



Methodological designs of clinical trials and their power to answer research question

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Clinical trial terminology - tower of Bable?

analytical study	ecological study	prospective cohort study
case control study (89)	etiological study	prospective follow-up study, observational or experimental
case serie	experimental study	prospective study (67)
case study, case report	explorative study	quasi-experimental study
cause-effect study	feasibility study (79)	randomized clinical trial, RTC
clinical trial (79)	follow-up study (67)	randomized controlled trial, RCT (89)
cohort study (89)	historical cohort study	retrospective cohort study
cohort study with historical controls	incidence study	retrospective follow-up study
controlled clinical trial (95)	intervention study	retrospective study (67)
cross-sectional study (89)	longitudinal study (79)	surveillance study
descriptive study	N=1 trial	survey, descriptive survey
diagnostic meta-analysis	non-randomized trial with contemporaneous controls	therapeutic meta-analysis
diagnostic study	non-randomized trial with historical controls	trohoc study
double blind randomized therapeutical trial with cross-over design	observational study	




Clinical trial terminology - MESH terms 1967

case serie		prospective study (67)
case study, case report		
	follow-up study (67)	
		retrospective study (67)




Clinical trial terminology - MESH terms 1979

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Clinical trial terminology - MESH terms 1989

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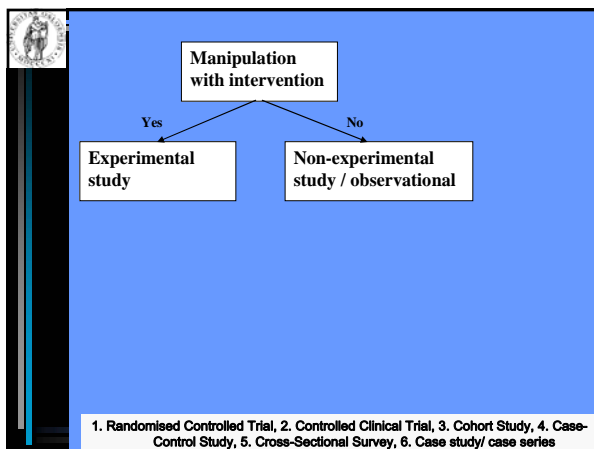
Clinical trial terminology - MESH terms 1995

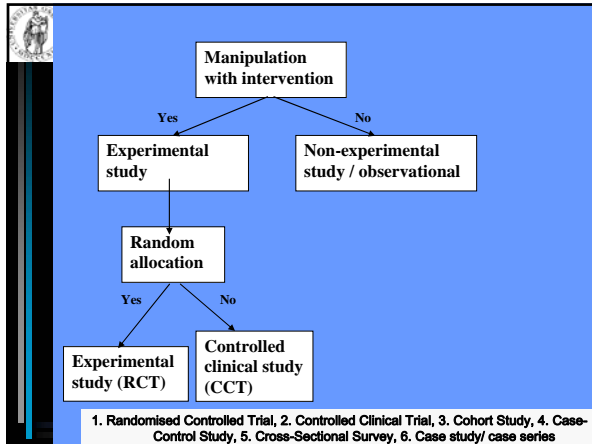
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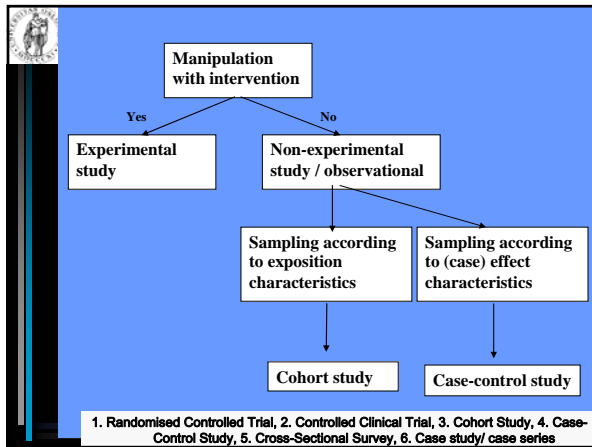
Clinical trial terminology - tower of Bable → MESH terms

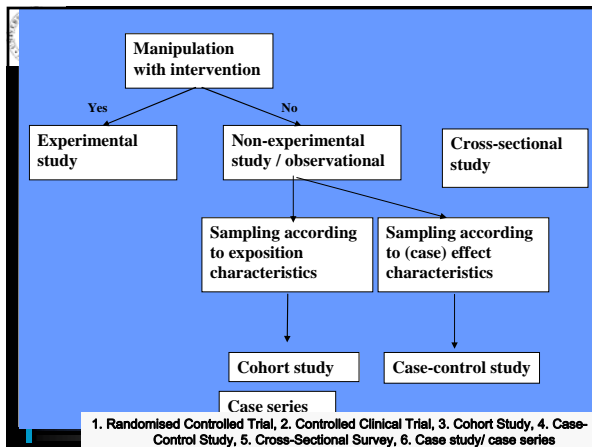
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double blind randomized	historical controls	
therapeutical trial with cross-	observational study	
over design		

