Some examples of appropriate designs to evaluate crenobalneotherapy.

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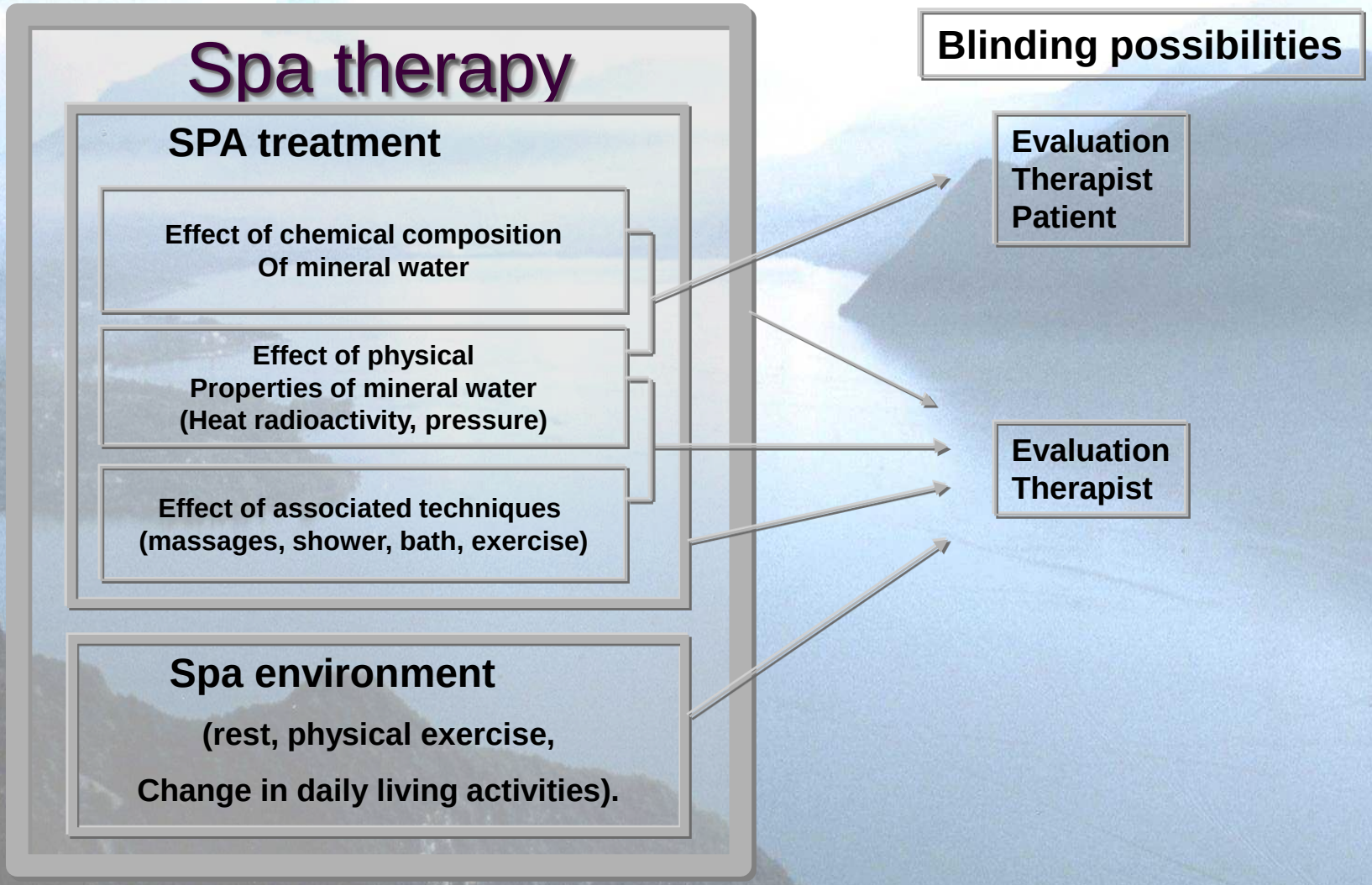
introduction

- There are two main particularities of studies on crenobalneotherapy:
  - it is a multicomponent treatment and
  - it is difficult to obtain blinding of subjects.
- Evaluation of crenobalneotherapy
  - should be based on a appropriate statistical analysis
  - but sometimes showing a statistical difference is not enough to show that the treatment is effective.

