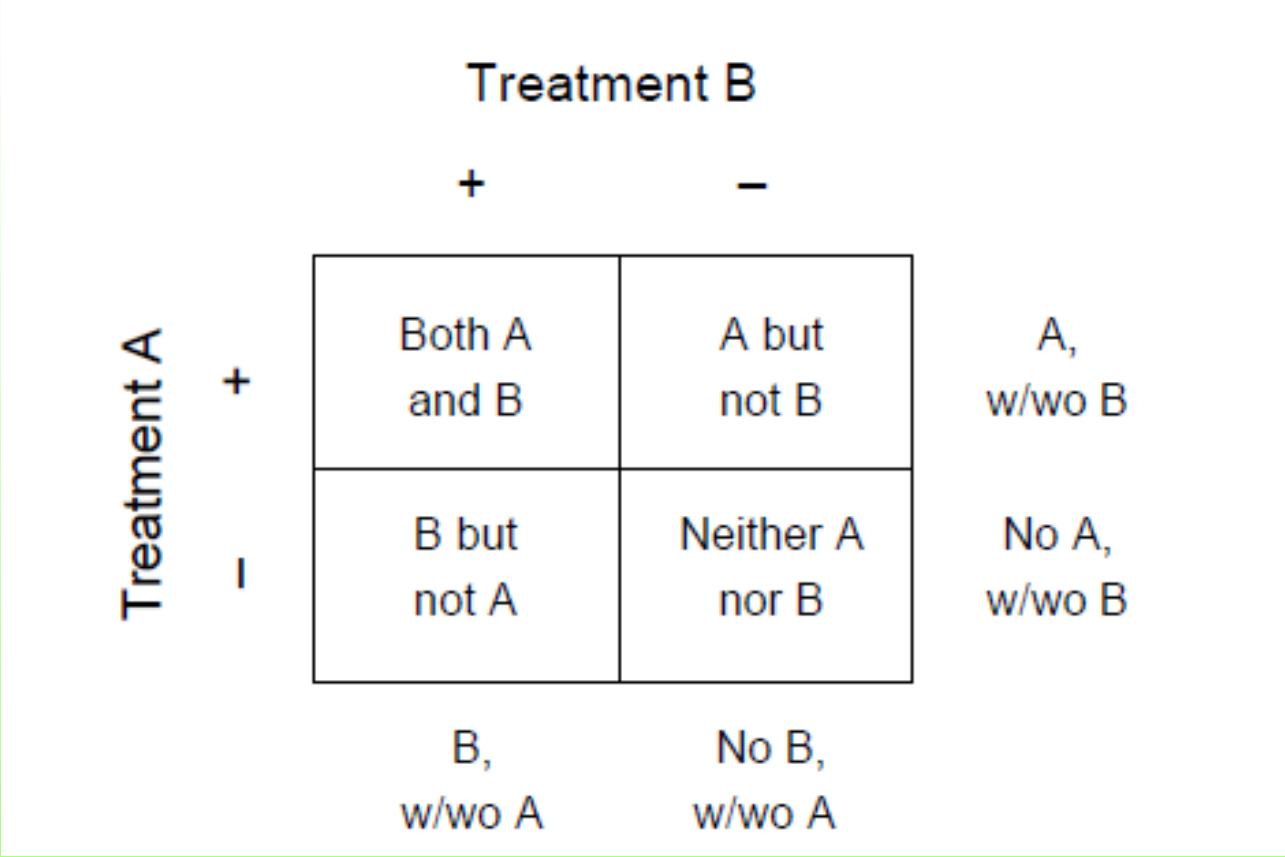


cross-over design



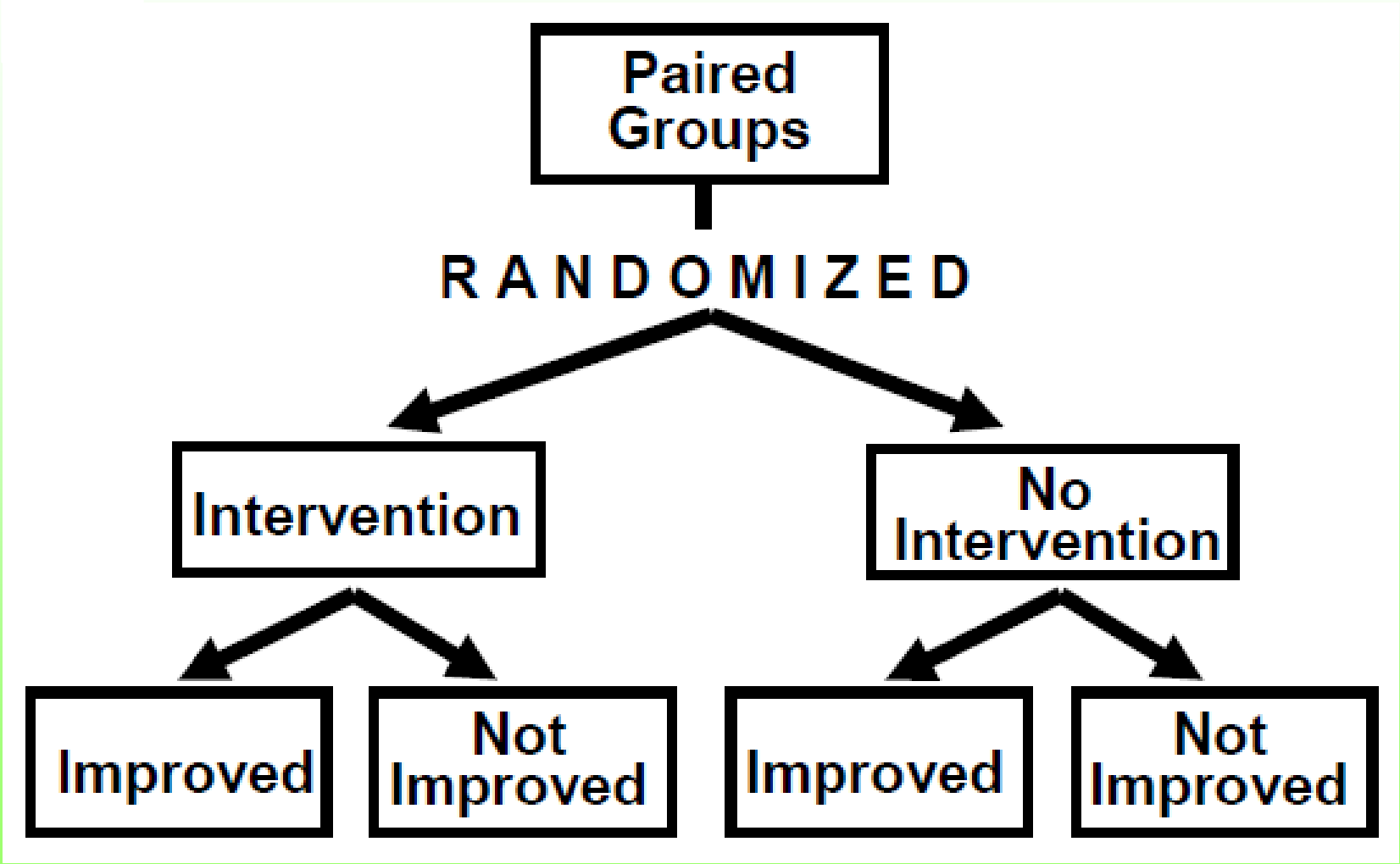
- hoidoilla ei saa olla pysyviä vaikutuksia

factorial design



- testataan samalla useita hoitoja
- taloudellinen

group allocation design



esim. tupakointi interventiot kouluihin

vertailuasetelmat

- *superiority design*
  - testataan onko uusi laite tai hoito parempi kuin vanha
- *equivalence design*
  - testataan onko uusi laite tai hoito yhtä hyvä kuin vanha
- *non-inferiority design*
  - testataan että uusi laite tai hoito ei ole huonompi kuin vanha

