



Patient Preferences and Study Designs of Clinical Trials in Dentistry

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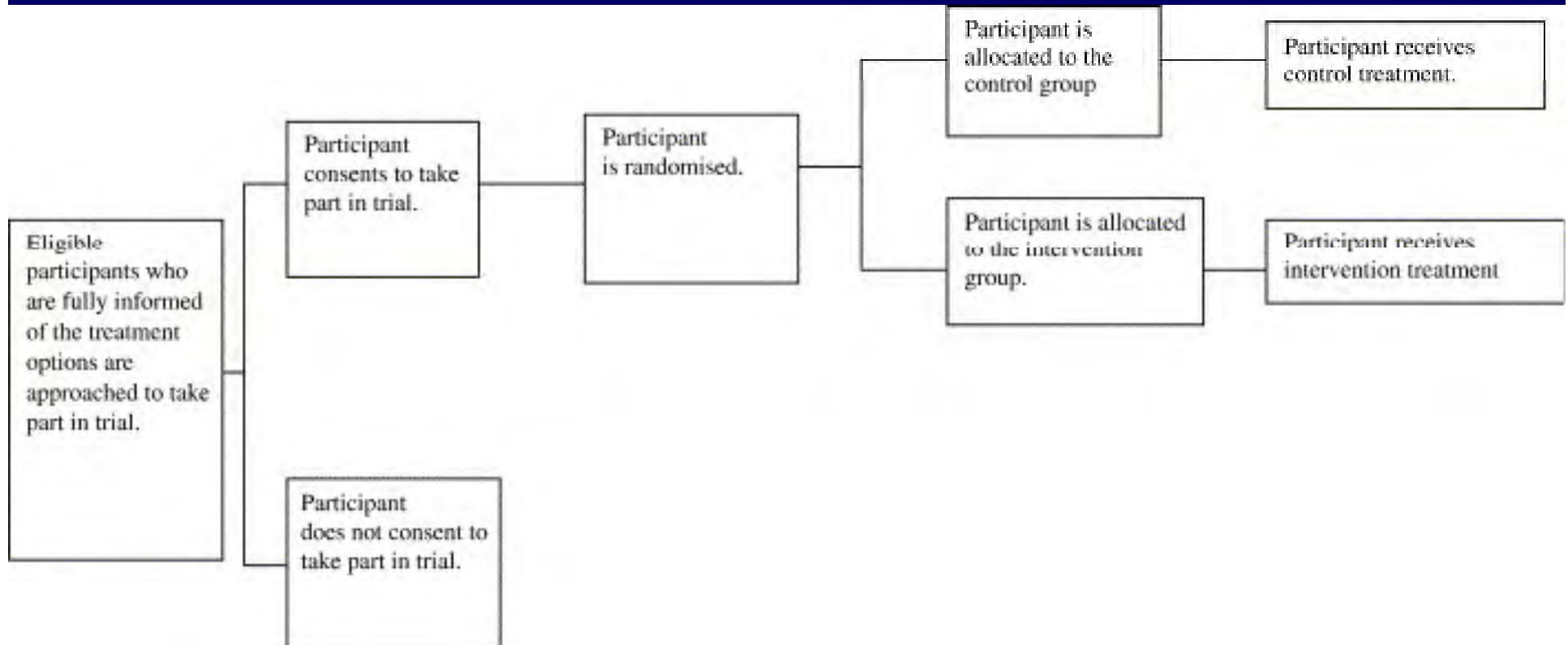
Prosthetic and Restorative (elective) dental care

1. RCTs are the preferred study design to compare effectiveness of interventions



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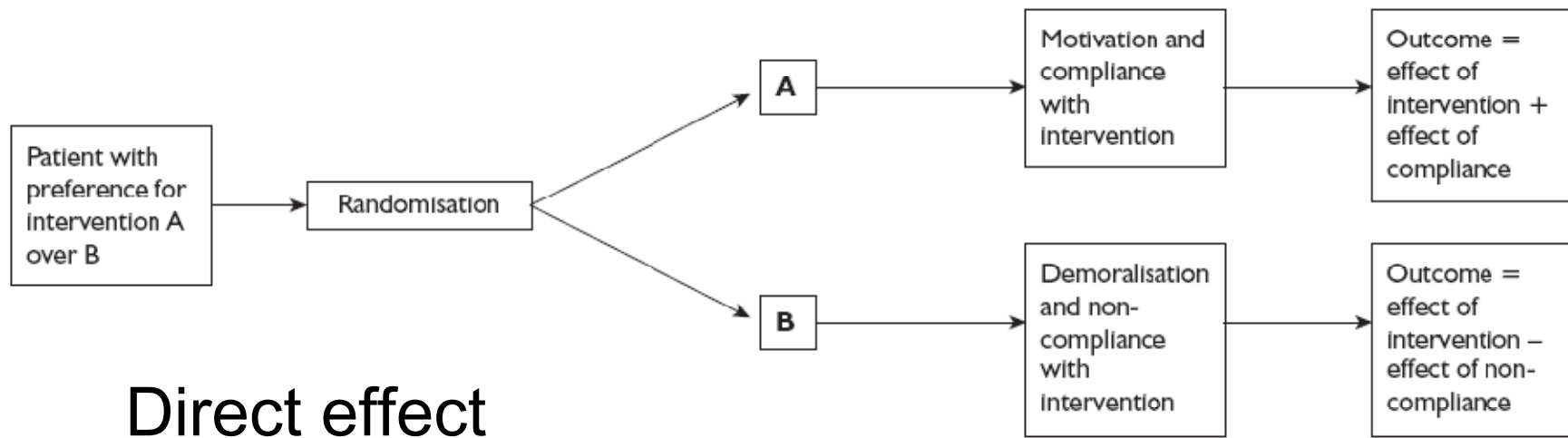


Prosthetic and Restorative (elective) dental care

1. RCTs are the preferred study design to compare effectiveness of interventions
2. RCTs are prone to bias if strong participant and/or clinician preferences – INTERNAL VALIDITY