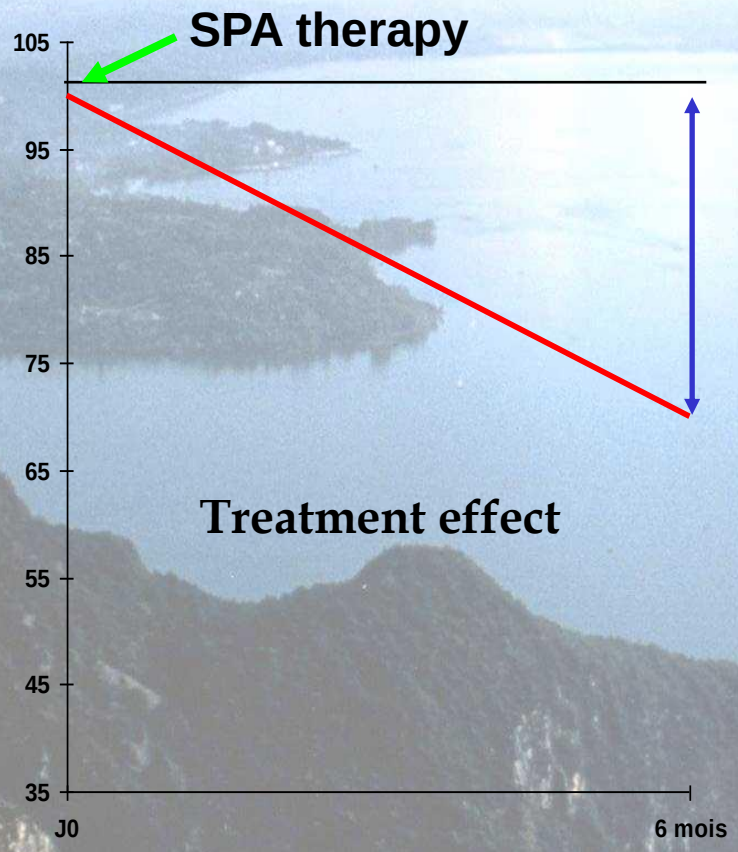


Components of spa therapy

Open study

- The most common way to evaluate is to use an open study. It is the simplest and also the cheapest evaluation method.

Open study



- Advantage :
  - Simple
  - Cheap
- Inconvenient
  - Many bias: the improvement is not always the consequence of the treatment

Open study

- History becomes a threat when other factors external to the subjects (in addition to the treatment variable) occur by virtue of the passage of time.
- The maturation threat can operate when biological or psychological changes occur within subjects and these changes may account in part or in total for effects discerned in the study.
- The testing threat may occur when changes in test scores occur not because of the intervention but rather because of repeated testing.
- Instrumentation bias: when study results are due to changes in instrument calibration or observer changes rather than to a true treatment effect.
- The regression threat can occur when subjects have been selected on the basis of extreme scores.

Comparative study

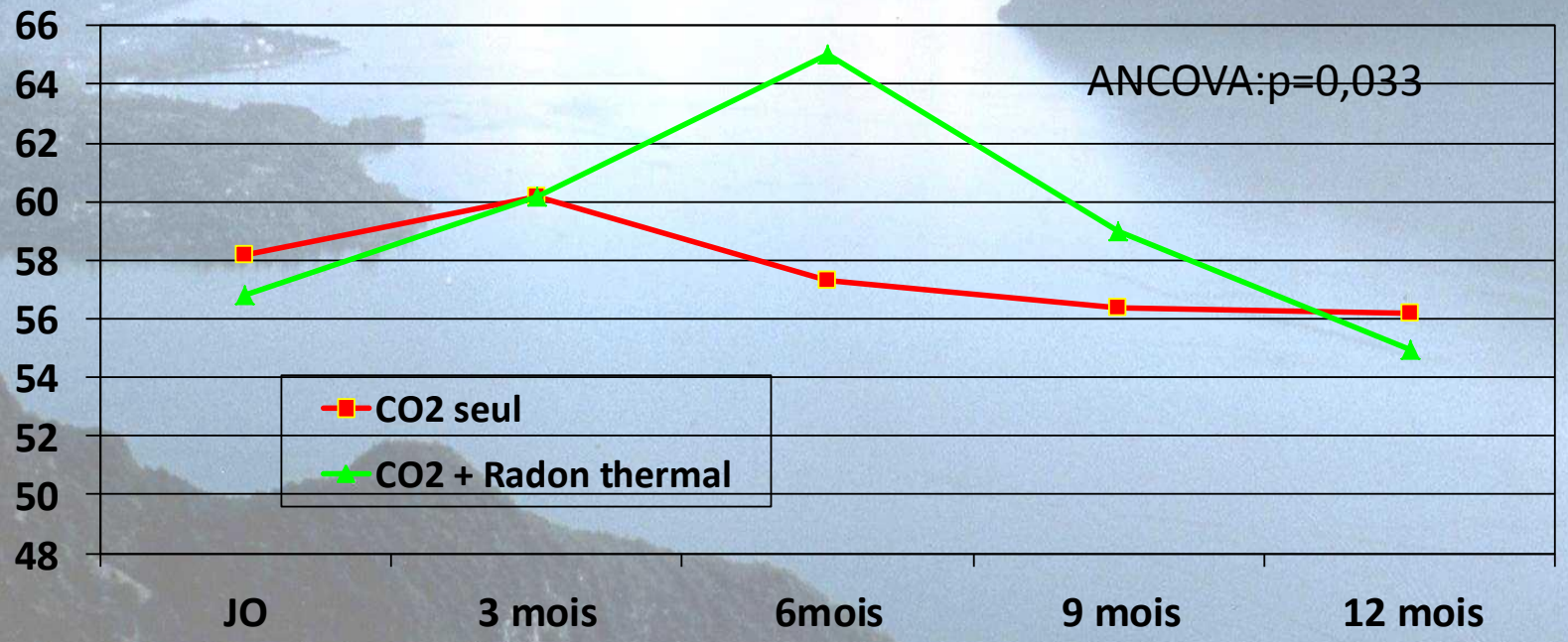
- Double blind is possible. It is appropriate to evaluate SPA products
  - Mineral water Vs flat water (but color and taste are usually different)
  - Mineral mud Vs depleted mud
  - Radon vs no radon