Effectiveness vs. Efficacy

- **Explanatory trial / selittävä koe**
  - tehoaako/vaikuttaako hoito tms. ihanneoloissa (*efficacy*)
  - kontrolloidaan tutkimus tarkasti
  - *internal validity*
- **Pragmatic trial / pragmaattinen koe**
  - tehoaako/vaikuttaako hoito käytännön elämässä (*effectiveness*)
  - Yleistettävyys
  - *external validity*

Table 1 | Key differences between trials with explanatory and pragmatic attitudes, adapted from a table presented at the 2008 Society for Clinical Trials meeting by Marion Campbell, University of Aberdeen

Question	Efficacy—can the intervention work?
Setting	Well resourced, "ideal" setting
Participants	Highly selected. Poorly adherent participants and those with conditions which might dilute the effect are often excluded
Intervention	Strictly enforced and adherence is monitored closely
Outcomes	Often short term surrogates or process measures
Relevance to practice	Indirect—little effort made to match design of trial to decision making needs of those in usual setting in which intervention will be implemented

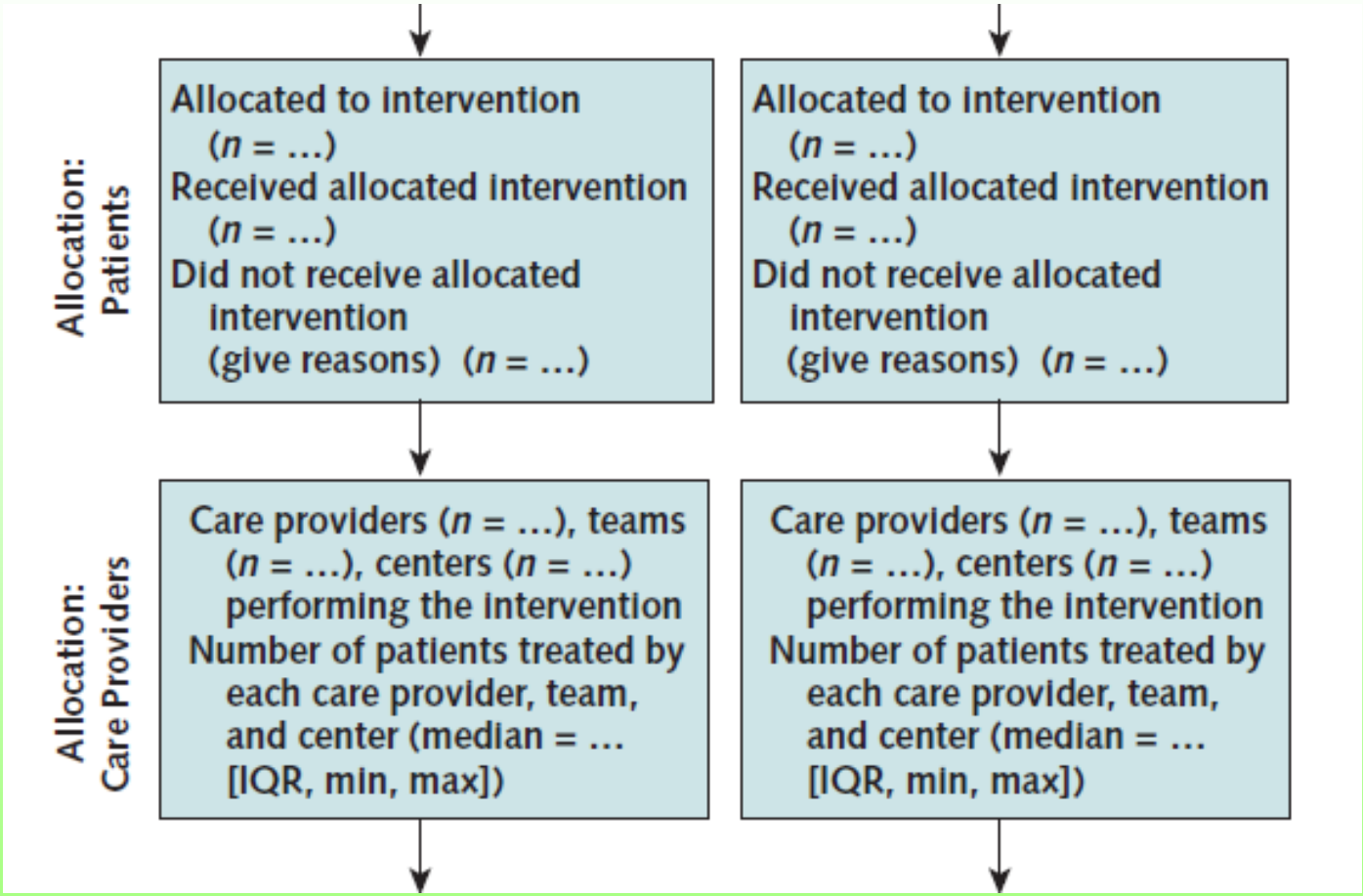
Zwarenstein M, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008; 337;a2390.

Table 1 | Key differences between trials with explanatory and pragmatic attitudes, adapted from a table presented at the 2008 Society for Clinical Trials meeting by Marion Campbell, University of Aberdeen

Question	Effectiveness—does the intervention work when used in normal practice?
Setting	Normal practice
Participants	Little or no selection beyond the clinical indication of interest
Intervention	Applied flexibly as it would be in normal practice
Outcomes	Directly relevant to participants, funders, communities, and healthcare practitioners
Relevance to practice	Direct—trial is designed to meet needs of those making decisions about treatment options in setting in which intervention will be implemented

Zwarenstein M, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008; 337;a2390.

muut kuin lääkehoidot



Boutron I, Moher D, Altman DG, Schulz K, Ravaud P, for the CONSORT group. Methods and Processes of the CONSORT Group: Example of an Extension for Trials Assessing Nonpharmacologic Treatments. Ann Intern Med. 2008:W60-W67.

Tutkimusetiikka

"This new mandatory STD vaccine shouldn't hurt a bit."

Tutkimusetiikka

- Eettinen lupa tutkimukselle
- Kliinisen kokeiden rekisteröinti
- Declaration of Helsinki
  - Ihmiskokeiden eettiset säännöt

EETTINEN TOIMIKUNTA

Pohjois-Pohjanmaan sairaanhoitopiiriin alueellinen eettinen toimikunta toimii potilas-/asiakaskeskeisesti. Toimikunta ohjaa, tukee sekä auttaa tutkijoita ja tutkijayhteisöjä tekemään eettisen arvioinnin kestävää tutkimusta lääketieteellisestä tutkimuksesta annetun lain ja asetuksen, sosiaali- ja terveysministeriön asetuksen ja eettisten toimikuntien työskentelyä ohjaavien muiden säädösten mukaan.

Eettisen toimikunnan tehtävänä on arvioida ennakolta tutkimushankkeet ja antaa niistä lausunto. Hankkeen käsittelee se eettinen toimikunta, jonka alueella tutkimuksesta vastaava henkilö toimii tai jonka alueella tutkimus on pääasiassa tarkoitus suorittaa. Huomioitava on, että eettisen toimikunnan lausunto ei ole vielä lupa tehdä tutkimusta. Pohjois-Pohjanmaan sairaanhoitopiirin alueella tutkimusluvan antaa laitoksen-/tulos-/vastuualueen johtaja ja/tai esimies.