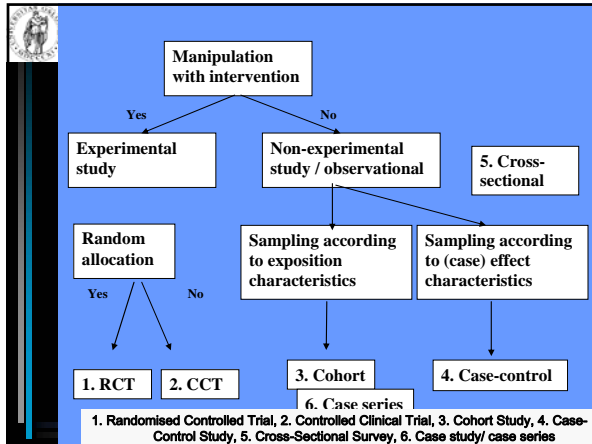
- Clinical study designs (MESH terms):**
1. Randomised Controlled Trial
 2. Controlled Clinical Trial
 3. Cohort Study
 4. Case-Control Study
 5. Cross-Sectional Survey
 6. Case study/ case series











Clinical problems: - Examples


- What is the value of RFA /Periotest /Periotest 2?
- Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?
- How does the implant "Fantisco" perform in the upper jaw?
- How many patients are suitable for implant prosthetics?
- How does implant protheses impact on the patient's daily life?
- How many patients have experienced fractured screws / implants?

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Examples of Clinical problems

A question of.	
Diagnosis	What is the value of RFA /Periotest /Periotest 2?
	Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?


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Examples of Clinical problems

Diagnosis	What is the value of RFA /Periotest /Periotest 2?
Therapy	Which implant design / surgical technique /maintenance regime / education strategy is the best (or the most damaging)?
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Prognosis	How does the implant "Fantisco" perform in the upper jaw?
	How many patients are suitable for implant prosthetics?


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Screening	How many patients are suitable for implant prosthetics?
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Views/beliefs perceptions	How does implant protheses impact on the patient's daily life?
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Prevalence/hypothesis generation	How many patients have experienced fractured screws / implants?


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NOS-M, Bergen May 2005. Presentations

Therapy	Diagnosis
1. Al-Sukhun, Jehad	1. Øzhayat, Esben
2. Eiriksson, Sigurdur	<u>Etiology / Causation / Harm</u>
3. Gjengedal, Harald	1. Elisasson, Alf
4. Meric, Göcke	2. Vamanu, Carmen
5. Obradovic, Srdjan	<u>Prognosis</u>
6. Mustafa, Kamel	1. Henriksson, Kristina
7. Meirelles, Luiz	
8. Persson, Anna	
9. Segerström, Susanna	
10. Øilo, Marit	
11. Örtorp, Anders	


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Clinical problem & Appropriate Study Design

	Qualitative	Cross-Sectional	Case Control	Cohort	RCT
Diagnosis				☆	☆☆
Therapy				☆	☆☆
Prognosis				☆☆☆	
Screening			☆	☆	☆☆
Views/beliefs perceptions	☆☆☆				
Prevalence/hypothesis generation	☆☆☆	☆☆☆			

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Scientific studies can be graded according to the theoretical possibility of an incorrect conclusion.

This is reflected by the design of the study.

... we will never know exact answers in science....

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Assumption of internal and external validity

Internal validity: extent to which systematic error (bias) is minimised in clinical trials

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Internal validity - systematic bias, e.g.

- Selection bias: biased allocation to comparison groups
- Performance bias: unequal provision of care apart from treatment under evaluation
- Detection bias: biased assessment of outcome
- Attrition bias: biased occurrence and handling of deviations from protocol and loss to follow up

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Assumption of internal and external validity

Internal validity: extent to which systematic error (bias) is minimised in clinical trials

External validity: extent to which results of trials provide a correct basis for generalisation to other circumstances

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External validity, focus on e.g.