Long term benefit of radon-spa therapy in the rehabilitation of rheumatoid arthritis: a randomized clinical trial. Franke A, Reiner L, Resch KL. Rheumatol int 2007;27:703-13.

- Comparison of radon baths rich in bicarbonate & artificial bicarbonate baths without Radon
- 134 patients included in a multimodal rehabilitation program (exercise, Physiotherapy, occupational therapy, baths, massages, support psychological))
- Method
  - Analyse en intention to treat analysis
  - Bliniding of patient, therapist and examining physician code-barres
  - Main criteria is maintain in physical activities

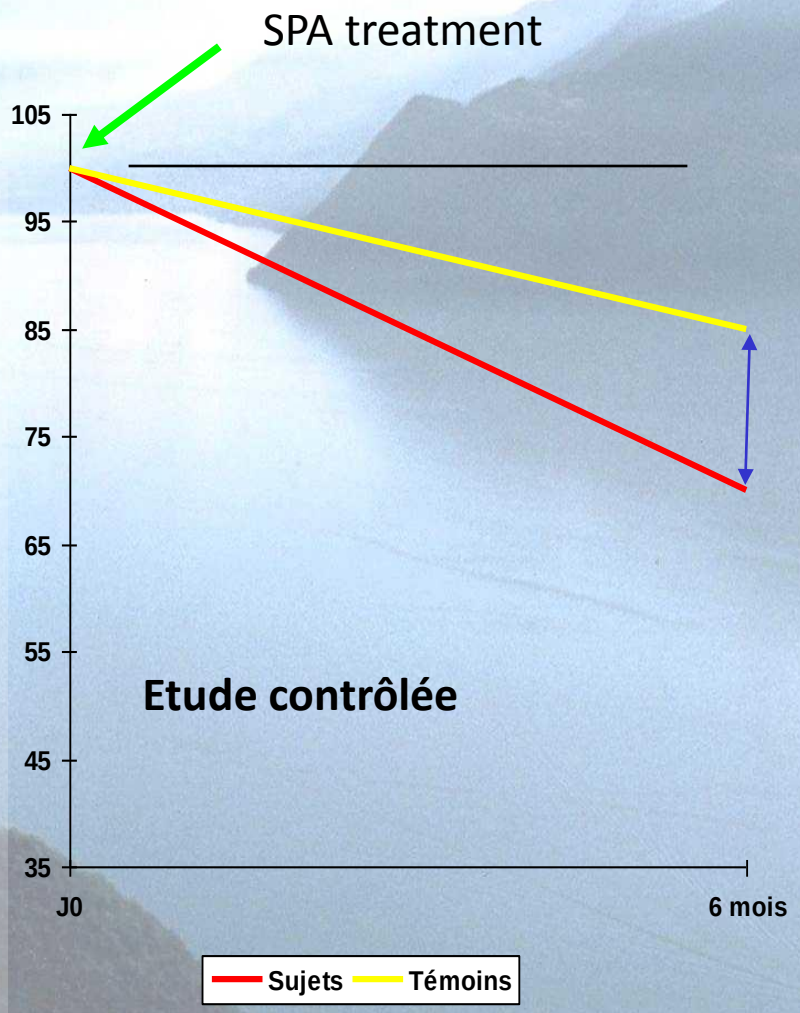
Franke 2007

physical activity in rheumatoid arthritis



Comparative study

- Avantage : control the previous bias
- Inconvénients
  - More expensive (X2)
  - More difficult to organize
  - Still some bias remaining ➔