Kliinisistä lääketutkimuksista lausunnon antaa Sosiaali- ja terveysalan lupa- ja valvontaviraston (Valvira) yhteydessä toimiva Lääketieteellinen tutkimuseettinen toimikunta (TUKIJA), jollei lausunnon antamista ole siirretty jonkin alueellisen eettisen toimikunnan tehtäväksi.

Tutkimuslupakäytännöt ja eettisen toimikunnan lausunnon tarve (Hallintokeskuksen tiedote 13/2009).

Tutkimuslupaprosessi "pähkinänkuoressa"

Eettinen toimikunta selvittää lausuntoaan varten, onko tutkimussuunnitelmassa otettu huomioon tutkimuslain säännökset, tietosuojasäännökset, tutkittavien asemaa koskevat kansainväliset velvoitteet sekä lääketieteellistä tutkimusta koskevat määräykset ja ohjeet. Eettinen toimikunta seuraa ja ohjaa myös tutkimuseettisten kysymysten käsittelyä alueellaan.

Kokousajat ja aineiston lähettäminen

Ohjeita

Lausuntomaksut

Toimikunnan jäsenet ja asiantuntijat

Lait, asetukset ja muut ohjeet

Pohjois-Pohjanmaan sairaanhoitopiiri

IHMISTIETEIDEN EETTINEN TOIMIKUNTA

OULUN YLIOPISTO
UNIVERSITY of OULU

Ihmistieteisiin liittyvän tutkimuksen eettisen ennakkoarvioinnin järjestämiseksi Oulun yliopistossa on perustettu ihmistieteiden eettinen toimikunta. Sen tehtävänä on antaa lausuntoja ihmistieteisiin liittyvän tutkimuksen alalta. Se toimii tiiviissä yhteystyössä Pohjois-Pohjanmaan sairaanhoitopiirin eettisen toimikunnan kanssa.

Ihmistieteiden eettinen toimikunta antaa lausuntoja tutkimuksista, joissa on Tutkimuseettisen neuvottelukunnan suositusten mukaisesti suoritettava eettinen ennakkoarviointi. Lisäksi tutkija pyytää eettisen toimikunnann lausuntoa, jos tutkimuskohde, tutkimuksen rahoittaja tai yhteistyökumppani sitä edellyttää, tai jos tutkimustuloksia suunnitellaan julkaistavan tiedelehdessä, joka edellyttää eettistä ennakkoarviointia. Opinnäytetyön osalta opiskelija tekee lausuntopyynnön yhdessä ohjaajansa kanssa.

Jäsenet:

professori Matti Lehtihalmes, puheenjohtaja, humanistinen tiedekunta
yliopiston lehtori Leena Kuure, humanistinen tiedekunta
tutkimusprofessori Arja Rautio, Thule-instituutti
professori Seppo Saarela, luonnontieteellinen tiedekunta
professori Tapio Seppänen, teknillinen tiedekunta
yliopistonlehtori Vappu Sunnari, kasvatustieteiden tiedekunta
professori Jaana Tähtinen, taloustieteiden tiedekunta
professori Juha Veijola, lääketieteellinen tiedekunta.

“*Informed consent*”

In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail.

He or she should be informed that he or she is a liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time.

The physician should then obtain the subject's freely-given informed consent, preferably in writing.

Declaration of Helsinki (1964-)

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

ClinicalTrials.gov currently lists 152,223 studies with locations in all 50 states and in 184 countries.

Text Size

Search for Studies

Example: "Heart attack" AND "Los Angeles"

Search

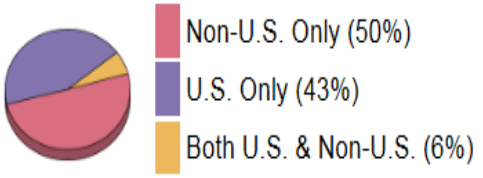
Advanced Search | See Studies by Topic

See Studies on a Map

Search Help

- How to search
- How to find results of studies
- How to read a study record

Locations of Recruiting Studies



Total N = 30,990 studies

Data as of September 17, 2013

- See more trends, charts, and maps

For Patients & Families

- How to find studies
- See studies by topic
- Learn about clinical studies
- Learn more...

For Researchers

- How to submit studies
- Download content for analysis
- About the results database
- Learn more...

For Study Record Managers

- Why register?
- How to register study records
- FDAAA 801 Requirements
- Learn more...

Learn More

- ClinicalTrials.gov Online Training
- Glossary of common site terms

For the Press

Using our RSS Feeds

clinicaltrials.gov (18.9.2013)

Study and Intervention Type		Number of Registered Studies and Percentage of Total	Number of Studies With Posted Results and Percentage of Total***
Total		152,296	9,926
Interventional		123,346 (80%)	9,286 (93%)
Type of Intervention*	**Drug or biologic**	81,818	7,890
	Behavioral, other	31,113	1,110
	Surgical procedure	13,767	422
	Device**	11,127	858
Observational		28,236 (18%)	640 (6%)
Expanded Access		215	N/A

CONSORT statement

Please join CONSORT in supporting the All Trials campaign to get all clinical trial results reported.

Reporting Examples

Submit Example

If you find an example of good reporting, login here to submit it to our Library.

Welcome to the CONSORT Statement Website

CONSORT, which stands for Consolidated Standards of Reporting Trials, encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials (RCTs).

The main product of CONSORT is the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting RCTs. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.

The CONSORT Statement comprises a 25-item checklist and a flow diagram, along with some brief descriptive text. The checklist items focus on reporting how the trial was designed, analyzed, and interpreted; the flow diagram displays the progress of all participants through the trial.

Considered an evolving document, the CONSORT Statement is subject to periodic changes as new evidence emerges. This website contains the current definitive version of the CONSORT Statement and up-to-date information on extensions.

News

In Memoriam

Dr. Vincent Kokich, Editor-in-Chief of the American Journal of Orthodontics and Dentofacial Orthopedics (AJODO) and strong promoter of CONSORT and PRISMA passes away

Read more

Peer Review Congress in Chicago in September 2013

Two new EQUATOR events at the upcoming Peer Review Congress in Chicago in September 2013 - Workshop Registration is now open.

Read more

CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials

David Moher,[1] Sally Hopewell,[2] Kenneth F Schulz,[3] Victor Montori,[4] Peter C Gøtzsche,[5] P J Devereaux,[6] Diana Elbourne,[7] Matthias Egger,[8] Douglas G Altman[2]

Title and abstract

- Identification as a randomised trial in the title
- Structured summary of trial design, methods, results, and conclusions

Background and objectives

- Scientific background and explanation of rationale
- Specific objectives or hypotheses

Table 2 | Items to include when reporting a randomised trial in a journal abstract

Item	Description
Authors	Contact details for the corresponding author
Trial design	Description of the trial design (such as parallel, cluster, non-inferiority)
Methods:	
Participants	Eligibility criteria for participants and the settings where the data were collected
Interventions	Interventions intended for each group
Objective	Specific objective or hypothesis
Outcome	Clearly defined primary outcome for this report
Randomisation	How participants were allocated to interventions
Blinding (masking)	Whether participants, care givers, and those assessing the outcomes were blinded to group assignment
Results:	
Numbers randomised	Number of participants randomised to each group
Recruitment	Trial status
Numbers analysed	Number of participants analysed in each group
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision
Harms	Important adverse events or side effects
Conclusions	General interpretation of the results
Trial registration	Registration number and name of trial register
Funding	Source of funding

Methods

Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines

- Intervention valinta
  - Lääkkeen ja vertailulääkkeen annos ?
  - Tutkimuksen kesto ?