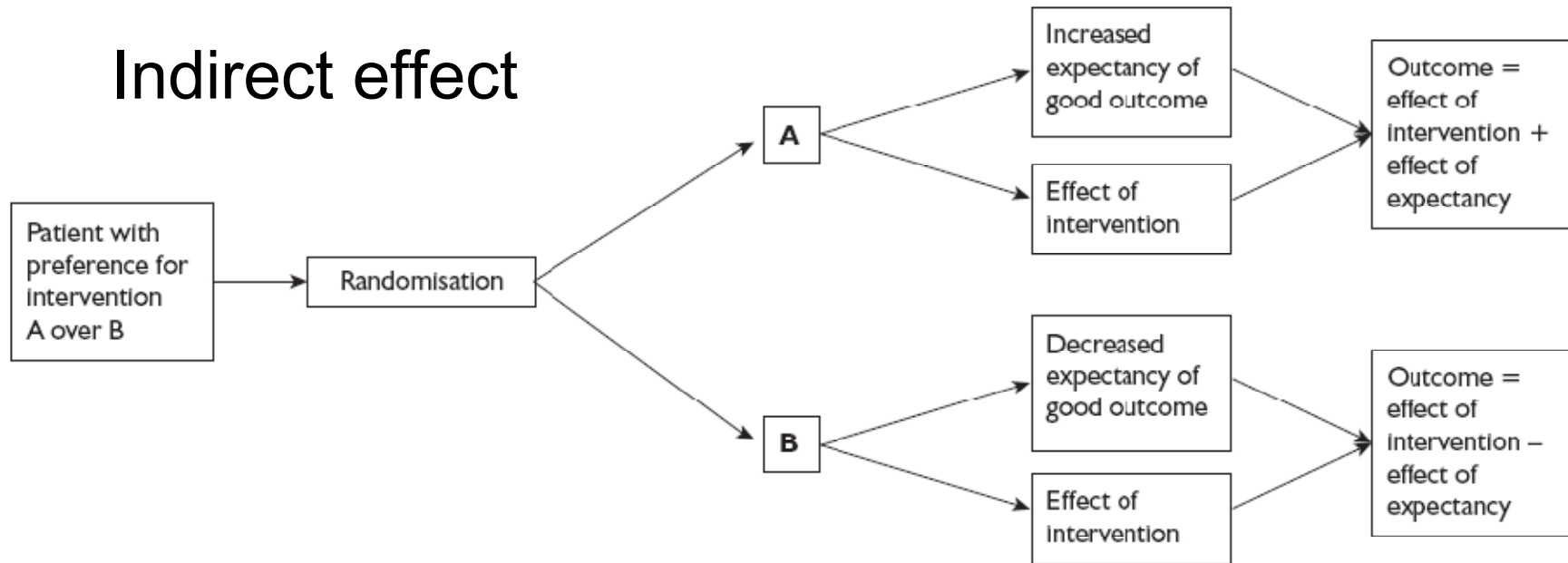
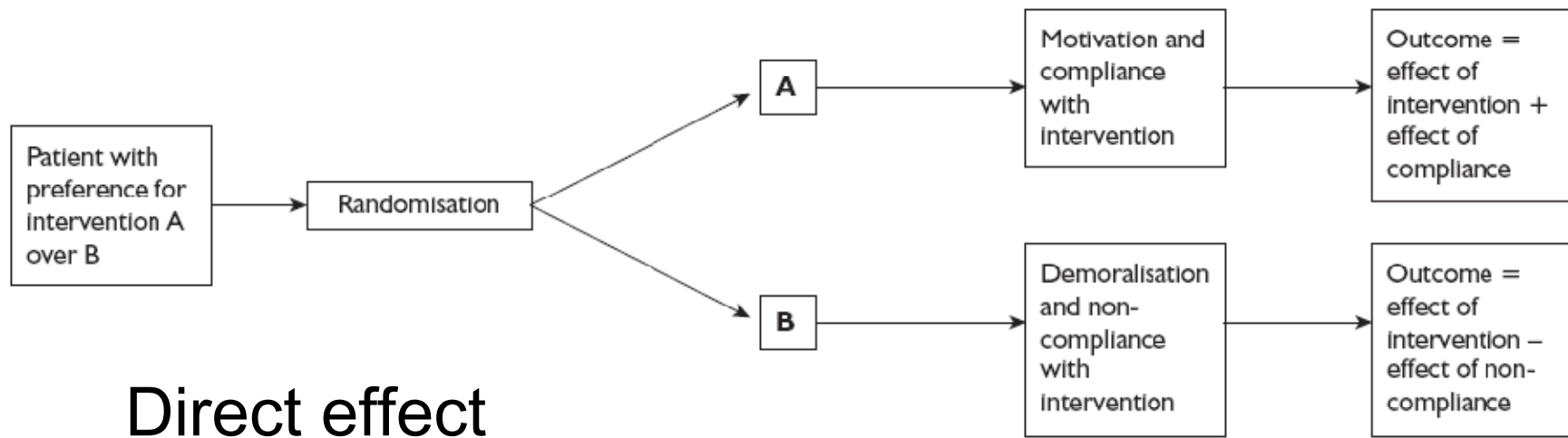


RCTs and possible effects of patient preferences on outcomes





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Prosthetic and Restorative (elective) dental care

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3. Participants in stringently controlled clinical studies are prone to *selection bias*
4. There are clear differences between individuals with preferences and those with no strong preferences. E.g. by levels of education, socio-economy and in the pre-treatment state – EXTERNAL VALIDITY



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4. There are clear differences between individuals with preferences and those with no strong preferences. E.g. by levels of education, socio-economy and in the pre-treatment state – EXTERNAL VALIDITY
5. Trials taking patient preferences into account provide, in theory, more reliable indicators of patient-centered outcomes than ordinary RCTs



RCT study designs that take patient preferences into consideration

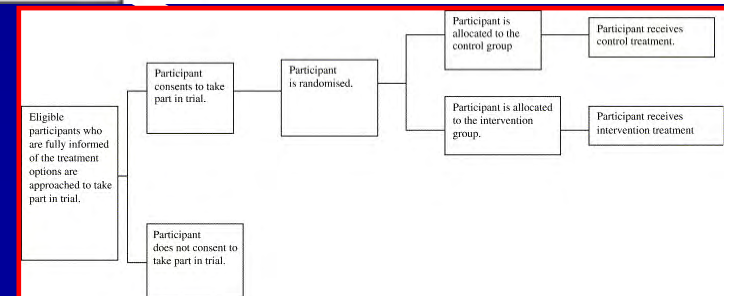
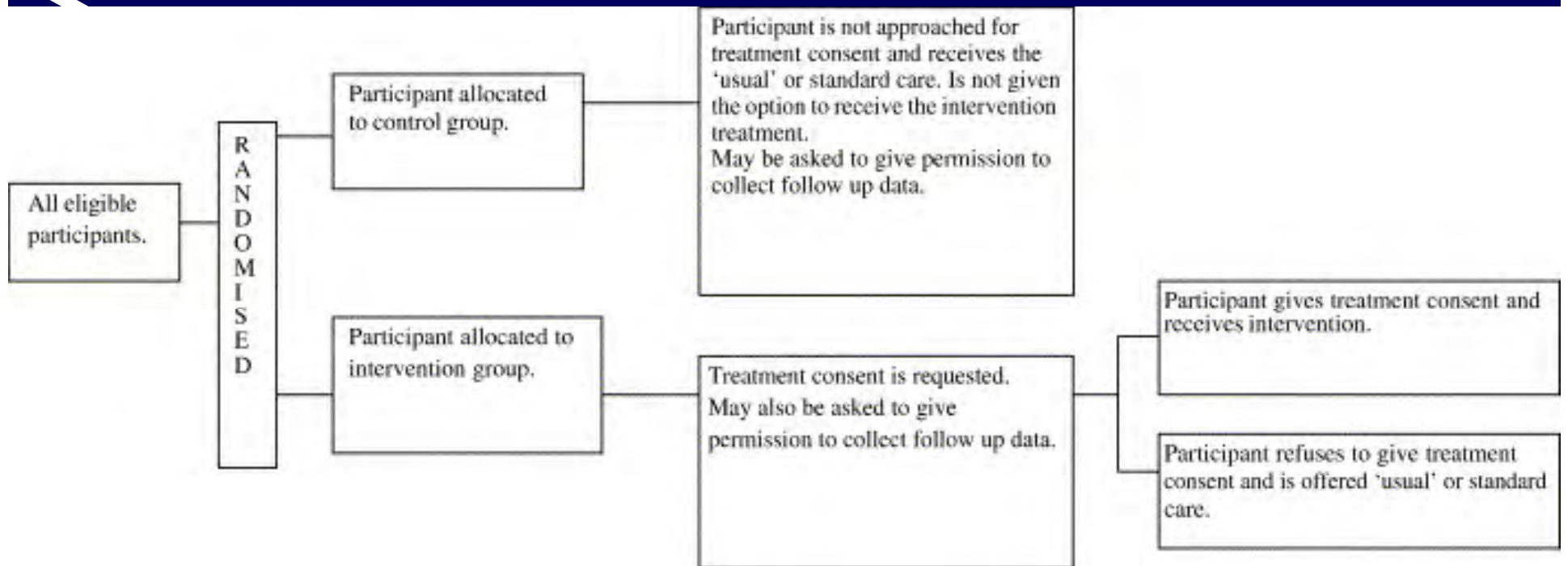
1979: Zelen “single consent” design





RCT study designs that take patient preferences into consideration

1979: Zelen “single consent” design





Zelen design

Zelen M. A new design for randomized controlled trials.
New Engl J Med 1979; 300: 1242-45.