Comparative study

- The selection threat is of utmost concern when subjects cannot be randomly assigned to treatment groups, particularly if groups are unequal in relevant variables before treatment intervention.
- Some trials are comparing balneotherapy with no treatment. It may induce other bias:
- Experimental mortality is also known as attrition, withdrawals, or dropouts and is problematic when there is a differential loss of subjects from comparison groups subsequent to randomization, resulting in unequal groups at the study's end.
- Selection-interaction: is an interaction of the selection threat with any of the other threats.

The control group receives no treatment but is proposed to receive the treatment at the end of the trial.

WAITING LIST DESIGN

Effectiveness of spa therapy in chronic low back pain: a randomised clinical trial. F Guillemin, F Constant, JF Collin, M Boulanger. Rheumatology (Oxford) 1994; 33:148-151

- 102 patients recruited around the spa center
- Randomized in 2 groups
  - 50 patients immediate SPA treatment
  - 52 patients delayed SPA treatment
- Blinding of the examining physician

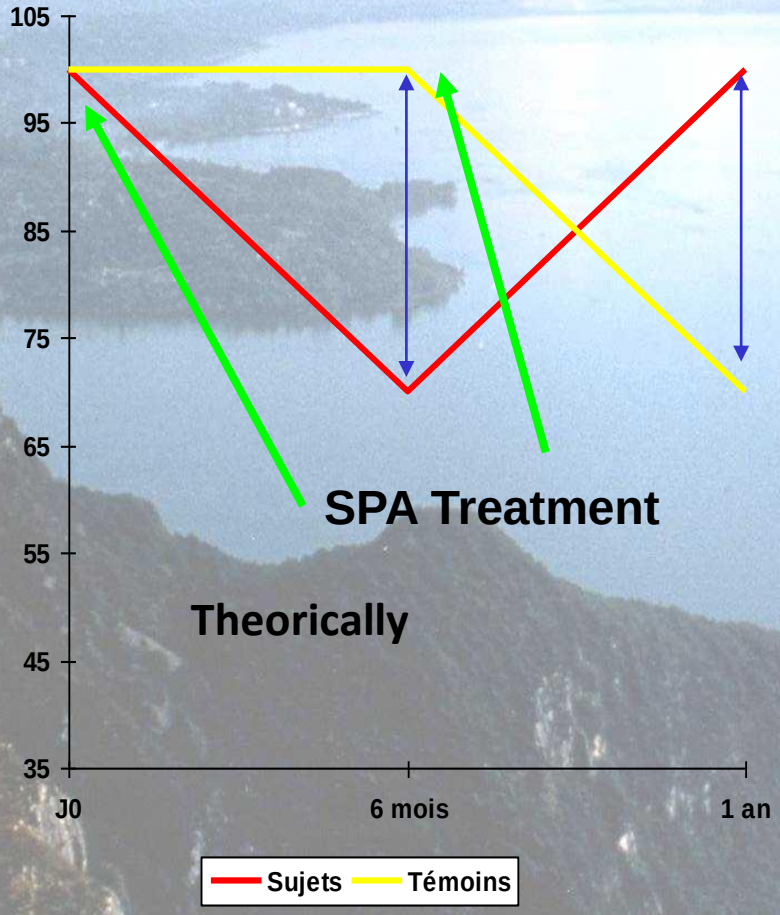
Guillemin 1994, low back pain

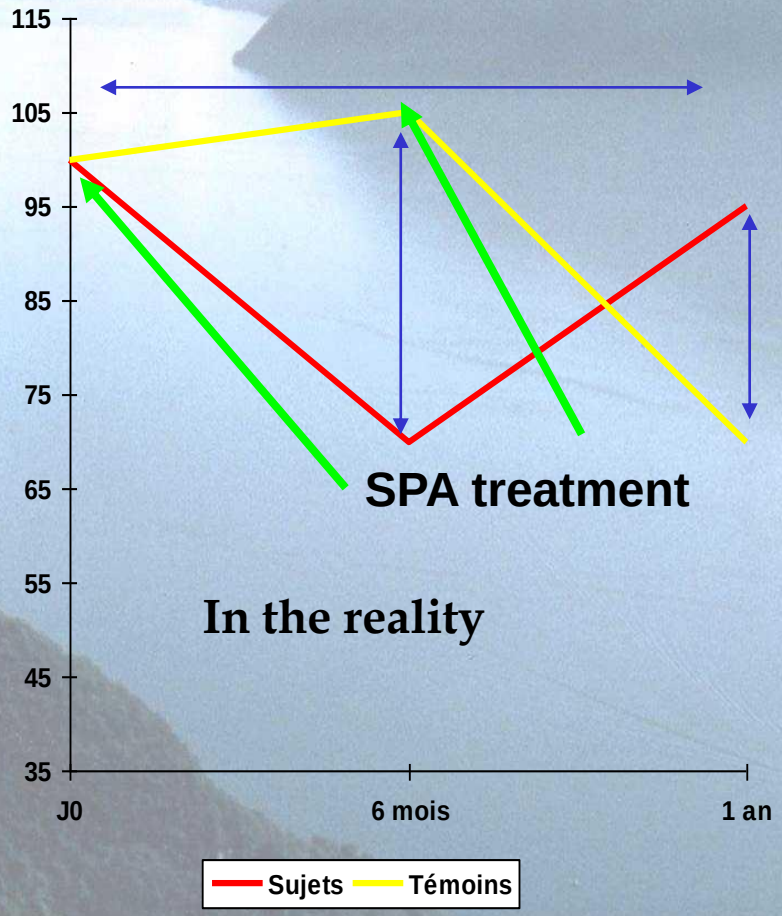
	3 weeks			6 months		
	Spa tt	control	p	Spa tt	control	p
Pain duration	-3,6	-0,3	<0.0001	-3,9	1,3	<0.0001
Pain intensity	-32,2	-0,2	<0.0001	-34,4	7,1	<0.0001
Hand-floor distance	-4,2	1,7	<0.0001	-4,9	3,4	<0.0001
Schöber index	5,8	-3,5	<0.0001	7	-5	<0.0001
Waddel score	-1,19	-0,005	<0.0001	0,09	0,18	NS
Pain killer	-60%	-2%	<0.0001	-40%	11%	<0.0001
NSAI	-58%	-5,80%	<0.0001	-58%	4,30%	<0.0001

Waiting list design

- Decrease the attrition bias in the control group when no treatment is delivered
- This may induce a “deception bias” in the control group that will cause an overestimation of the treatment effect.