Otoskoko

Power analysis - otoskokolaskelma

- huolelliset aineistokokolaskelmat tulisi sisällyttää jokaiseen hyvin tehtyyn tutkimussuunnitelmaan
- tutkimuksia tehdään paljon liian pienillä aineistoilla!

Power analysis - otoskokolaskelma

- Kliinisten kokeiden otoskoot ovat pieniä, esim.
  - nivelreuman hoidossa mediaani otoskoko 54 potilasta (196 koetta)
  - Ihotaudeissa mediaani 46 potilasta (73 koetta)
  - skitsofreniassa 65 potilasta (2000 koetta)
- Otoskokoa perustellaan erittäin harvoin!
- Voiman post hoc laskeminen on turhaa, luottamusvälit kertovat voimasta

Moher ym. CONSORT statement 2010

Power analysis - otoskokolaskelma

Tarvittavat tiedot

- Henkilöiden määrä
- Vasteen esiintyvyys, jakauma (odotettu tapahtumien määrä)

Tehtävät oletukset

- Vaikutuksen suuruus
- Merkitsevyystaso (α)
- Tilastollinen voima (1-β)

- Tutkimusasetelma
  - Kliinisessä kokeessa pienempi otoskoko riittää
- Varianssin merkitys
  - Isompi varianssi vaatii isomman aineiston ryhmien eron tunnistamiseksi
- Oletettava vaikutus eli *effect size*
- Seurantatutkimuksissa huomioitava kato!

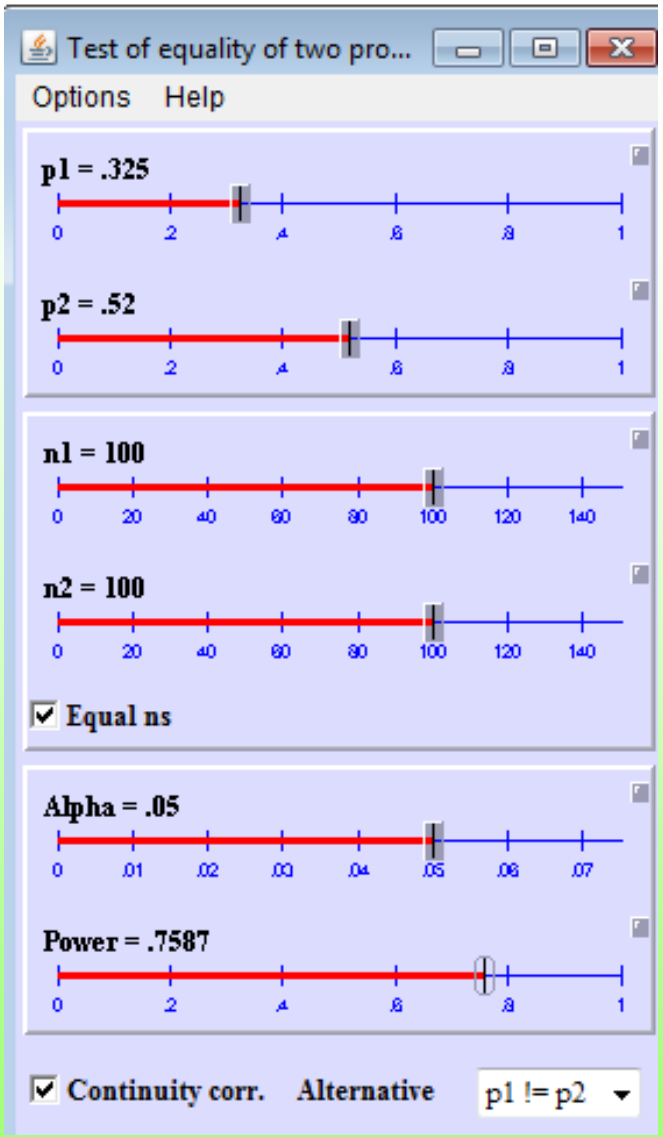
Suresh KP & Chandrashekara S. Sample size estimation and power analysis for clinical research studies. J Hum Reprod Sci 2012; 5(1): 7–13.

- Alpha eli merkitsevyystaso (esim. 0.05 tai 5%)
  - Todennäköisyys etä ero löytyy vaikka sitä ei ole olemassa (väärä positiivinen löydös)
- Beta eli voima (power) (esim. 0.8 tai 80%)
  - Todennäköisyys jolla ero löytyy jos se on olemassa

- Välianalyysi ”*interim analysis*” on mikä tahansa etukäteen suunniteltu kliinisen tutkimuksen kuluessa suoritettu analyysi.
  - Syyt suorittamiseen ovat joko eettisiä tai taloudellisia.
  - α - virhe kasvaa.

Suresh KP & Chandrashekara S. Sample size estimation and power analysis for clinical research studies. J Hum Reprod Sci 2012; 5(1): 7–13.

- Useita eri tilanteita
  - Keskiarvojen ero
  - Suhteellisten osuuksien ero
  - Monimuuttujamallit?
- Erilaisia ohjelmia voiman laskemiseksi
  - Useita nettilaskureita
  - Spesifejä ohjelmia
    - SPSS sample power, …



http://homepage.stat.uiowa.edu/~rlenth/Power/index.html

Methods

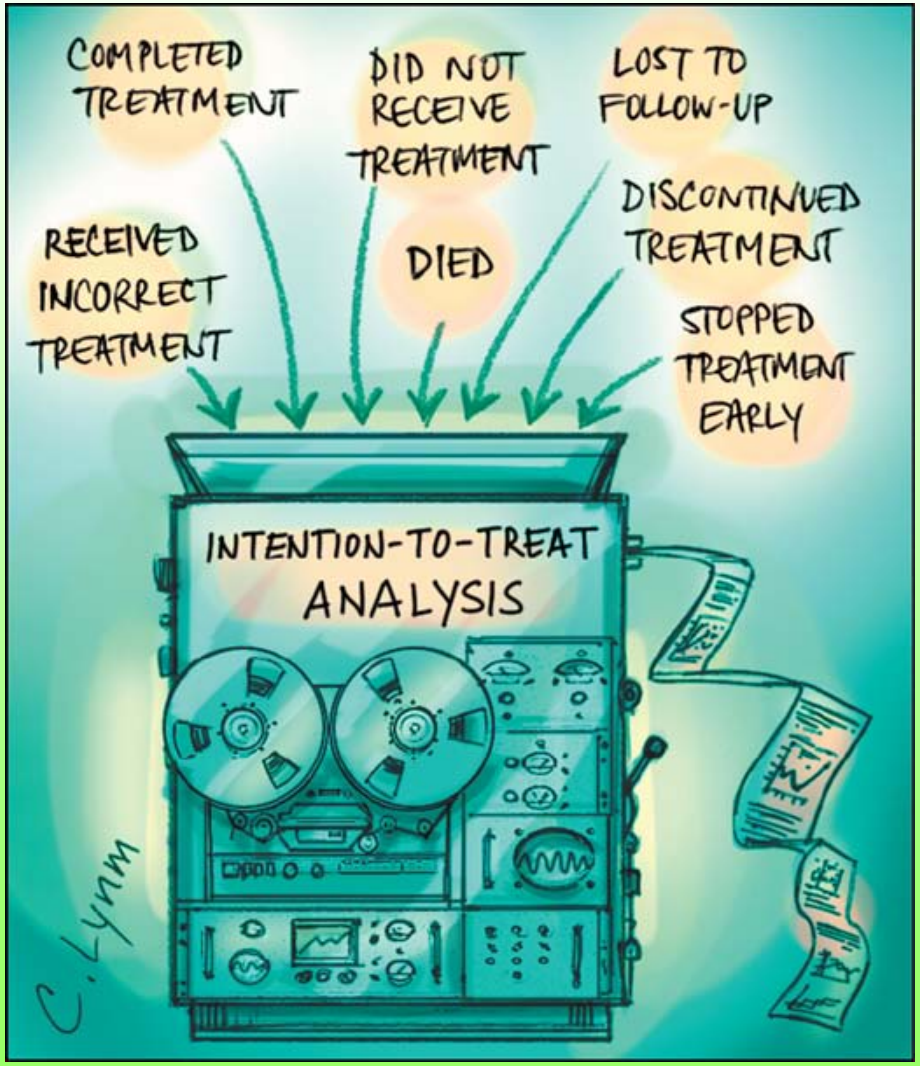
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses

- Sokkoutus
  - potilas / osallistuja ?
  - tutkija / hoitava lääkäri ?
  - vasteen arvioija ?
  - analyysien tekijä ?

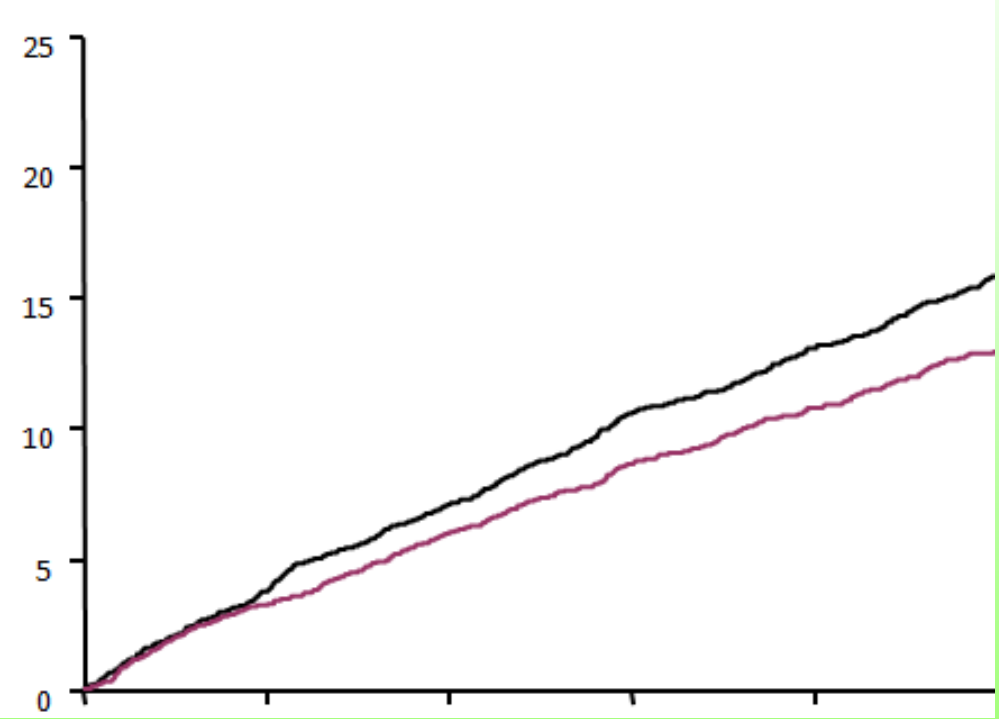
Intention-to-treat

- Hoitoaikeen mukainen analyysi eli tulokset analysoidaan alkuperäisen satunnaistamisen mukaan ei toteutuneen hoidon mukaan!

säilyttää satunnaistamisen vaikutuksen!



Results



Results

Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[42])

- tilastomenetelmät esitettävä selkeästi
- luottamusvälit ensisijainen vaikutuksen varmuuden kuvaaja
- tarkat p-arvot (ei <0.05 tms.)

Table 1. Statistical baseline comparisons in a randomized trial. By chance, the groups differ in median albumin scores ($P = 0.03$); the difference does not indicate selection bias. Here, P values need not be reported for this reason

Variable	Control (n = 43)	Treatment (n = 51)	Difference	P
Median age (years)	85	84	1	0.88
Men (n, %)	21 (49)	21 (51)	3%	0.99
Median albumin (g/L)	30.0	33.0	3.0 g/L	0.03
Diabetes (n,%)	11 (26)	8 (20)	6%	0.83

Assuming that alpha is set at 0.05, of every 100 baseline comparisons in randomized trials, 5 should be statistically significant, just by chance. However, one study found that among 1,076 baseline comparisons in 125 trials, only 2% were significant at the 0.05 level (23).

Twenty Statistical Errors Even *YOU* Can Find in Biomedical Research Articles

Tom Lang. Croatian Medical Journal 2004;45:361-70

Haittojen raportointi puutteellista

1. Using generic or vague statements, such as “the drug was generally well tolerated” or “the comparator drug was relatively poorly tolerated.”

2. Failing to provide separate data for each study arm.

3. Providing summed numbers for all adverse events for each study arm, without separate data for each type of adverse event.

4. Providing summed numbers for a specific type of adverse event, regardless of severity or seriousness.

5. Reporting only the adverse events observed at a certain frequency or rate threshold (for example, _3% or _10% of participants).

6. Reporting only the adverse events that reach a *P* value threshold in the comparison of the randomized arms (for example, *P* _ 0.05).

7. Reporting measures of central tendency (for example, means or medians) for continuous variables without any information on extreme values.

8. Improperly handling or disregarding the relative timing of the events, when timing is an important determinant of the adverse event in question.

9. Not distinguishing between patients with 1 adverse event and participants with multiple adverse events.

10. Providing statements about whether data were statistically significant without giving the exact counts of events.

11. Not providing data on harms for all randomly assigned participants.

Ioannidis JP, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004; 141(10):781-788.

Haittojen arviointiin sopii myös havaintotutkimukset!