AKAs: (or Zelen's...)

Zelen randomized consent design

Zelen randomized single consent design

(Zelen) pre-randomization design

(Zelen) post-randomized consent design

Problems: Ethics: no consent to randomization & data collection, power, routine outcome measures

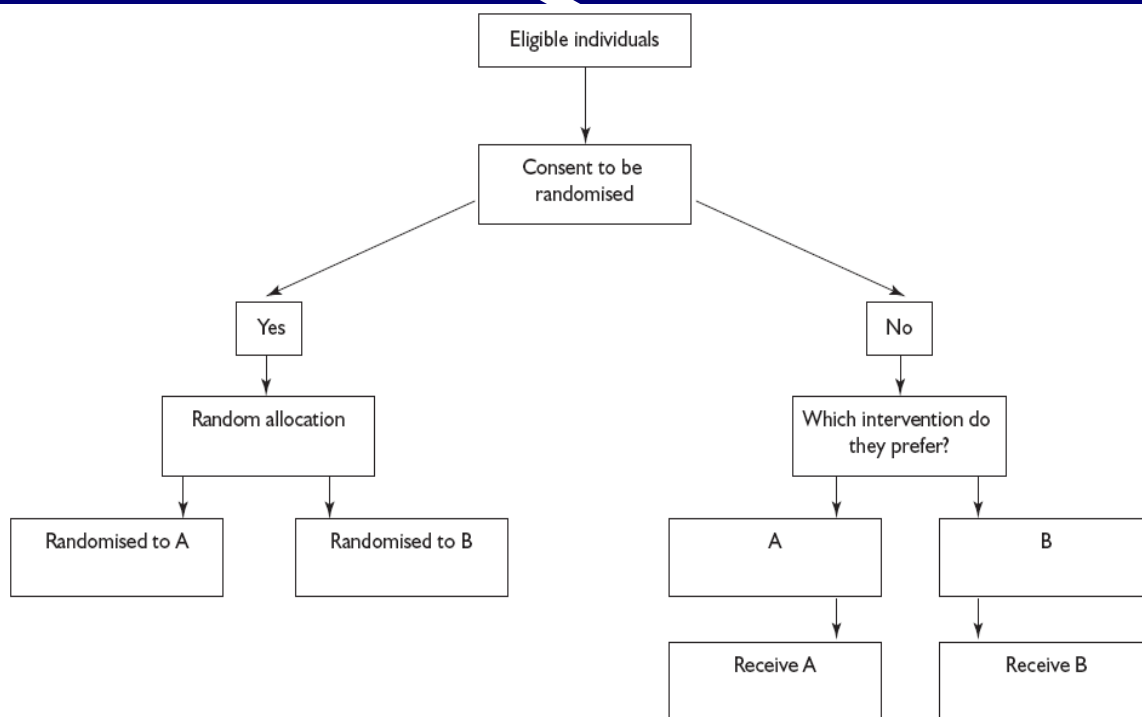
Fields: Psychiatry, neonatal medicine, addiction, experimental interventions



RCT study designs that take patient preferences into consideration

1979: Zelen “single consent”

1985: Olschewski/Scheuren
“comprehensive cohort design”





RCT study designs that take patient preferences into consideration

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“partially randomized (patient
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1993: Wennberg (design)



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“partially rand. pat.-pref. design”

1989: Rücker

“two stage trial design”

1990 Zelen “double consent”

1991: Korn & Baumrind

1993: Wennberg (design)

2005 : Millat ea. Surgical eval. design



Study aim

Systematic review of the dental literature to identify the use of clinical trials that have used a study design that report taking into account the patient and/or the clinician's preferences for intervention(s).



Materials and methods

1. Search for systematic reviews in:
 - Medline
 - Embase
 - Cochrane Library
 - & hand search tables and reference lists

King et al. Health Technol Assess 2005; 9(35): 1-186.

Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials

M King, I Nazareth, F Lampe, P Bower, M Chandler, M Morou, B Sibbald and R Lal



September 2005

Health Technology Assessment NHS R&D HTA Programme

REVIEW

Impact of Participant and Physician Intervention Preferences on Randomized Trials A Systematic Review

Michael King, PhD
Irwin Nazareth, PhD
Fiona Lampe, PhD
Peter Bower, PhD
Martin Chandler, MSc
Maria Morou, MSc
Bonnie Sibbald, PhD
Rosalind Lal, MLib

Context: Allocation on the basis of randomization rather than patient choice is the gold standard of unbiased estimates of efficacy in clinical medicine. However, randomly allocating patients to treatments that do not accord with their preferences may influence internal and external validity.

Objective: To determine whether preferences affect recruitment to trials (external validity) and outcome in trials (internal validity).

Data Sources: We searched MEDLINE, EMBASE, PsycINFO, CINAHL, AMED, and the Cochrane Library for articles published between 1966 and September 2004. We also hand-searched several major medical journals, searched reference lists of relevant articles, and contacted authors of published preference designs. The 2 themes in the first filter of the search strategy were preferences and possible determinants of preferences.

Study Selection: Comprehensive cohorts and 2-stage trials that measured or recorded patient or physician preference, included allocation of participants to random and preference cohorts, and followed up all participants. We excluded trials with no recording of preference; of decision aids; with measurements of preferences for economic analysis; in which patients who refused randomization were followed up without reference to preferences; and of nonclinical populations.

Data Extraction: Up to 4 reviewers independently evaluated the articles, and disagreements were resolved at project steering group meetings. We extracted data on study design, measurement of preference, recruitment, attrition, and summary data on the primary outcome(s) at baseline and each follow-up point.

Data Synthesis: Of 10023 citations identified, 170 articles met screening criteria and 32 (27 comprehensive cohorts and 5 two-stage trials) were determined to be eligible and were used in the final review. Although treatment preferences led to a substantial proportion of people refusing randomization, there was less evidence of bias in the characteristics of individuals agreeing to be randomized. Differences in outcome across the trials between randomized and preference groups were generally small, particularly in large trials and after accounting for baseline measure of outcome. Therefore, there was little evidence that preferences substantially interfere with the internal validity of randomized trials.

Conclusions: Preferences influence whether people participate in randomized trials, but there is little evidence that they significantly affect validity.

RANDOMIZED CONTROLLED trials (RCTs) provide the most reliable evidence for treatment efficacy.¹ Although trial participants are often conceptualized as passive recipients of interventions, many have preferences for treatments under evaluation and may decline to consent to randomization. This may limit generalizability of the results in clinical populations (ie, reduce external validity). When treatments cannot be blinded, patients randomly allocated to their nonpreferred intervention may experience resentful demoralization,² which may lead to worse outcomes, either directly (through poor adherence to treatment) or indirectly (through a negative placebo-like effect).³ Thus, preferences may introduce bias (ie, reduce internal validity). Trial designs have been developed to address such problems (BOX 1), but their results have not been systematically evaluated.^{4,5} There is little consensus on the magnitude of preference effects or the value of information from nonrandomized "preference" co-

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JAMA 2005;293:1089-1099



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Contemporary Clinical Trials 27 (2006) 305–319

Contemporary Clinical Trials

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Review

Review of randomised trials using the post-randomised consent (Zelen's) design

Joy Adamson, Sarah Cockayne, Suezann Puffer, David J. Torgerson*

York Trials Unit, Department of Health Sciences, University of York, York YO10 5DD, UK

Received 7 September 2004; accepted 14 November 2005

Abstract

Background: In 1979, Zelen described a trial method of randomising participants before acquiring consent in order to enhance recruitment to clinical trials. The method has been criticised ethically due to lack of consent and scientifically due to high crossover rates. This paper reviews recent published trials using this method and describes the reasons authors gave for using the method, examines the crossover rates, and looks at the quality of identified trials.

Methods: Literature review searching for all citations to the relevant Zelen's papers of trials published since 1990 plus inclusion of trials from personal knowledge.

