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Quality of life & regulatory issues

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Where is the gap ?

- Rationale for HRQoL assessment in chronic diseases is recognized by firms, and regulatory authorities.
- Huge amount of HRQoL data published or included in the dossiers of drugs for drug approval submission.

Ü Still low number of drug approvals with HRQoL benefit claims

Quality of HRQoL trials ?

- Poor quality and flawed HRQoL assessment in clinical trials.

- Thus reporting on quality of life should follow some guidelines like CONSORT.

Sanders C et al. Reporting on quality of life in randomised controlled trials: bibliographic study. BMJ 1998; 317: 1191-1194.

Chassany O et al. Reporting on quality of life in randomised controlled trials. BMJ 1999; 318: 1142.

Regulatory authorities

Big challenge, especially regarding the EMEA and national European Drug Agencies

- To convince them — that HRQoL is a relevant key outcome

- To make them confident — in the quality of the HRQoL results

- To help them — in reviewing and interpreting HRQoL results

Where is HRQoL assessment ?

- Proton pump inhibitor / oesophagitis
- Phase III : 2 studies in USA, 1 study in Europe
- > 700 patients included

HRQoL claim

Ü but no clear definition of HRQoL neither in the study report, nor in the protocol

- Overall physical well being (0 to 4)
- Time lost from usual activities of daily living

(less time lost in placebo group !)

HRQoL questionnaire validated ?

- Proton pump inhibitor / dyspepsia
- Phase III, RCT, DB, vs comparator & placebo
- n = 810, 2 weeks duration

HRQoL assessment (secondary)

Some unknown QoL index was used

Ü no description of validation data, no reference

Ü 10 additional items concerning gastro-intestinal symptoms were approved by Pr X !

International trials and linguistic validation of questionnaire

- Treatment in claudication
- Phase III, RCT, DB, vs placebo, n=422, 6 months
- Setting in France and Italy

Results : initial change distance : D 32% vs placebo

HRQoL assessment (secondary)

- PQVS French generic questionnaire

Ü Italian version : not a word about linguistic validation

European mutual recognition procedure

Intent to treat analysis and missing data

- Treatment in claudication
- Phase III, RCT, DB, vs placebo, n=422, 6 months
- Results : initial change distance : D 32% vs placebo

HRQoL assessment (secondary)

- PQVS French generic questionnaire
- First factor of principal component analysis : global satisfaction (p=0.049, t-test)

Ü Analysis performed on 324 patients

Ü How many and how were handled missing data ?

European mutual recognition procedure

Multiple test comparisons

- Treatment in claudication
- Phase III, RCT, DB, vs comparator, n=324, 3 months
- Results : NO difference in walking in ITT

HRQoL assessment (secondary) : PQVS

- First factor of principal component analysis : global satisfaction (p=0.038, t-test)

Ü univariate analysis : statistical difference for 5 items among 19 (Per protocol analysis, n=268)

Ü A statistical difference is likely to appear by random in about 5 items (type I error = 25%) !

European mutual recognition procedure

Type I error value

Number of tests	Global Type I error
1	0.05
2	0.08
3	0.11
4	0.13
5	0.14
10	**0.19**
20	0.25
50	0.32

according to the number of statistical tests performed within a study at the 0.05 level of significance

Clinical relevance of a difference

- Treatment in rheumatoid arthritis
- Phase III, RCT, DB, vs comparator, n=99, 6 months
- Results : Large improvement of ACR criteria (> 20% improvement : 71% (new drug) vs 27% (comparator)

HRQoL assessment (secondary)

- Health assessment questionnaire (HAQ)
- Differences on “disability”, “vitality” and “mental health” domains

Ü e.g.”disability” score (range : 0 to 3) at 6 months : 1.2 (comparator) vs 0.9 (new drug), how to interpret ?

Claim of HRQoL improvement ?

- Treatment in claudication
- Phase II, RCT, DB, dose-ranging vs placebo, n=340

Results : NO difference (absolute change distance)

HRQoL assessment (secondary) :

- SF36 : significant differences on “social function” and “mental health” scales
- NO difference on “pain”, “physical function”

Ü Improvement of HRQoL ? (i.e. how many domains)
Ü Can it replace clinical end-point ?