Monitestausongelma

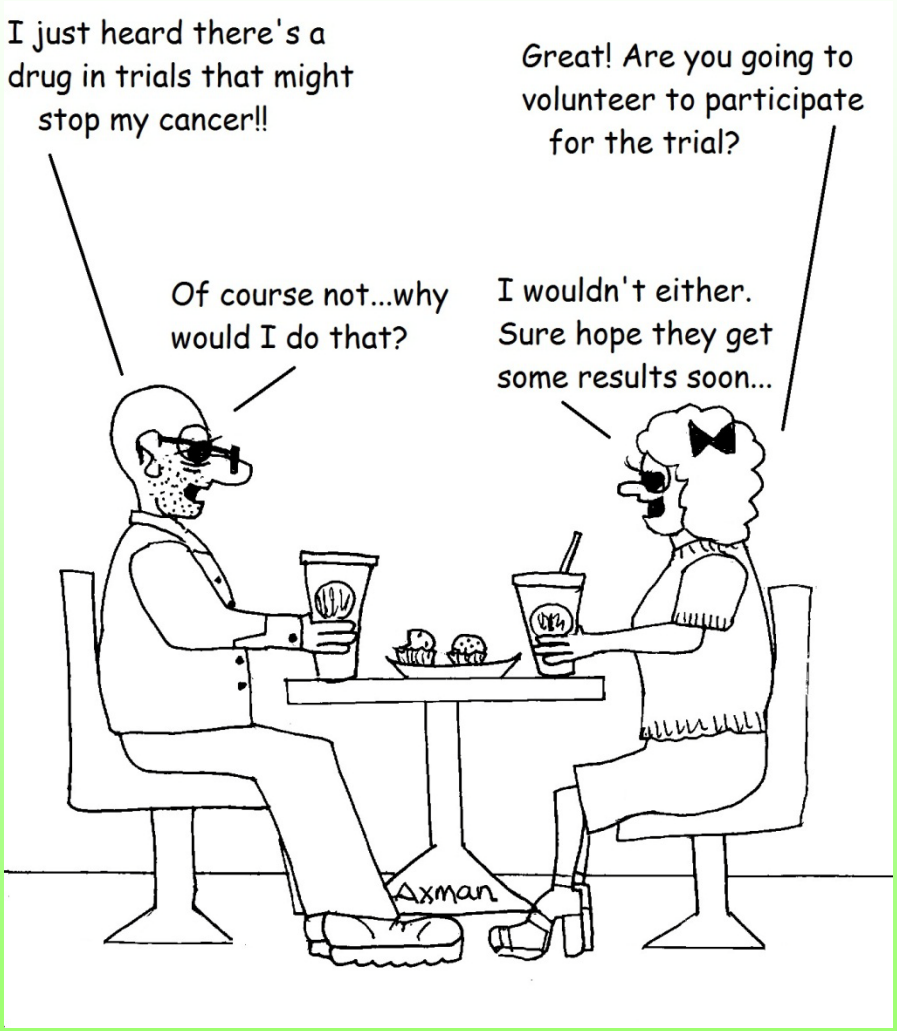
Table 3 | Information required to document the flow of participants through each stage of a randomised trial

Stage	Number of people included	Number of people not included or excluded	Rationale
Enrolment	People evaluated for potential enrolment	People who did not meet the inclusion criteria or met the inclusion criteria but declined to be enrolled	These counts indicate whether trial participants were likely to be representative of all patients seen; they are relevant to assessment of external validity only, and they are often not available.
Randomisation	Participants randomly assigned		Crucial count for defining trial size and assessing whether a trial has been analysed by intention to treat
Treatment allocation	Participants who completed treatment as allocated, by study group	Participants who did not complete treatment as allocated, by study group	Important counts for assessment of internal validity and interpretation of results; reasons for not receiving treatment as allocated should be given.
Follow-up	Participants who completed treatment as allocated, by study group	Participants who did not complete treatment as allocated, by study group	Important counts for assessment of internal validity and interpretation of results; reasons for not completing treatment or follow-up should be given.
	Participants who completed follow-up as planned, by study group	Participants who did not complete follow-up as planned, by study group	
Analysis	Participants included in main analysis, by study group	Participants excluded from main analysis, by study group	Crucial count for assessing whether a trial has been analysed by intention to treat; reasons for excluding participants should be given.

- seurannan kesto ja onnistuminen ?
  - Jos alle 80% mukana lopullisissa analyyseissa, tuloksia ei pitäisi ottaa huomioon ! (EBM toolkit).

osallistuminen

- potilaat ja lääkärit osallistuvat huonosti kliinisiin kokeisiin
- lääkäri haluavat päättää potilaidensa hoidosta
- usko standardihoitoon on vahva
- esim. syöpäpotilaista vain 3% osallistuu



Lieberman JA, et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry. 2005 Apr;62(4):361-70.

OBJECTIVE:
To test a priori hypotheses that olanzapine-treated patients have less change over time in whole brain gray matter volumes and lateral ventricle volumes than haloperidol-treated patients.
DESIGN:
Longitudinal, randomized, controlled, multisite, double-blind study. Patients treated and followed up for up to 104 weeks. Neurocognitive and magnetic resonance imaging (MRI) assessments performed at weeks 0 (baseline), 12, 24, 52, and 104.
INTERVENTIONS:
Random allocation to a conventional antipsychotic, haloperidol (2-20 mg/d), or an atypical antipsychotic, olanzapine (5-20 mg/d).
RESULTS:
Of 263 randomized patients, 161 had baseline and at least 1 postbaseline MRI evaluation. Haloperidol-treated patients exhibited significant decreases in gray matter volume, whereas olanzapine-treated patients did not. A matched sample of healthy volunteers (n = 58) examined contemporaneously showed no change in gray matter volume.
CONCLUSIONS:
Patients with first-episode psychosis exhibited a significant between-treatment difference in MRI volume changes. Haloperidol was associated with significant reductions in gray matter volume, whereas olanzapine was not. Post hoc analyses suggested that treatment effects on brain volume and psychopathology of schizophrenia may be associated. The differential treatment effects on brain morphology could be due to haloperidol-associated toxicity or greater therapeutic effects of olanzapine.

Table 2. Changes in MRI Volumes for Primary Regions of Interest by Treatment Group (Baseline to Weeks 12, 24, 52, and 104)

		Observed Case Mean Changes From Baseline and Mixed-Model *P* Values								
		Baseline	Week 12				Week 24			
ROI	Therapy	N	Mean (SE), cm³	N	Mean (SE), cm³	*P* Value*	*P* Value†	N	Mean (SE), cm³	*P* Value*
CN	Olz	80	8.89 (0.19)	71	−0.36 (0.13)	.12	.18	64	−0.23 (0.15)	.03
	Hal	77	8.62 (0.15)	68	0.03 (0.13)		.92	46	−0.04 (0.14)	
	Con	52	9.09 (0.16)	52	−0.01 (0.15)					

		Week 52				Week 104		
ROI	Therapy	N	Mean (SE), cm³	*P* Value*	*P* Value†	N	Mean (SE), cm³	*P* Value*
CN	Olz	42	−0.52 (0.16)	.02	.003	25	−0.30 (0.28)	.04
	Hal	31	0.12 (0.18)		.58	10	0.39 (0.37)	
	Con	44	0.17 (0.13)					

Abbreviations: CN, caudate nucleus; Con, control; Hal, haloperidol; LV, lateral ventricle; MRI, magnetic resonance imaging; Olz, olanzapine; ROIs, regions of interest; TV, third ventricle; WB, whole brain; WBF, whole brain fluid; WBGM, whole brain gray matter; WBWM, whole brain white matter.

**P* values are from an F test at each time point, comparing olanzapine- and haloperidol-treated patients with respect to mean change for each ROI from baseline, within the context of a mixed model. Each model contained a random intercept and therapy, therapy by week, therapy by week squared, and duration of illness fixed effects. Each model was fit assuming a compound symmetric covariance structure with different variance components for each therapy.

†*P* values are from an F test at each time point, comparing olanzapine-treated and control patients or haloperidol-treated and control patients with respect to mean change for each ROI from baseline, within the context of a mixed model. Each model contained a random intercept fixed effects for therapy and the therapy × week interaction. The model was fit assuming a compound symmetric covariance structure with different variance components for each of the 3 therapy groups.

Letters to the Editor|November 2006

Is Olanzapine a Brain-Sparing Medication?

Ridha Joober, MD, PhD; Norbert Schmitz, PhD; Ashok Malla, MD; Sarojini Sengupta, PhD; Sherif Karma, MD

Although Lieberman et al took into consideration several possible confounding factors, weight gain induced by neuroleptics was not accounted for. In a previous study, using a sample overlapping with the present one, it was shown that patients treated with olanzapine gained significantly more weight compared with those treated with haloperidol...

In view of some evidence showing that brain ventricles and brain volume could be affected by the overall body weight[3] and nutritional status, controlling for weight gain may be important...