Results: We identified 58 relevant trials. The most common justification for the use of Zelen method was to avoid the introduction of bias (e.g., to avoid the Hawthorne effect). Few trialists had explicitly used the design to enhance participant recruitment. Most trials ($n=41$) experienced some crossover from one group to the other (median crossover=8.9%, mean=13.8%, IQR 2.6% to 15%) although this was usually within acceptable limits.

Conclusion: The most important reason stated by authors for using Zelen's method was to limit bias. Zelen's method, if carefully used, can avoid 'resentful demoralisation' and the Hawthorne effect biasing a trial. Unlike a previous review, we found that crossover was not a problem for most trials.

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King et al. JAMA 2005; 293(9): 1089-99

May 2007

IDEALS Toronto



Materials and methods

1. SRs in: Medline – Embase -Cochrane
Library & hand search lists

n=3



Materials and methods

1. SRs in: Medline – Embase -Cochrane
Library & hand search lists

n=3

2. Search for clinical trials in:
Medline – Embase - Cochrane
Library

alt. 1: HTA Search Strategy



#	Search History	Results	Display
1	zelen.tw.	28	DISPLAY
2	((single or double) adj (random\$ adj consent\$)).tw.	0	
3	(non adj random\$ adj assign\$).tw.	10	
4	(nonrandom\$ adj assign\$).tw.	36	
5	(comprehensive adj cohort\$ adj stud\$).tw.	6	
6	(partial\$ adj randomi?ation).tw.	5	
7	(nonrandom\$ adj (patient\$ or participant\$)).tw.	63	
8	(nonrandom\$ adj (patient\$ or participant\$)).tw.	63	
9	(preference adj arm\$).tw.	12	
10	or/1-9	159	
11	exp Dentistry/	72003	
12	dent\$.mp.	97236	
13	exp Dentistry/	72003	
14	or/11-13	109818	
15	10 and 14	3	DISPLAY

Combine Searches |
 Delete Searches |
 Save Search/Alert

Health Technology Assessment 2005;14

Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials

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September 2005

Health Technology Assessment NHS R&D HTA Programme



Materials and methods

1. SRs in: Medline – Embase -Cochrane
Library & hand search lists

n=3

2. Search for clinical trials in:
Medline – Embase - Cochrane
Library

alt. 1: HTA Search Strategy

n=3

alt 2.: Hand-search of RCTs in the dental literature
reporting intention-to-treat analyses



"Search Strategy:

intention to treat"[All Fields] AND (((("dental clinics"[TIAB] NOT Medline[SB]) OR "dental clinics"[MeSH Terms] OR dental[Text Word]) OR ("dentistry"[MeSH Terms] OR dentistry[Text Word]))

Medline: n=17

Cochrane: n= 11

NCBI PubMed A service of the National Library of Medicine and the National Institutes of Health www.pubmed.gov

Search PubMed for "intention to treat" (dental OR dentistry) Go Clear Save Search

Limits Preview/Index History Clipboard Details

Display Summary Show 20 Sort by Send to

All: 17 Review: 2

Items 1 - 17 of 17

- 1: [Binnie W, McHugh S, Jenkins W, Borland W, Macpherson LM.](#)
A randomised controlled trial of a smoking cessation intervention delivered by dental hygienists: a feasibility study. *BMC Oral Health.* 2007 May 2;7(1):5 [Epub ahead of print]
PMID: 17475005 [PubMed - as supplied by publisher]
- 2: [Robinson PG, Damien Walmsley A, Heanue M, Deacon S, Deery C, Glenny AM, Worthington H, Shaw W.](#)
Quality of trials in a systematic review of powered toothbrushes: suggestions for future clinical trials. *J Periodontol.* 2006 Dec;77(12):1944-53. Review.
PMID: 17209777 [PubMed - indexed for MEDLINE]
- 3: [Schiffman EL, Look JO, Hodges JS, Swift JO, Decker KL, Hathaway KM, Templeton RB, Friction JR.](#)
Randomized effectiveness study of four therapeutic strategies for TMJ closed lock. *J Dent Res.* 2007 Jan;86(1):58-63.
PMID: 17189464 [PubMed - indexed for MEDLINE]
- 4: [Iokstad A.](#)
Implant retained or conventional dentures, which give more patients satisfaction?
Evid Based Dent. 2006;7(4):96-7.
PMID: 17187039 [PubMed]
- 5: [Bonner BC, Clarkson JE, Dobbyn I, Khanna S.](#)

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There are 11 results out of 495002 records for: "intention to treat" (dental OR dentistry) in The Cochrane Central Register of Controlled Trials

View: 1-11

Export All Results

Record Information Sort by: [Record Title](#) | [Match %](#) | [Year](#)

- A randomized clinical multicentre trial comparing enamel matrix derivative and membrane treatment of buccal class II furcation involvement in mandibular molars. Part III: patient factors and treatment outcome.**
Hoffmann T, Richter S, Meyle J, Gonzales JR, Heinz B, Arjomand M, Sculean A, Reich E, Jepsen K, Jepsen S, Boedeker RH
Year: 2006
[Record](#)
- A randomized controlled trial of implant-retained mandibular overdentures.**
Allen PF, Thomason JM, Jepsen NJ, Nohlf F, Smith DG, Ellis J
Year: 2006
[Record](#)
- Increased excretion of collagen crosslinks in irradiated patients indicates destruction of collagen.**
Niehoff P, Wittfang J, Springer IN, Weppner N, Kimmig B, Acl J
Year: 2006
[Record](#)



Materials and methods

1. SRs in: Medline – Embase -Cochrane Library
+ hand search of reference lists
2. Clinical trials in: Medline – Embase - *n=3*
Cochrane Library + hand search of reference
lists *n=12*
3. Web of Science search for all citations to
original papers:
 - Zelen (1979 New England J Medicine) *n=3*
 - Olschewski/Scheuren (1985 Inf Meth Med) *n=0*
 - Brewin&Bradley (1989 BMJ) *n=8*
 - Wennberg et al. (1993 Ann NY Acad Sciences) *n=6*



Results (n=9 (+13))

1. Review or discussion papers	2
2. Descriptive studies or surveys (with no experimental elements)	0
3. Studies with a preference cohort	2*
4. Studies with assessment and analysis of preference within a RCT	5**
5. Irrelevant (report pt preference as outcome measure)	13

** 1 trial*

Zitzmann NU, et al. 2 papers reporting one preference cohort study

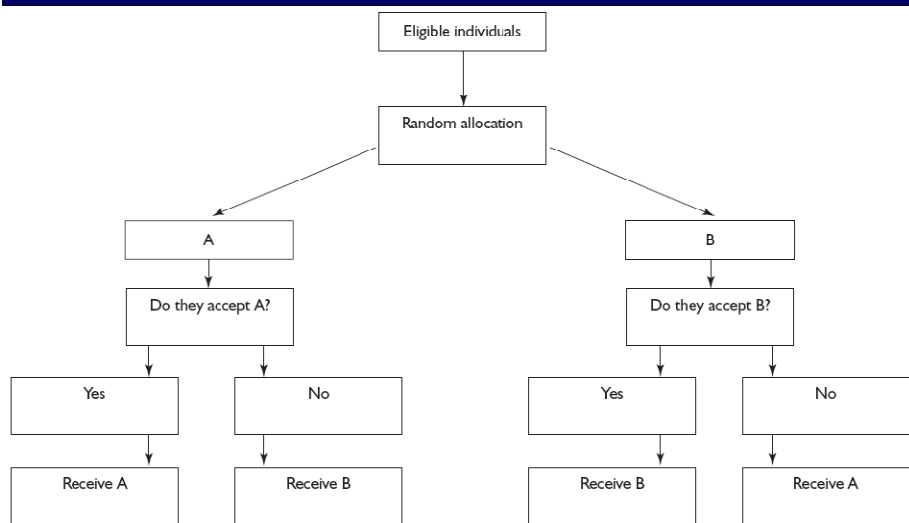
***2 trials:*

1. Feine J, Awad MA, Lund JP. 4 papers reporting one two-arm RCT.

2. Allen PF, et al. A Randomized Controlled Trial Of Implant-Retained Mandibular Overdentures. J Dent Res 2006; 85: 547-51 (Zelen design)