Waiting list design



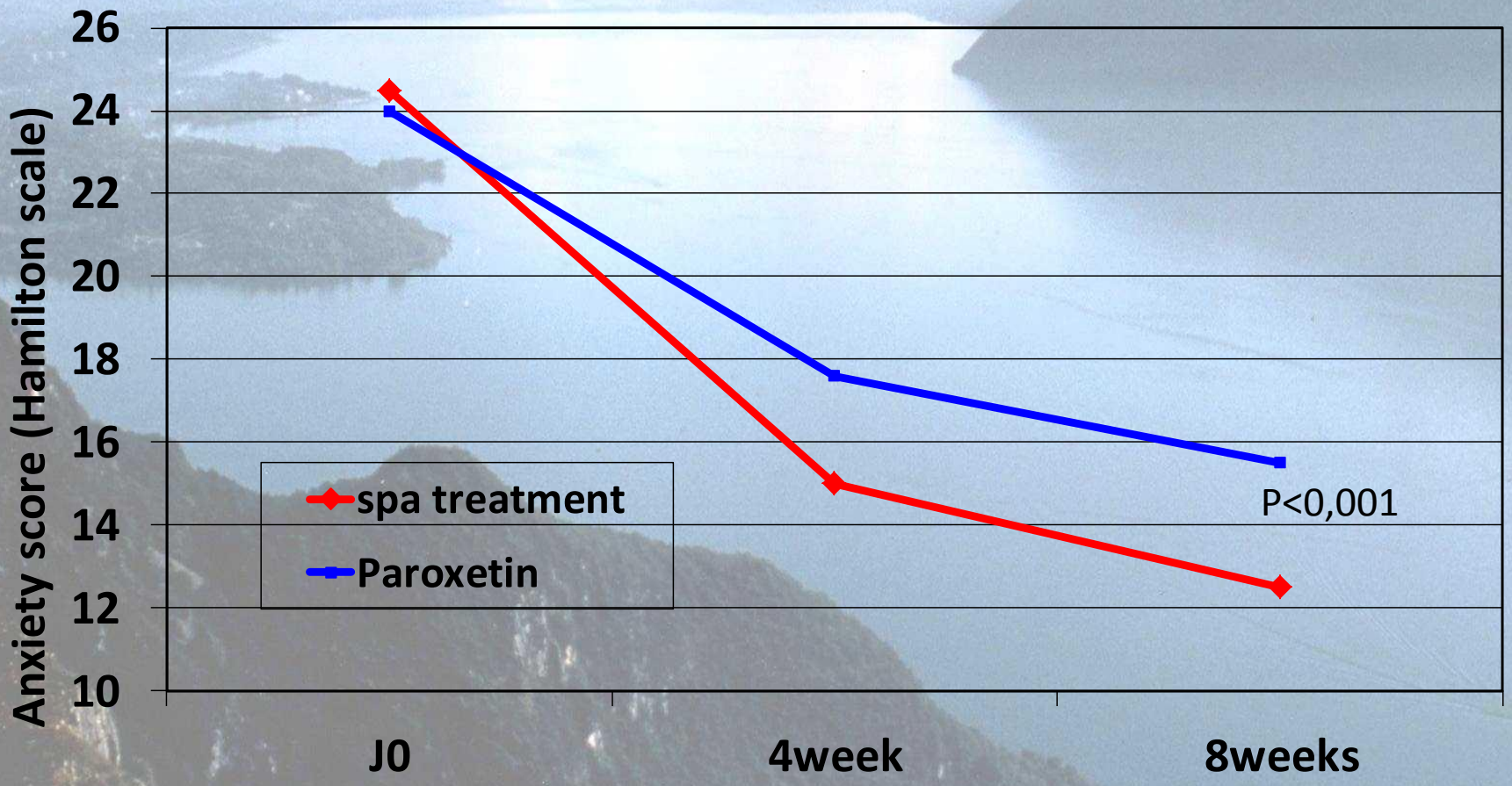


COMPARISON OF SPA THERAPY WITH A VALIDATED TREATMENT

Balneotherapy versus paroxetin in the treatment of generalized anxiety disorder. Dubois O, Salamon R, Germain C & al. Compl Ther Med 2010;18(1):1-7.

- 237 patients in 4 SPA center, block randomization, blinding of randomization, blinding of assessment
  - 117 patients in the SPA therapy group: 10' of bath in swimming pool, 3' shower, 10' massages.
  - 120 patients with 20mg/day paroxetin
- At 8 weeks Hamilton scale is more improved in the SPA group than in paroxetin group (-12 vs -8.7; $p<0.001$)