- Patients: age, gender, severity of disease/situation and risk factors, co-morbidity
- Treatment regimens: type of treatment within a class of treatments, concomitant treatments
- Settings: level of care (primary to tertiary) and experience and specialisation of care provider
- Modalities of outcomes: type or definition of outcomes and duration of follow up

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Diagnostic tests

- Does the use of RFA or the Periotest have any merits?
- What is the validity of the Zarb and Lekholm bone quality classification?

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Diagnostic tests, Differential diagnosis

Diagnosis	Background	Outcome	Yes	No
Diagnosis			Yes	No
Diagnosis			Yes	No
Diagnosis			Yes	No
Diagnosis			Yes	No
Diagnosis			Yes	No
Diagnosis			Yes	No
Diagnosis			Yes	No
Diagnosis			Yes	No
Diagnosis			Yes	No

- Clearly identified comparison groups, at least one of which is free of the target disorder
- Either an objective diagnostic standard/contemporary clinical diagnostic standard with reproducible criteria for any objectively interpreted component
- Interpretation of the test without knowledge of the diagnostic standard result
- Interpretation of the diagnostic standard without knowledge of the test result
- A statistical analysis consistent with study design

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Therapy /Prevention /Education

- Which implant design / surgical technique / maintenance regime / education strategy provides the *best result*?

**Clinical, patient centred, surrogate or economic*

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Therapy / Prevention / Education

	Intervention	Control	n	n/N
Primary			9	9/9
Secondary			9	9/9
Intention to treat	9/9	9/9		
Per-protocol	9/9	9/9		
As-treated				

- Random allocation of the participants to the different interventions
- Outcome measures of known or probably clinical importance for at least 80 per cent of participants who entered the investigation
- A statistical analysis consistent with the study design

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Prognosis

- How does the implant "Fantisco" perform in the upper jaw?

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Prognosis

	Intervention	Control	n	n/N
Primary			9	9/9
Secondary			9	9/9
Intention to treat	9/9	9/9		
Per-protocol	9/9	9/9		
As-treated				

- An inception cohort of persons, all initially free of the outcome of interest
- Follow-up of at least 80 per cent of patients until the occurrence of either a major study criteria or the end of the study
- A statistical analysis consistent with the study design.

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Views /beliefs /perceptions

- How does implant prostheses impact on the patient's daily life?
- Why are colleagues hesitant to implement implant prosthetics in their practices?

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Qualitative research

Method	Strengths	Weaknesses	Number	Yes	No
Interviews				Yes	No
Focus groups				Yes	No
Participant observation				Yes	No
Case studies				Yes	No
Content analysis				Yes	No
Discourse analysis				Yes	No
Grounded theory				Yes	No
Phenomenology				Yes	No
Triangulation				Yes	No

- Aim to make sense of, or interpret, phenomena in terms of the meanings people bring to them
- May define preliminary questions which can then be addressed in quantitative studies
- Address a clinical problem through a clearly formulated question and using more than one research method (triangulation)
- Analysis of qualitative data can and should be done using explicit, systematic, and reproducible methods

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Implementation of a new implant concept and appropriate study design

	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?	☆☆	☆☆	☆	☆			☆

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Are implants harmful?

- How many patients have experienced fractured screws / implants?
- Does trace elements from implants cause adverse general effects?
- Has a certain batch of implants been contaminated during the production process?

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Etiology - Harm - Causation

- Evidence levels: Randomised clinical trial > clinical trial > case-control > cross-sectional > single case
- Clearly identified comparison group for those at risk for, or having, the outcome of interest
- Observers of outcomes masked to exposures
- Observers of exposures masked to outcomes for case-control studies and individuals masked to exposure for all other study designs
- A statistical analysis consistent with the study design.

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Cross-Sectional Survey

	Exposed	Non-exposed	Total
Disease	10	10	20
No disease	10	10	20
Total	20	20	40

Advantages

1. Cheap and simple
2. Ethically safe

Disadvantages

1. Establishes association at most, not causality
2. Recall bias susceptibility
3. Confounders may be unequally distributed
4. Group sizes may be unequal

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Case-Control Study

	Exposed	Control		
Cases	10	10	10	10
Controls	10	10	10	10
Total	20	20	20	20

Advantages:

1. Quick and cheap
2. Only feasible method for very rare clinical situations or those with long lag between exposure and outcome
3. Fewer individuals needed than cross-sectional studies

Disadvantages:

1. Rely on recall or records to determine exposure status
2. Confounders
3. selection of control groups is difficult
4. Potential bias: recall, selection

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Questions to ask:

	Exposed	Control		
Cases	10	10	10	10
Controls	10	10	10	10
Total	20	20	20	20

- How were cases defined and selected?
- How were controls defined and selected?
- Does the study adequately control for demographic characteristics and important potential confounders in the design or analysis?
- Was measurement of exposure to the factor of interest (eg the new intervention) adequate and kept blinded to case/control status?
- Were all selected subjects included in the analysis?