Allen et al. 2006



(Zelen double randomised consent design)

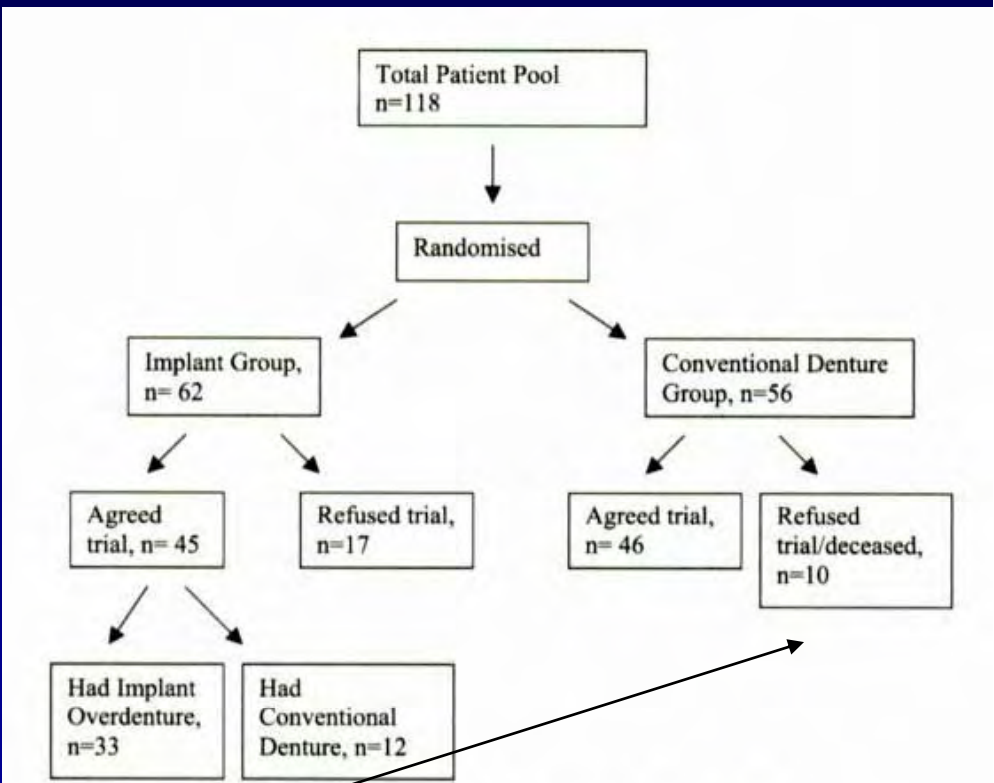


Figure 1. Trial profile, indicating allocation of study patients.



Discussion and conclusions

- Identifying clinical trials in bibliographic database is complex due to poor indexing
- Incorporating patient preferences in clinical trials in dentistry seems to be rare
- A few trials have been identified comparing implant-prosthetics with traditional prothodontic interventions
- There seems to exist a need for trials in dentistry taking patient-preferences into account





Appropriate Study Designs to address implementation of interventions

	Qualitative research	Survey	Case Control	Cohort	RCT	Non-exper	Systematic review
Effectiveness: Does it work?				☆	☆☆	☆	☆☆☆
Process of intervention/delivery: How does it work?	☆☆	☆				☆	☆☆☆
Salience: Does it matter?	☆☆	☆☆					☆☆☆
Safety: Will it do more good than harm?	☆		☆	☆	☆☆	☆	☆☆☆
Acceptability: Will the patient accept the intervention?	☆☆	☆			☆	☆	☆☆☆
Cost effectiveness: Is it worth paying for the intervention?					☆☆		☆☆☆
Appropriateness: Is this the right intervention for this patient?	☆☆	☆☆					☆☆
Satisfaction with the intervention: Are users, providers and other stakeholders satisfied?	☆☆	☆☆	☆	☆			☆



*“Guerir quelquefois,
soulager souvent,
consoler toujours”*

*“Cure occasionally,
relieve often,
console always”*



Ambroise Paré
(1510 –1590)



*Thank
you for
your
kind
attention*







References

King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al.* Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials. *Health Technol Assess* 2005; 9(35).

Brewin CR, Bradley C. Patients' preferences and randomized clinical trials" *BMJ* 1989; 289: 313-315

Wennberg et al. (*Ann N Y Acad Sci* 1993;703:52-62)

Howard L, Thornicroft G. Patient preference randomised controlled trials in mental health research. *Br J Psychiatry* 2006; 188:303-4.



1985: Comprehensive cohort design

Olschewski et al., 1985; Brewlin & Bradley, 1989.

- n All participants are followed up, regardless of randomization status.
- n Outcomes of RCT and cohort groups can be compared.
- n Ideal where it is likely that many patients will refuse, because patients or operators have a strong preference for one intervention.
- n A disadvantage is no status of differences in baseline characteristics in the RCT and preference groups.
- n Satisfaction with existing conditions very likely influence.



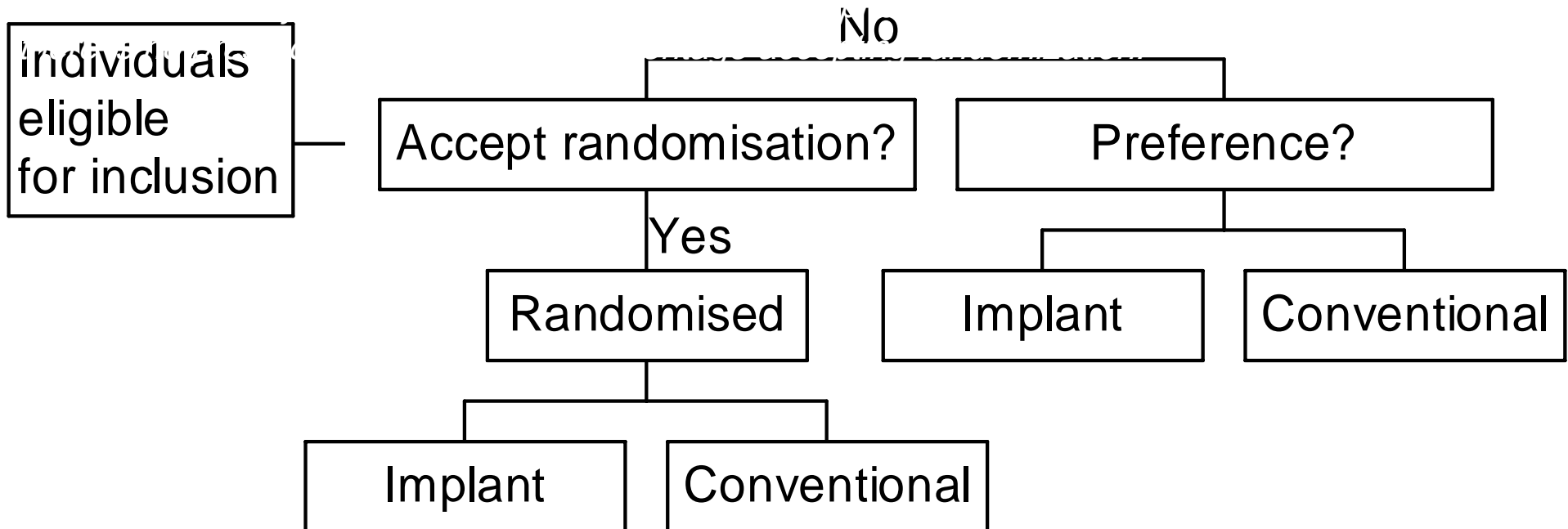
1985: Comprehensive cohort design

Design. Patients with strong preferences are offered their treatment of choice, while those without strong preferences are randomized in the conventional fashion. All patients (whether randomized or not) are followed up in the same way.