Dubois 2010 treatment thermal de anxiety generalized



Comparison with a validated treatment

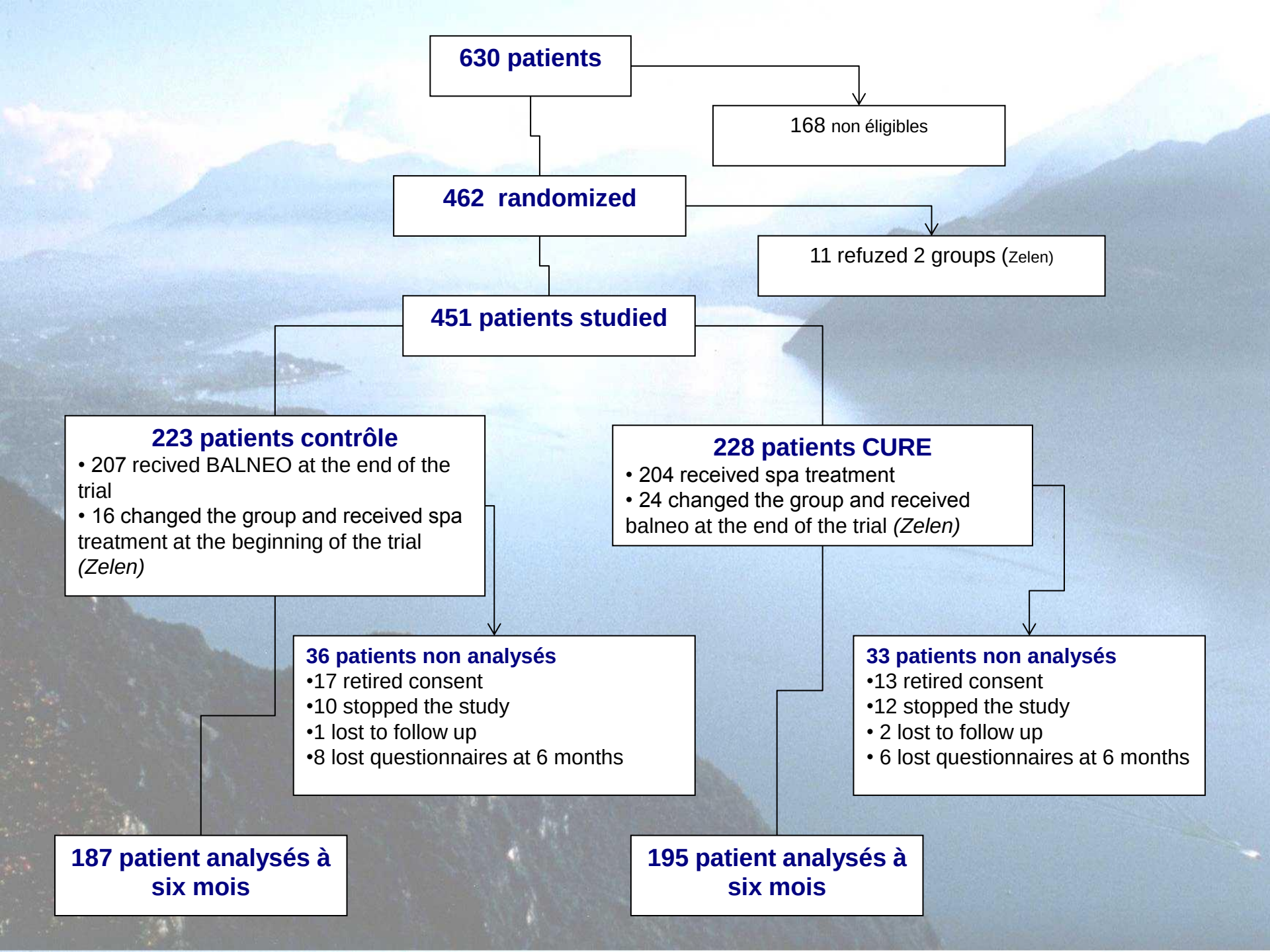
- Not always validated treatment
- More difficult to show the superiority of the spa treatment → more patients, more expensive.

