Meten is Weten – Toch?

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Het probiotica affaire PROPATRIA

- RCT: **R**andomized double(triple?)-blind **C**linical **T**rial to test probiotics in **S**evere **A**cute **P**ancreatitis (pancreas = *alvleesklier*)
- *Severe* means *necropathy* (dead tissue)
- Theory: Necropathy => Infectious complications => Death
- Theory: 1st acute phase => immune (over)response; 2nd phase: depressed immune reaction => spread of infections (breakdown of ... barriers) => ...

Theory (cont.)

- *Antibiotics* don't work
- *Probiotics* can stimulate immune response; can compete with "bad bacteria"
- Treatment must be *immediate* to be effective
- Must be given to patients with ***P****redicted* ***S A P***

Theory (cont.)

- Suppose rate of SAP within **P**SAP is 90%
- Suppose rate of infectious complications in SAP (6 mnth follow-up), standard treatment, is 50%
- Suppose rate of infectious complications in SAP, probiotica treatment, is 30%
- Then 200 patients needed for (2-sided) type I error (*alpha*) 5%, type II error (*beta*) 20%
- [*Death rate* presently 10%]

Only in NL ...

- Even the biggest hospital has only a handful of cases per year
- At admission, we can only guess if acute pancreatitis is *severe*
- 15 top hospitals together - 100 patients per year - two years
- Couldn’t be done in US ... nor in UK/FR/DE ... nor in China/India/Brasil...

Ethical Issues

- Shouldn't knowingly give *bad* treatment
- Can't prove probiotica is *good* treatment without trying it out
- Shouldn't give standard treatment if we believe probiotica is better
- Interests of individual patient in trial vs. interests of future patients

Ethical issues (cont.)

- A randomized trial is *much much* better than a non-randomized trial
- A double-blind trial is *much much* better than a non-blinded trial
- Double-blind => individual *doctors* delegate some of their responsibility to *Monitoring and Safety Committee*
- *Triple-blind*: the MSC only knows about "group A" and "group B" but *must* deblind if their conclusions would depend on the identity of the two groups
- Why? because doctors tend to stop trials too soon because outcome is looking good!

Ethical issues (cont.)

- "Because of ethical issues" (Helsinki declaration...), we will do an *interim analysis* à la Snapinn
- Take a look at N=100 (one year)
- If interim result is already strongly in favour of priobiotica, *stop for significance* (it is almost certain final result will be significant *for* probiotica)
- If interim result does not much favour probiotica, *stop for futility* (it is almost certain final result will not be significant *for* probiotica)
- *Stopping for futility* is not just economics, it's also a *safety* measure!

Interim analysis (à la Snapinn)

- We will take a look at N=100
- Compare rates of IC in two groups
  - If (1-sided) p-value<0.001 then *stop for significance*
  - If (1-sided) p-value>0.30 then *stop for futility*
  - Theory: alpha (type I error) is unchanged; beta (type II error) is hardly worsened

[Aside]

- Phase III experiment before phases I or II?
- Role CENTERNOVEM, ...
- Experiments with animals?
- Food-supplement or medical treatment?
- Microbiology...

[Aside]

- Was the *ethical-testing committee* competent? (the 15 committees!?)
- What *was* the protocol?

What happened (start)

- PROPATRIA starts

January 2005

What happened (1 yr)

- After one year, N=100, MSC saw over-all rate of death "as normal", little difference between groups, overall rate of IC 30%, so far no *safety issues*
    - MSC proposed to add 3rd year, ie run till N=300, *in order to safeguard statistical power*

January 2006

What happened (1.6 yrs)

- MSC did interim analysis at N=168 (should have been 150?)
- Advice: trial may run to completion

End of Summer 2006

What happened (3 yrs)

- Identity of groups A and B revealed
- Rate of IC in *placebo* group and *treatment* group almost same (30%)
- Rate of Death in *placebo* group half that in *treatment* group (*overall* rate: 10%)
- 9 cases (8 deaths) of "bowel ischaemia" in *treatment* group, *none* in placebo group (non IC)

December 2007

What happened (4th yr)

- Press conference
- Media interest
- Sales of Yakult collapse
- Recruitment in RCT's collapses
- Data is kept secret
- Publication in Lancet!!!
- IGZ, CCMO, WGZ start investigation
- Patients (patients' relatives) file law suits

2008

What happened (4th yr)

- Meester & ... *Trouw*: they must have known half-way that it was going to turn out bad
- RDG attacks *triple-blind*
- Gooszen c.s. deny everything
- Hester van Zanten (NRC) finds data from interim analysis
- RDG meets Gooszen c.s.
- The MSC used SPSS; SPSS doesn't ask *which* 1-sided hypothesis to test but reports "best result" of two

What happened (5th yr)

- TNO report comes out: probitioca as *food supplement* is completely safe; but use in PROPATRIA trial was *medical*
- RDG meets CCMO & IGZ
- RDG meets Gooszens and Besselink

2009

Meten is weten?

- Was the probiotica treatment bad for the patients?
- Long slow struggle to restore people's trust of doctors and in medical research (!?)
- The data is still secret (!!!!!!!)
- If I show you the official protocol, I pay a fine of E.15 000

Conclusions

- Early stopping in RCT's [a good thing!] raises complex statistical issues and requires professional statistical expertise
- Blinded MCT's should include in an advisory role a professional statistician, who is not blinded
- The traditional secrecy/closedness of the medical establishment is contrary to science