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Characteristics of a poor case-control study:

	Exposed	Control		
Cases	10	10	10	10
Controls	10	10	10	10
Total	20	20	20	20

Fail to:

- clearly define comparison groups
- and/or fail to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls
- and/or fail to identify or appropriately control known confounders.

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Cohort Study

	Exposed	Non-exposed	Control	n	OR
Exposure				5	0.2
Non-exposure				5	0.2
Control				5	0.2
Outcome				5	0.2
Non-outcome				5	0.2
Total				5	0.2

Advantages:

1. Ethically safe
2. individuals can be matched
3. Can establish timing and directionality of events
4. Eligibility criteria and outcome assessments can be standardised
5. Administratively easier and cheaper than RCT

Disadvantages:

1. Controls may be difficult to identify
2. Exposure may be linked to a hidden confounder
3. Blinding is difficult
4. Randomisation not present
5. For rare disease, large sample sizes or long follow-up necessary

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Questions to ask:

	Exposed	Non-exposed	Control	n	OR
Exposure				5	0.2
Non-exposure				5	0.2
Control				5	0.2
Outcome				5	0.2
Non-outcome				5	0.2
Total				5	0.2

- How were subjects selected for the cohort?
- How were subjects selected for the comparison or control group?
- Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the design or analysis?
- Was the measurement of outcomes unbiased (ie blinded and comparable across groups)?
- Was follow-up long enough for outcomes to occur?
- Was follow-up complete and were there exclusions from the analysis?

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Characteristics of a poor cohort study:

	Exposed	Non-exposed	Control	n	OR
Exposure				5	0.2
Non-exposure				5	0.2
Control				5	0.2
Outcome				5	0.2
Non-outcome				5	0.2
Total				5	0.2

Fail to :

- 1. clearly define comparison groups and/or measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or
- 2. identify or appropriately control known confounders and/or
- 3. carry out a sufficiently long and complete follow-up of patients.

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Randomised Controlled Trial - RCT

	Treatment	Control	n	SD
Age			5	0.12
Sex			5	0.12
Height			0.12	0.12
Weight			5	0.12
Diastolic blood pressure	0.12	0.12		
Systolic blood pressure	0.12	0.12		

Advantages

1. Unbiased distribution of confounders
2. Blinding more likely
3. Randomisation facilitates statistical analysis

Disadvantages

1. Size, time and money - Expensive!
2. Volunteer bias
3. Ethically problematic at times

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Questions to ask:

	Treatment	Control	n	SD
Age			5	0.12
Sex			5	0.12
Height			0.12	0.12
Weight			5	0.12
Diastolic blood pressure	0.12	0.12		
Systolic blood pressure	0.12	0.12		

- Was the study double blinded?
- Was allocation to treatment groups concealed from those responsible for recruiting the subjects?
- Were all randomised participants included in the analysis?

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Crossover Designs: Cohort & RCT studies

Advantages

1. All individuals serve as own controls → reduced error variance → reduced need of large samples
2. All individuals receive treatment (at least once)
3. Statistical tests assuming randomisation can be used
4. Blinding can be maintained

Disadvantages

1. Can't be used for treatments with permanent effects
2. All individuals receive placebo or alternative treatment at some point
3. "Washout period" can be lengthy or unknown

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NOS-M, Bergen May 2005.
Presentations with focus on therapy

- | | |
|------------------------|---------------------------------|
| | <u>Study designs</u> |
| 1. Al-Sukhun, Jihad | Case series |
| 2. Eiriksson, Sigurdur | Vitro* |
| 3. Gjengedal, Harald | RCT |
| 4. Meric, Göcke | Vitro* |
| 5. Obradovic, Srdjan | Vitro* |
| 6. Mustafa, Kamel | Vitro* |
| 7. Meirelles, Luiz | Animal / vitro* |
| 8. Persson, Anna | Vitro* |
| 9. Segerström, Susanna | Vitro* /planned RCT-multicentre |
| 10. Øilo, Marit | Survey/vitro* /planned cohort |
| 11. Örtorp, Anders | Vitro* |

*clinical inference?

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What can you show with a trial?

		The truth	
		A is better than B	A is no better than B
What the trial shows	A is better than B	✓	X
	A is no better than B	X	✓

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What can you show with a trial?

		The truth	
		A is better than B	A is no better than B
What the trial shows	A is better than B	✓	X
	A is no better than B	X	✓

Type 1 error
Alfa error
Optimism error

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What can you show with a trial?