In addition, the fact that patients treated with olanzapine gained gray matter at week 12 is not compatible with the hypothesis of slowing a putative atrophic effect of the disease but rather with other mechanisms of action of olanzapine that may be related to its effects on body mass…

In fact, a formal test for differences in the course of gray matter loss over time could have been provided in the form of treatment × time of assessment interaction (excluding week 104 because of small sample sizes).

tutkimusprotokolla

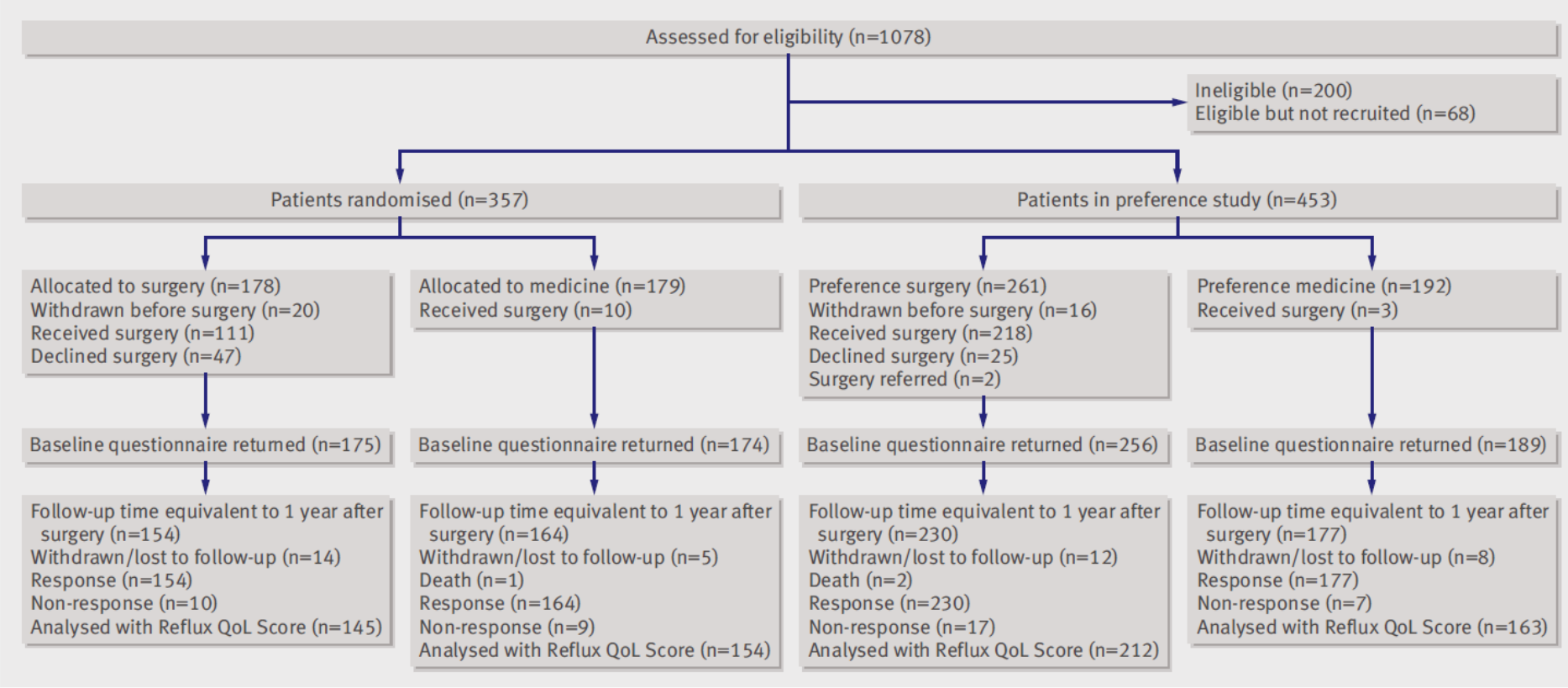


Fig 3 | Flow diagram of minimal surgery compared with medical management for chronic gastro-oesophageal reflux disease (adapted from Grant et al[196]). The diagram shows a multicentre trial with a parallel non-randomised preference group.

Discussion

Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

- Puutteet ?
- Vertailu aiempiin juttuihin ?
- Yleistettävyys ?
- Tulkinta ?
- Johtopäätökset ?

Muuta tietoa

Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

- Kuka tutkimuksen teetti ?
  - Lääkeyhtiö
  - Interventiokeskus
  - Valtio
  - Tutkimuslaitos
  - Muu?

Industry bias

In an analysis of 33 industry-sponsored head-to-head comparisons of SGAs, our blind ratings of abstracts found that 90% favored the sponsor's drug, which provides an answer to our title 'why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine' (Heres *et al*. 2006). However, Davis *et al*. (2008) examined the efficacy effect sizes and found no difference between industry and non-industry sponsored trials, a finding consistent with our two later meta-analyses (SGA *versus* FGA and SGA *versus* SGA; Leucht *et al*. 2009*a*, *b*). We conclude that most of the 'industry sponsorship' effect (Heres *et al*. 2006) is due to the spin that the authors put on the data, which contributes to enormous confusion and creates misinformation. That being said, there are of course some studies with obviously flawed designs such as using too low clozapine doses or omitting a result. Failure to report a specific finding can blur interpretation; for example, positive symptoms have never been published in the single comparison of ziprasidone with amisulpride (Olie *et al*. 2006).

potency FGA comparators. We recommend that each new drug is compared with a low-potency, a mid-potency, and a high-potency FGA. However, in the absence of such data, 'no evidence of effect does not mean evidence of no effect' (Tarnow-Mordi & Healy, 1999).

Leucht ym. Psychol Med 2009; 39:1591-1602

Extensions of the CONSORT Statement

Due to the recent publication of CONSORT 2010, work is underway to update the various CONSORT extensions to reflect the 2010 checklist.

The main CONSORT Statement is based on the 'standard' two-group parallel design. However, there are several different types of randomized trials, some of which have different designs (e.g., cluster), interventions (e.g., herbals) and data (e.g., harms).

To help improve the reporting of these trials the CONSORT Group has been involved in extending and modifying the main CONSORT Statement for application in these various areas, and the resulting CONSORT extensions are presented in this section. This list is, by no means, exhaustive; and work is constantly in progress.

Please note that modifications to the CONSORT checklist or flow diagram that are not developed with the involvement of the CONSORT Group do not have permission to name their work 'CONSORT'.

Shortcuts:

Design Extensions

- *Cluster trials*
- *Non-inferiority and equivalence trials*
- *Pragmatic Trials*

Intervention Extensions

- *Herbal medicinal interventions*
- *Non-pharmacological treatment interventions*
- *Acupuncture Interventions*

Data Extensions

- *Patient-Reported Outcomes*
- *Harms*
- *Abstracts*

Plasebovaikutus

Plasebollakin voi olla vaikutusta

- keskimäärin 35% potilaista saa apua lumelääkkeestä
- plasebovaikutuksen arvioinniksi voi olla kolmas ryhmä jolle ei anneta mitään hoitoa
- psykoterapian efekti?

Are Treatments More Effective than Placebos?

Background: Placebos are widely used in clinical practice in spite of ethical restrictions. Whether such use is justified depends in part on the relative benefit of placebos compared to 'active' treatments. A direct test for differences between placebo and 'active' treatment effects has not been conducted.

Objectives: We aimed to test for differences between treatment and placebo effects within similar trial populations.

Data Sources: A Cochrane Review compared placebos with no treatment in three-armed trials (no treatment, placebo, and treatment). We added an analysis of treatment and placebo differences within the same trials.