European mutual recognition procedure

What measures the questionnaire ?

- Treatment in rheumatoid arthritis
- Phase III, RCT, DB, vs comparator & placebo, n=485, 52 weeks

Results : **some improvement in clinical end-points**

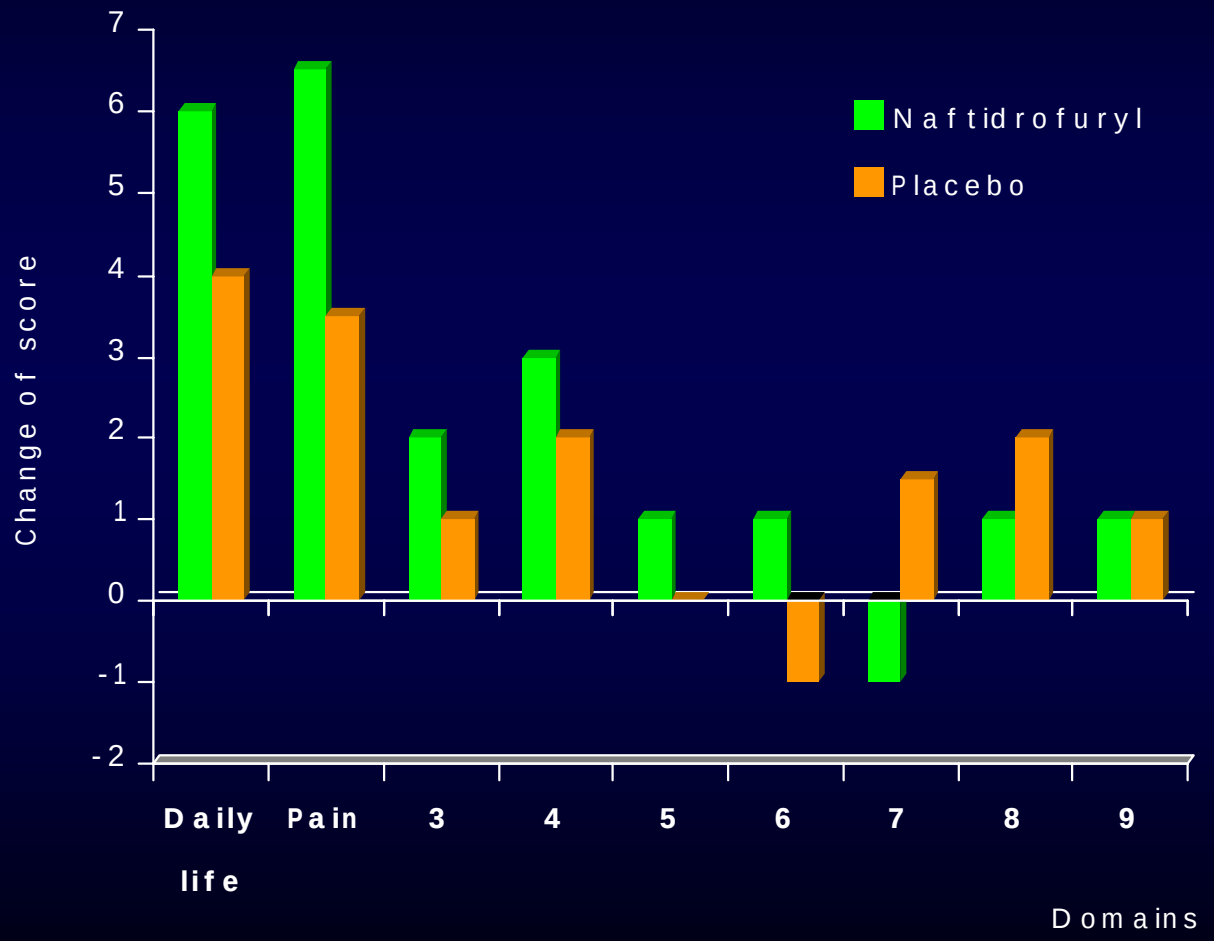
HRQoL assessment (secondary) : **HAQ and SF36**

- **QoL appears better with the new drug, but**

Ü 280 patients analysed, missing data ?
Ü Type I error ? (multiple comparisons)
Ü many adverse events (22% withdrawal vs 8% for placebo) : is the impact of AE recorded by instruments ?