		The truth	
		A is better than B	A is no better than B
What the trial shows	A is better than B	✓	X
	A is no better than B	X	✓

Type 2 error
Beta error
Pessimism error

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Type 2 error

1. Underpowered study
2. Fallacies of observed clinical failures

-

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The scientific merits of any clinical study is improved when it is:

- Large
- Multicentered
- Multidimensional

SO:
START COOPERATING WITH OTHER CENTRES WHEN PLANNING YOUR NEXT CLINICAL TRIAL!

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**THE EFFICACY OF DENTAL IMPLANTS:
EVIDENCE-BASED OVERVIEWS**

From 10 Cochrane reviews on
osseointegrated dental implants

Last update, Nov 2004

Esposito, Coulthard, Worthington, Thomson,
Wennerberg, Jokstad

<http://www.cochrane-oral.man.ac.uk>

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Cochrane systematic reviews

1. Zygomatic implants	0 RCT
2. Hyperbaric oxygen therapy	0 RCT
3. Use of prophylactic antibiotics	0 RCT
4. Perimplantitis	1 RCT (chinese)
5. Preprosthetic surgery vs implants	1 RCT with 60 particip.
6. Bone augmentation techniques	4 RCTs with 95 particip.
7. Surgical techniques	4 RCTs with 190 particip.
8. Immediate, early or conventional loading	5 RCTs with 124 particip.
9. Maintenance	5 RCTs with 127 particip.
10. Various implant characteristics/ systems	12 RCTs with 512 particip.

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10. Various implant characteristics & systems

Is a surface modification, an implant shape or material more effective than the others?

Last literature search: June 2004

12 RCTs with 512 participants and 12 different implant systems (19 RCTs were excluded). 4 RCTs with a 5-year follow-up

Minor significant differences in marginal bone loss and in the occurrence of periimplantitis. No statistically significant difference in failure rates. We do not know whether any implant system is superior to the others.

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9. Maintenance

Which is the most effective maintenance technique or regimen?

Last literature search: June 2004

5 RCTs with 127 participants (9 RCTs were excluded); electric (1 RCT) and sonic (1 RCT) vs manual toothbrush; phosphoric acid gel vs debridement (1 RCT); subgingival vs chlorhexidine mouthrinses (1 RCT); adjunctive listerin mouthrinse (1 RCT). Follow-up: 6 weeks-5 months

Adjunctive listerin mouthrinse reduces dental plaque and marginal bleeding

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8. Immediate, early or conventional loading

Is there any difference if implants are immediately or early loaded?

Last literature search: February 2004

5 RCTs with 124 participants (2 RCTs excluded)

For "good quality bone" mandibles we do not know whether a difference does exist.

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7. Surgical techniques

Is there any surgical technique associated to higher success rates?

Last literature search: September 2002

4 RCTs (5 RCTs were excluded). 2 RCTs compared 2 versus 4 implants with mandibular overdentures (170 participants); 2 RCTs compared a crestal surgical incision with a vestibular incision (20 participants)

We do not know whether a surgical technique is superior.

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6. Bone augmentation techniques

Which is the most effective technique?

Last literature search: December 2002

4 RCTs with 95 participants (6 RCTs were excluded): GTR vs no GTR (2 RCTs); onlay bone graft ± barrier (1 RCT); BioOss + resorbable or nonresorbable barriers (1 RCT). Follow-up with implants in function = 0 days(!)

Non resorbable barriers increase bone regeneration. Resorbable barrier on BioOss induce less infections than nonresorbable barriers on BioOss

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5. Preprosthetic surgery vs implants

Which intervention is more effective: preprosthetic surgery and dentures vs a implant supported denture?

Last literature search: February 2004

1 RCT with 60 participants

Patients treated with preprosthetic surgery and dentures are less satisfied than patients who received an mandibular overdenture on implants

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4. Perimplantitis

Which is the most effective treatment for perimplantitis?

Last literature search: June 2004

1 Chinese RCT (1 RCT was excluded) compared local antibiotics versus debridement in "slight" forms of perimplantitis.

We do not know which intervention is superior.

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3. Use of prophylactic antibiotics

Does the use of prophylactic antibiotics decrease postoperative complications and early failures?

Last literature search: June 2004

0 RCT

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2. Zygomatic implants

Zygomatic implants without bone grafting versus conventional implants in grafted or regenerated bone

Last literature search: June 2004

0 RCT

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1. Hyperbaric oxygen therapy

Does hyperbaric oxygen (HBO) therapy decrease implant failures and complications in irradiated patients?

Last literature search: June 2004

0 RCT

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