External validity. Almost all eligible patients enter the study, allowing examination of patients' characteristics with all strengths of preferences.

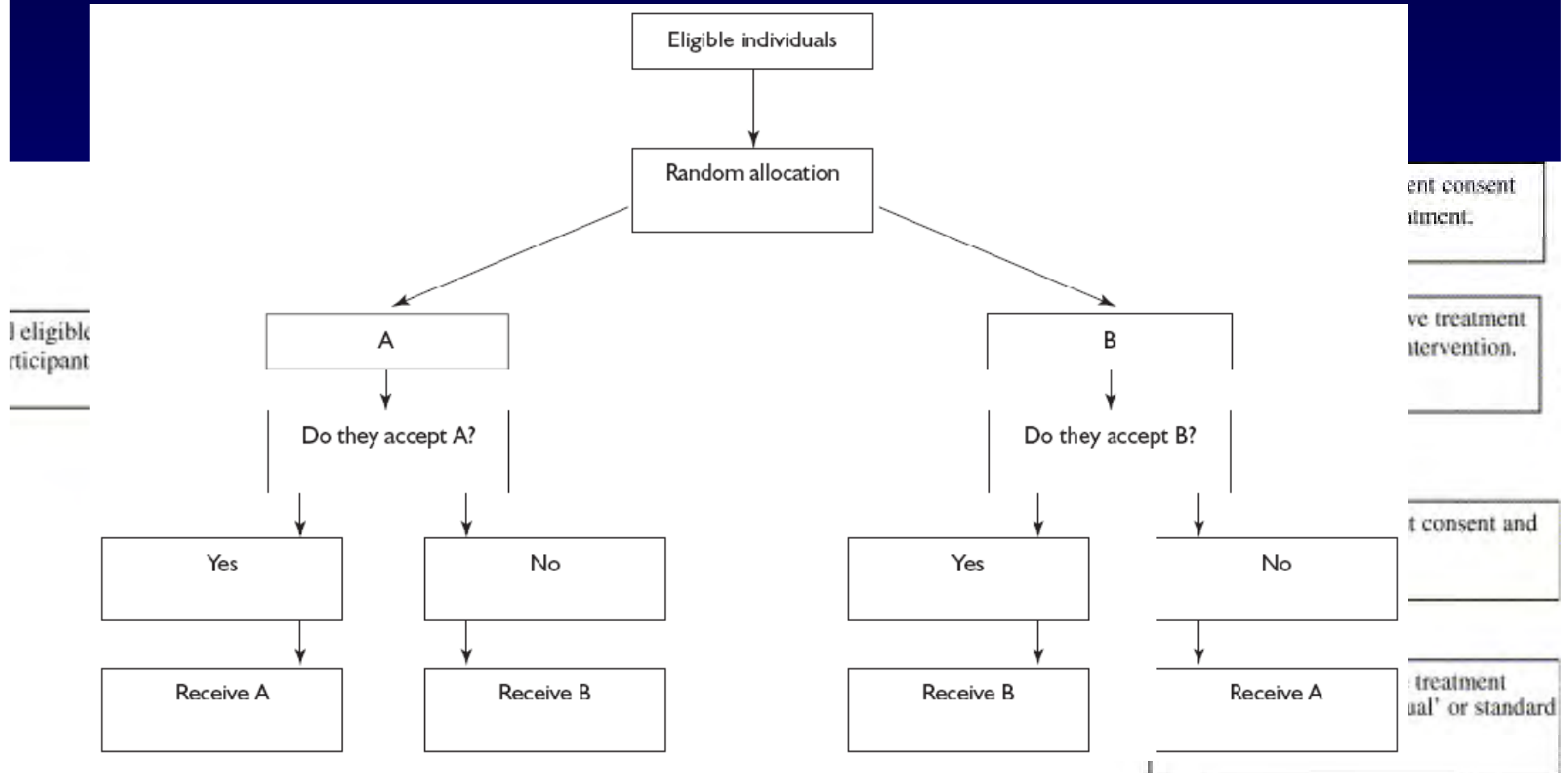
Internal validity. Preference effects (eg, randomization vs preference) are confounded although can be controlled.

Study administration. Potentially costly if large numbers of patients express a preference and





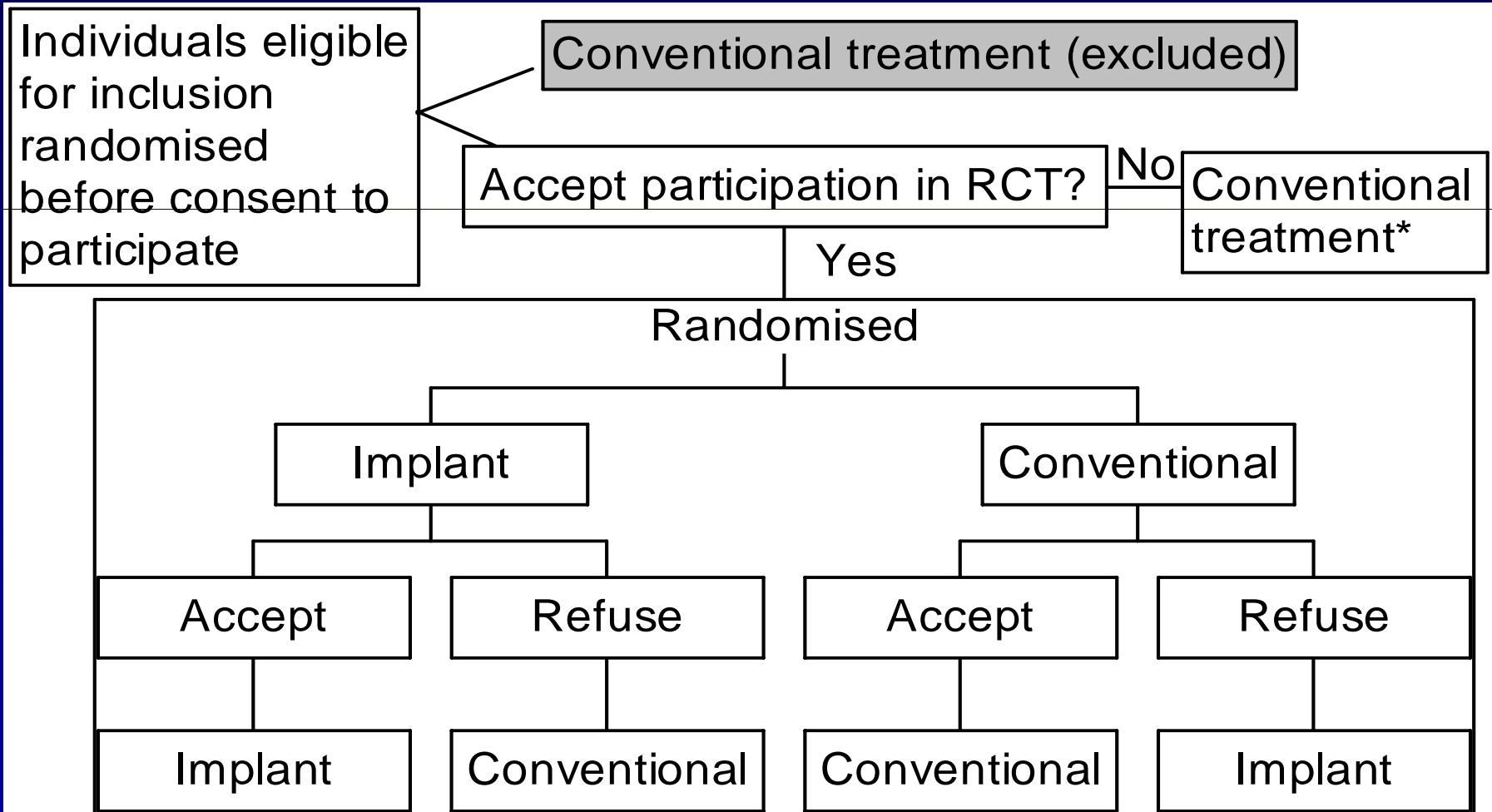
1990: Zelen double randomised consent design





1990: Zelen double randomised consent design

Ethical concerns overcome by offering the opportunity to switch to other group



* Given conventional treatment but analysed as if they have received exp. treatm.