Intermittent claudication

- RCT, DB, versus placebo
- Family practice
- 6 months
- HRQoL : primary end-point
- CLAU-S : 9 domains, 80 items
- ITT (234/250 included)
- Statistical significance set at 0.05/9
- Missing data : LVCF
- Not a value, just p-value and a graph



Liard F et al. The effects of naftidrofuryl on quality of life. Dis Manage Health Outcomes 1997; 2 (Suppl. 1): 71-78.

Does it improve HRQoL or not ?

The 2 scales measures only a clinical improvement

Reasons that explain this negative results

- Questionnaire not validated/not responsive
- Underpowered study
- Patients not severe enough
- Treatment inefficient in claudication

The author ’s conclusion in not acceptable : « *this study is the first RCT vs placebo to show a significant improvement of HRQoL* ».

Use and abuse of QoL

QoL is a vague and ethereal entity, something that many people talk about, but which nobody clearly knows what to do about.
(Campbell 1976)

The idea has become of an umbrella under which are placed many different indexes dealing with whatever the user wants to focus on.
(Feinstein 1987)

Checklist on reporting on HRQoL in RCT

- No objective
- No implementation of HRQoL
- No justification of sample size
- No clear handling of missing data
- No description of follow-up
- Not all the patients are analyzed
- No correct presentation of results
- No adjustment for multiple test comparisons
- No interpretation of results

Checklist on reporting on HRQoL in RCT

- **No objective**

Ü Justify study objective

Ü Justify rationale for HRQoL use

Ü Justify choice of instrument (validated, adapted for the disease-condition)

- **No implementation of HRQoL**

Ü Consider the practical issues

Ü Training of personnel

Ü Standard operatory procedures

Ü Extra resources

Ü Eligibility criteria

Ü Timing of assessment

Ü Mode of administration

Ü Completion time

Ü Data collection

Ü Multicenter trials

Ü International trials

Ü Scoring scheme

All these issues must be resolved before the start of the trial and described in the protocol and study report

Checklist on reporting on HRQoL in RCT

- **No justification of sample size**

Ü Justify sample size (primary end-point)

- **No clear handling of missing data**

Ü How to prevent missing data

Ü Description of missing data

Ü Handling of missing data (LVCF, imputation)

- **No description of follow-up**

Ü Description of all the patients included

(flow chart)

All these issues must be resolved before the start of the trial and described in the protocol and study report

Checklist on reporting on HRQoL in RCT

- **Not all the patients are analyzed**
  - Ü Intent to treat analysis
- **No correct presentation of results**
  - Ü Clear distribution of **all** scores in each group
  - Ü Score differences between groups
- **No adjustment for multiple test comparisons**
  - Ü Adjusting (statistical test, level significance)
  - Ü Reducing number of comparisons (index)

All these issues must be resolved before the start of the trial and described in the protocol and study report

Checklist on reporting on HRQoL in RCT

- **No interpretation of results**

  Ü **Try at least something !**

    Ü Effect size

    Ü Comparison with other end-points

    Ü Comparison to norm values in other diseases or general population

    Ü Determination of a minimal important difference

    Ü Number (of patients) needed to treat

Conclusion

Even if some major issues of HRQoL are still unresolved (e.g. interpretation), regulatory authorities will accept more easily HRQoL statistical significant results if they have confidence in the quality of the trial itself and finds in the clinical report and the protocol all the information, description and justification described above. Thus, the clinical relevance of results will appear less important.

Whether the endpoint is considered primary or secondary, the scientific principles of clinical trial design must apply to Health-Related Quality of Life.