Synthesis Methods: For continuous outcomes we compared mean differences between placebo and no treatment with mean differences between treatment and placebo. For binary outcomes we compared the risk ratio for treatment benefit (versus placebo) with the risk ratio for placebo benefit (versus no treatment). We conducted several preplanned subgroup analyses: objective versus subjective outcomes, conditions tested in three or more trials, and trials with varying degrees of bias.

Results: In trials with continuous outcomes ($n=115$) we found no difference between treatment and placebo effects (MD = −0.29, 95% CI −0.62 to 0.05, $P=0.10$). In trials with binary outcomes ($n=37$) treatments were significantly more effective than placebos (RRR = 0.72, 95%CI = 0.61 to 0.86, $P=0.0003$). Treatment and placebo effects were not different in 22 out of 28 predefined subgroup analyses. Of the six subgroups with differences treatments were more effective than placebos in five. However when all criteria for reducing bias were ruled out (continuous outcomes) placebos were more effective than treatments (MD = 1.59, 95% CI = 0.40 to 2.77, $P=0.009$).

Conclusions and Implications: Placebos and treatments often have similar effect sizes. Placebos with comparatively powerful effects can benefit patients either alone or as part of a therapeutic regime, and trials involving such placebos must be adequately blinded.

Citation: Howick J, Friedemann C, Tsakok M, Watson R, Tsakok T, et al. (2013) Are Treatments More Effective than Placebos? A Systematic Review and Meta-Analysis. PLoS ONE 8(5): e62599. doi:10.1371/journal.pone.0062599

“Hawthorne effect”

1924-32 Chicago

Kvasikokeellinen tutkimus

- muistuttaa varsinaista kokeellista tutkimusta
- ei kontrolloida kaikkia muuttujia
- pyritään lähelle todellista kokeellista tarkkuutta kuin olosuhteet sallivat ottaen huolellisesti huomioon ja määritellen poikkeavuudet ja rajoitukset.

Helsinki Businessmen Study

JAMA. 1985 Oct 18;254(15):2097-102.

Multifactorial primary prevention of cardiovascular diseases in middle-aged men. Risk factor changes, incidence, and mortality.

Miettinen TA, Huttunen JK, Naukkarinen V, Strandberg T, Mattila S, Kumlin T, Sarna S.

In a randomized five-year multifactorial primary prevention trial of vascular diseases, hyperlipidemias, hypertension, smoking, obesity, and abnormal glucose tolerance of the high-risk test group (n=612 men) were treated with dietetic-hygienic measures and hypolipidemic (mainly probucol and clofibrate) and antihypertensive (mainly diuretics and β-blockers) agents. A matched high-risk control group (n=610) and a low-risk control group (n=593) were not treated.

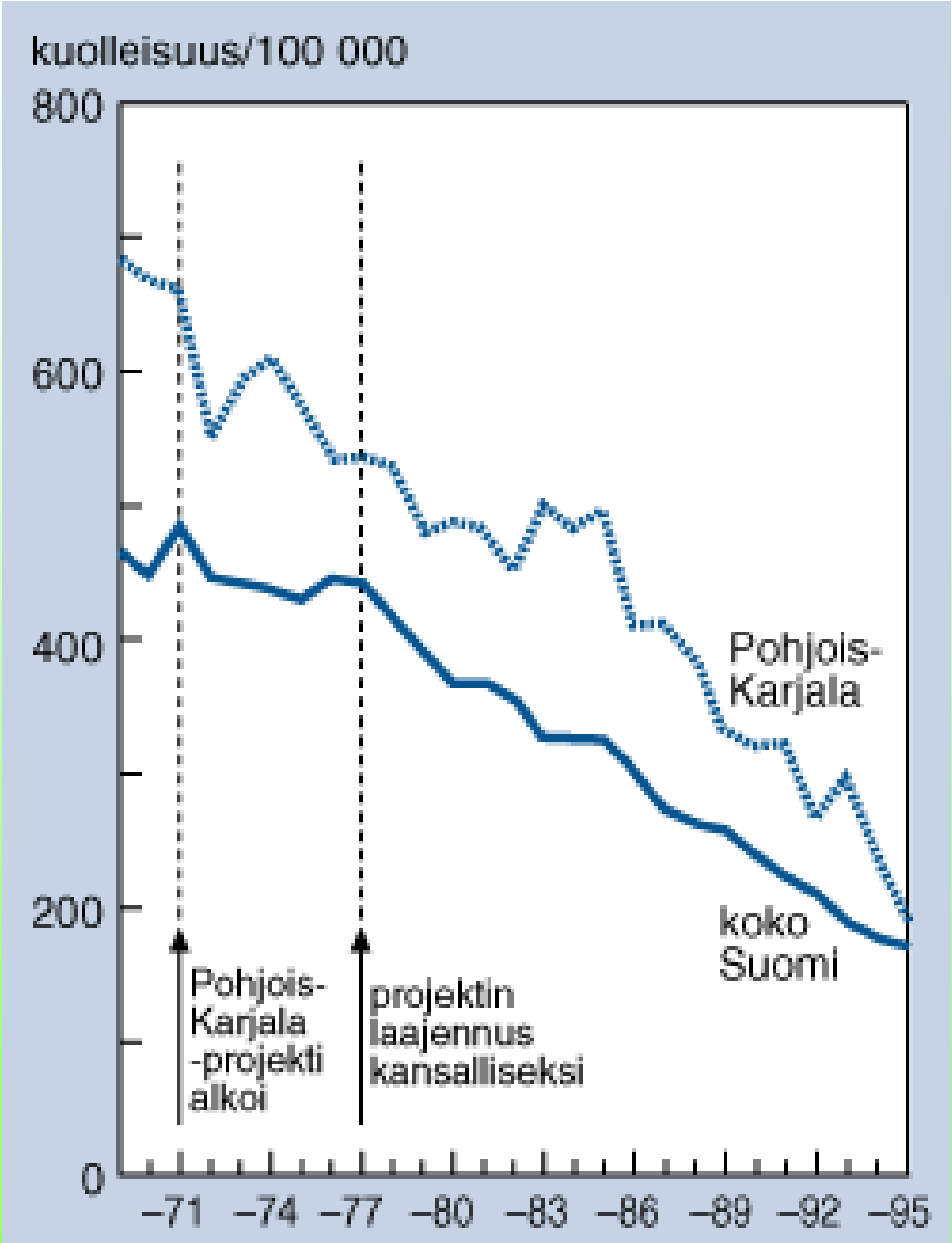
The program markedly improved the risk factor status, yet the five-year coronary incidence tended to be higher in the intervention group than in the control group (3.1% vs 1.5%), while the stroke incidence was significantly reduced (1.3% vs 0%). The coronary events tended to be accumulated in subgroups treated with β-blocking agents or clofibrate, but there were few in those receiving probucol or diuretics. Thus, the intervention program significantly reduced development of stroke, but the occurrence of cardiac events was not prevented. Possible adverse drug effects offsetting the probable benefit of improved risk profile are not excluded.

Väestöinterventio

Pohjois-Karjala projekti

- Sydän- ja verisuonitautien vähentämiseksi tehty väestöinterventio
- Puska ym. The North Karelia Project – 20 year results and experiences. KTL, Helsinki, 1995.

Sepelvaltimotautikuolleisuus koko Suomessa ja Pohjois-Karjalassa 100 000:ta miestä kohti vuosina 1969–1995, 35–64-vuotiaat miehet. Lähde: Kansanterveyslaitos ja tilastokeskus 1997.



Kliiniset kokeet - kirjallisuutta

- www.consort-statement.org
- WHO: Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995