Two-stage, Randomized design

Design. In the Wennberg design participants are initially randomized to 2 groups: in the first they are offered a choice of treatment while in the second they are randomized to treatment. The Rücker design is similar but participants randomized to preference in the first randomization, who do not have a strong preference for a treatment, are randomized a second time to a treatment.

External validity. Reduced because only patients accepting randomization enter the study.

Internal validity. All patients are randomized, increasing internal validity. However, randomization vs preference comparisons are still subject to confounding because patients' characteristics may determine choice of treatment.

Study administration. Individuals with strong preferences may refuse randomization.



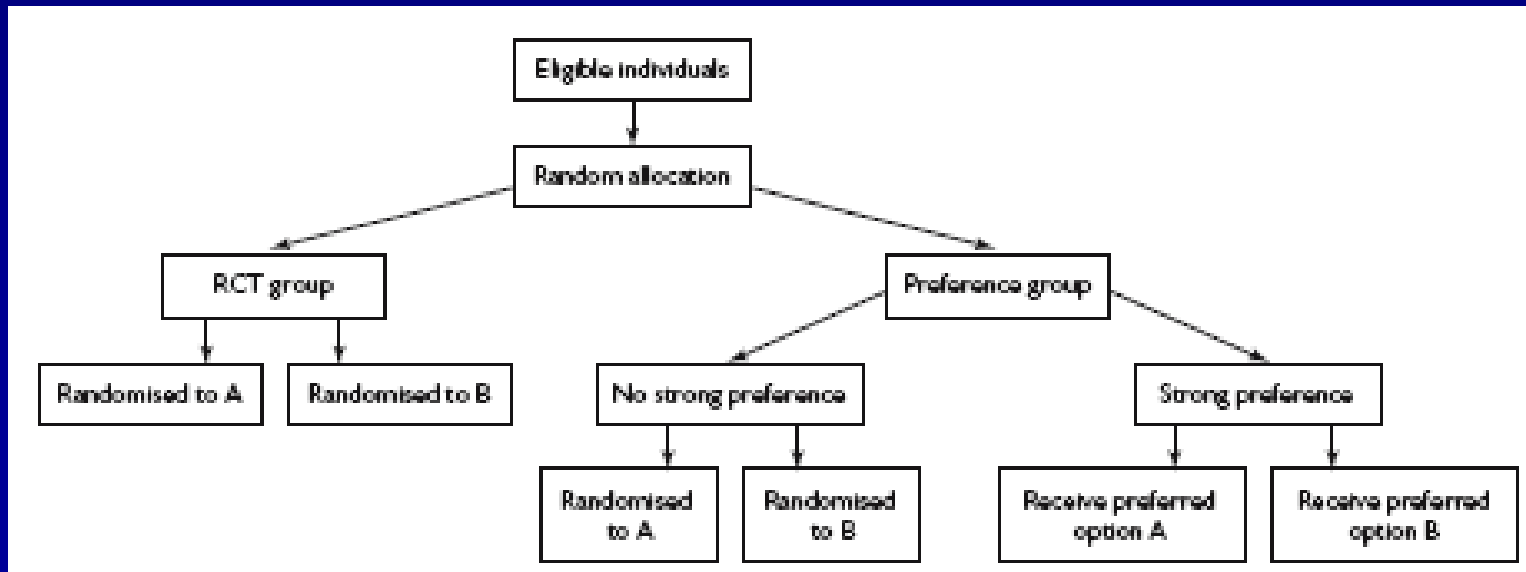
Rücker Design

Design. Similar to Wennberg design but participants randomized to preference in the first randomization, who do not have a strong preference for a treatment, are randomized a second time to a treatment.

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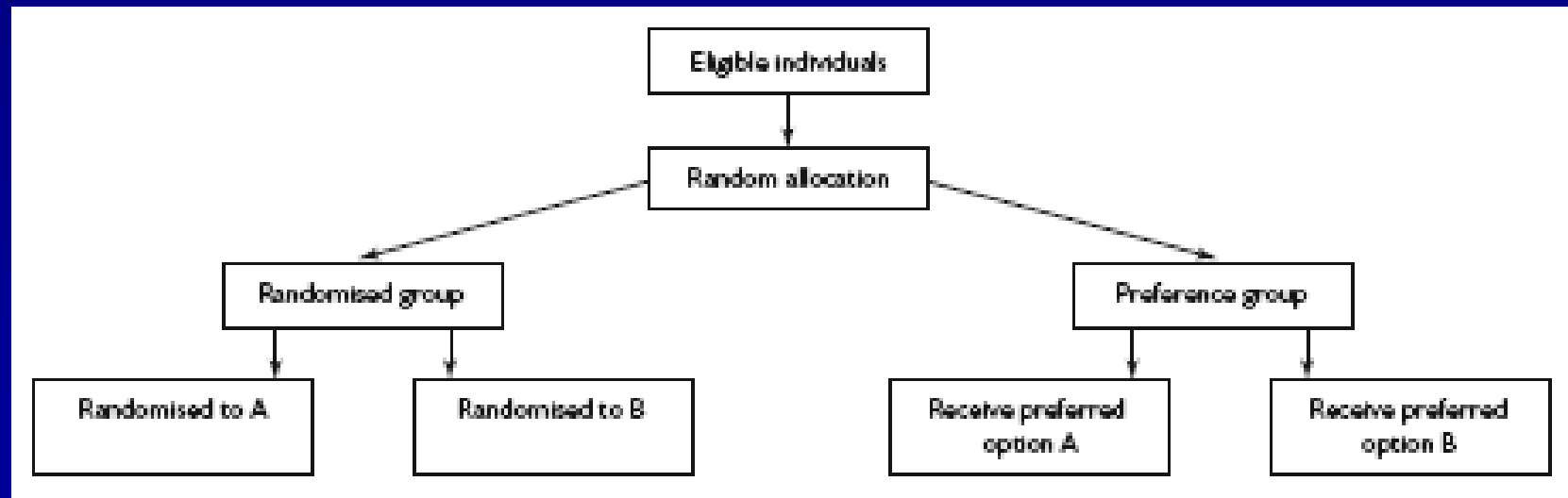
1993: Wennberg design

Design. Participants are initially randomized to 2 groups: in the first they are offered a choice of treatment while in the second they are randomized to treatment. (Similar to the Rücker design, but here the participants randomized to preference in the first randomization, who do not have a strong preference for a treatment, are randomized a second time to a treatment.