Zelen randomization

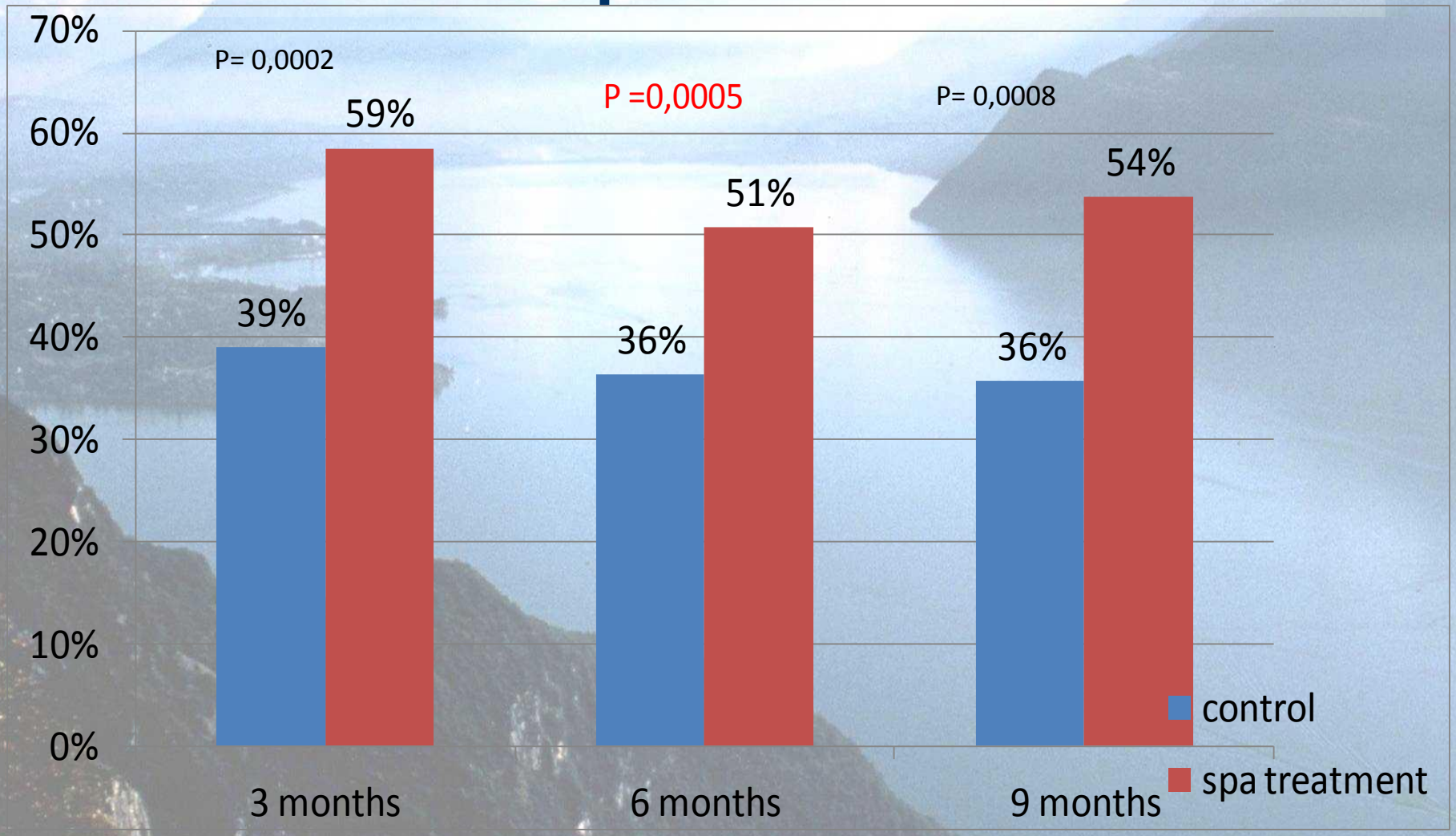
- In this design, none of the groups are informed about the treatment delivered to the other group.
- It is sometimes difficult to obtain ethic committee approval with this design because of difference of information given to the different groups which is not allowed by the Helsinki Declaration.
- In order to solve the problem Zelen design accepts that the patient refuses the randomization group.
  - In that case he receives the treatment delivered to the other group but,
  - in order to preserve their comparability, he is analyzed in the initial group,.

Spa therapy in the treatment of knee osteoarthritis, a large randomized multicenter trial. R Forestier, H Desfour, J-M Tessier, A Françon, A Foote, C Genty, C Rolland, C-F Roques, J-L Bosson. *Ann Rheum Dis 2010;* doi:10.1136/ard.2009.113209

- 462 patients randomized in 2 groups
  - 1 group home exercise
  - 1 group home exercise + SPA therapy (mud application, supervised water exercise , underwater massages)
- Methodology
  - 3 SPA center in France
  - Blinding of randomization Zelen randomization, blinding of therapists
  - Independence of examining physician, statistical analysis
  - Patients' self questionnaire
  - Main judgment criteria qualitative and clinically relevant


630 patients
168 non éligibles
462 randomized
11 refuzed 2 groups (Zelen)
451 patients studied
223 patients contrôle
• 207 recived BALNEO at the end of the trial
• 16 changed the group and received spa treatment at the beginning of the trial (Zelen)
228 patients CURE
• 204 received spa treatment
• 24 changed the group and received balneo at the end of the trial (Zelen)
36 patients non analysés
•17 retired consent
•10 stopped the study
•1 lost to follow up
•8 lost questionnaires at 6 months
33 patients non analysés
•13 retired consent
•12 stopped the study
• 2 lost to follow up
• 6 lost questionnaires at 6 months
187 patient analysés à six mois
195 patient analysés à six mois

Number of patients with important improvement



Zelen Randomization

- Advantages
  - Some kind of blinding in the control group not informed of the existence of the other group (decrease demoralization bias)
- Constraints
  - Credibility of the control treatment ➔ It will be more difficult to detect a between group difference
  - Necessity of a bigger sample size because of the patient changing groups

Patient’s preference design

- In fact, in the background patient's blinding problem reflects the problem of patient’s preference that may influence the result of the comparison.
- Patient’s preference design is delivering
  - the treatment A to those that prefer treatment A,
  - treatment B to those that prefer treatment B
  - and performs the randomization only for those who don’t have any preference. Potential difficulties of this design that has never been used in crenobalneotherapy will be discussed.

Patient's preference design

- Can estimate the treatment effect in each situation
- More objective evaluation of the treatment