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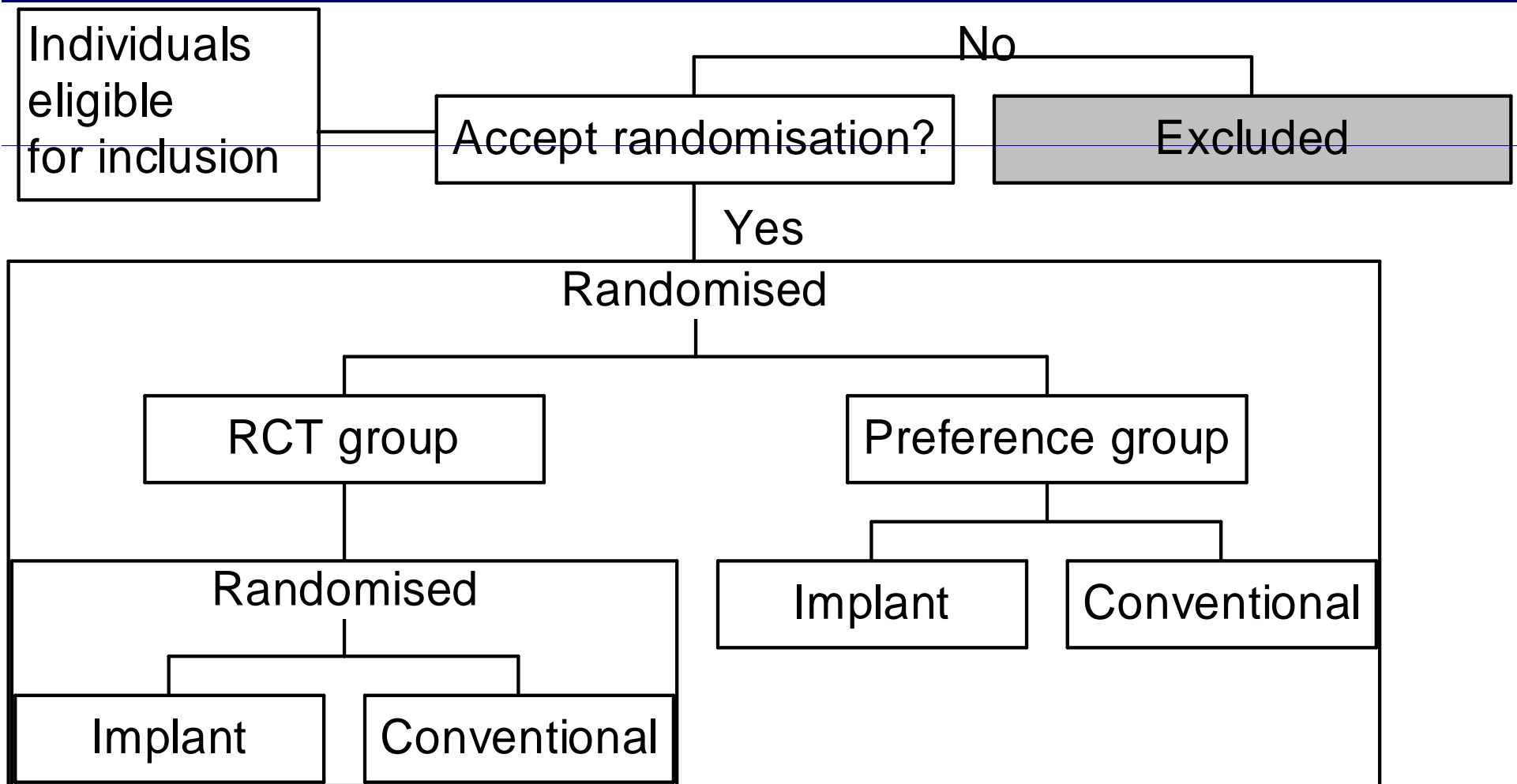
Study administration. Individuals with strong preferences may refuse randomization.





1993: Wennberg design

Include individuals who agree to be randomised





Feine & Awad

Feine J, Awad MA. Community Dent Oral Epidemiol 1998.

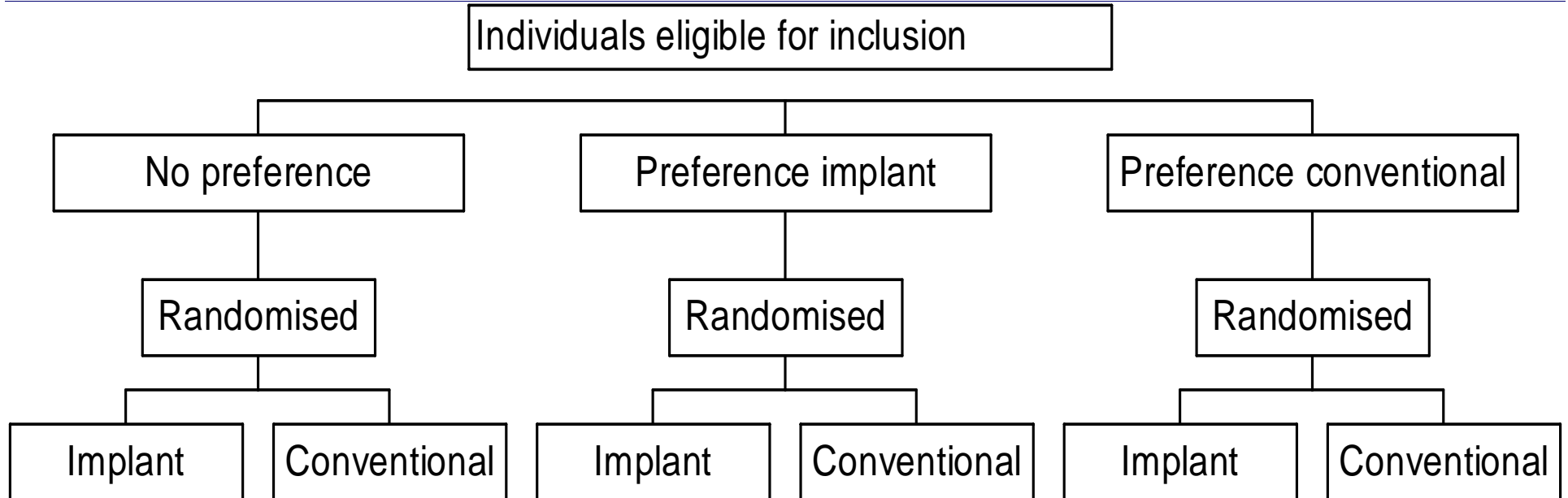


TABLE 1 Advantages and disadvantages of each type of design

Measurement of preference at baseline in a standard RCT

Internal validity – preference effects can be used as a stratification factor (to reduce the impact of preferences) or as a predictor of outcome

External validity – patients with very strong preferences may not enter the study, which may reduce or remove preference effects

Study administration – no increase in sample size, but large sample size may be required to detect preference interaction effects, valid and reliable measures of preferences required

Comprehensive cohort design

Internal validity – preference effects (e.g. R vs P) confounded, although can be controlled

External validity – almost all eligible patients enter the study and allows examination of characteristics of patients with all strengths of preferences

Study administration – potentially costly if large numbers of patients express a preference and not feasible if very few patients have a preference. *A priori* power calculations difficult if there is no prestudy estimate of the percentage accepting randomisation

Prerandomised (Zelen) design

Internal validity – all patients randomised but, depending on consent process, uneven drop-out may occur between intervention and control arms

External validity – all eligible patients enter study but ethical objections exist over lack of fully informed consent

Study administration – potentially low cost as all eligible patients will enter study but depending on later consent process, drop-out or switching between arms may make increased recruitment necessary. Ethical concerns in designs with partial or no patient consent

Two-stage, randomised designs (Wennberg and Rucker)

Internal validity – all patients randomised, increasing internal validity. However, P vs P and R vs P comparisons still subject to confounding as patients' characteristics may determine choice of treatment

External validity – reduced because only patients accepting randomisation enter the study

Study administration – people with strong preferences may refuse randomisation



	External validity	Internal validity	Study administration
RCT			
Prerandomized			
Two-stage, random design			
Comprehensive Cohort	<i>Almost all eligible patients enter the study, allowing examination of patients' characteristics with all strengths of preferences.</i>	Preference effects (eg, randomization vs preference) are confounded although can be controlled.	Potentially costly if large numbers of patients express a preference and not feasible if very few patients have a preference. A priori power calculations are difficult if there is no prestudy estimate of the percentage accepting randomization.