

## How to Deal with the “Worse Than Death” and the Intercurrent Events of “Death”

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## Result

## Estimand strategies : each endpoint

Three estimand strategies are detailed below :

## (1) CFB at visit(t)

**Hypothetical strategy**

## • Handling of ICEs

QOL values in the period after death need to be evaluated because the analysis is performed under the assumption that Actual Deaths (ICEs) did not occur. Therefore, QOL values that were not collected because of Actual Deaths are complemented by certain values.

(e.g.) - Single imputation : Values obtained immediately before death are used as LOCF

- Multiple imputation

## • Relationship between ICEs and WTD

The WTD-related problem does not need to be considered because the analysis is performed under the assumption that no ICEs occurred.

**Composite strategy**

## • Handling of ICEs

Index Value of Actual Death is defined as 0.

## • Relationship between ICEs and WTD

The phenomenon of WTD < Actual Death occurs.

## • Considerations

It is necessary to determine whether Index Value of Actual Death can be defined as 0.

## (5) CFB at visit(t)

**Composite strategy**

## • Handling of ICEs

Actual Death is defined as worse than WTD (Score: BTD > WTD > actual death).

Regarding the QOL at a given time point X, the composite endpoint is defined such that higher scores indicate a better health state. Responder Rate are then used to compare two groups.

## • Relationship between ICEs and WTD

The assumption that the QOL of actual death (ICE) cases is worse than that of WTD cases can be reflected in the results.

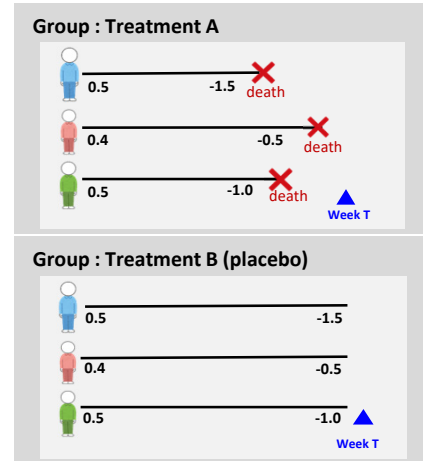
## • Considerations

- Clinically interpreting the win-ratio might be difficult.
- ‘Win’ needs to be defined when scores are compared.

## The example of win-ratio

Parallel-design placebo-controlled study of treatment A under development

**Clinical Question:** Improvement in EQ-5D-5L index values at Week T is compared between the patients who received Treatment A and those who received a placebo (Treatment B).

**Composite strategy**

In the analysis of data obtained at Week T, the Index Values of all patients in the Treatment B were WTD, whereas all patients in the Treatment A actually died.

## (1) Change from baseline

treatment A:  $CFB = \text{mean}(-0.5, -0.4, -0.5) = -0.47$

treatment B:  $CFB = \text{mean}(-2.0, -0.9, -1.5) \div -1.47$

**Conclusion:** The QOL in the Treatment A group is higher than that in the Treatment B even though all patients in the Treatment A died.

## (3) win-ratio at visit(t)

treatment A:  $(0[d], 0[d], 0[d])$

treatment B:  $(-1.5, -0.5, -1.0)$  [d] = Actual Death

**Conclusion:** The use of the win-ratio enables the QOL of Actual Death to be lower than that of WTD. This proposal offers an approach to rating the QOL of Actual Death lower than that of WTD.

## Appendix

## Estimand attributes and strategies

The ICH-E9R1 provides five attributes and strategies that are important for applying an estimand framework. Tables 2 and 3 show an example of the application of these attributes and strategies.

**Example: Parallel-design placebo-controlled comparative study of a treatment A under development**

**Clinical Question:** Improvement in EQ-5D-5L score at Week T is compared between the patients who received treatment A and placebo.

Table 2. 5 Estimand Attributes.

Attributes	Description (example)
Treatment condition	Treatment effect in terms of the clinical question (comparison) Group A: New treatment; Group B : Placebo
Population	Population subject to the clinical question The patient who has pain
Variable (endpoint)	Endpoints to be obtained from patients to study the clinical question The change from baseline in Index Value of EQ-5D-5L at Week T
Intercurrent events	Events that affect the study of the clinical question Actual Death
Population-level summary	Population-level summary regarding the clinical question LS mean difference in each treatment group

Table 3. Strategy addressing ICEs when Defining the Clinical Question.

Strategies	Description (how to deal with the ICEs)
Treatment policy	ICEs are considered unrelated to the treatment effect. EQ-5D-5L scores are complemented by estimated EQ-5D-5L scores of dead participants in the period after death. -> Does not occur in the real world.
Hypothetical	ICEs are considered to have never occurred. EQ-5D-5L scores are assumed to be continuously improved if no actual death occurs.
Composite	ICEs are considered a part of variables. EQ-5D-5L score is dealt with as zero (i.e., as bad as dead) when an actual death occurs.
While on treatment	ICEs are considered to have occurred before the end of treatment. Data are complemented by estimated EQ-5D-5L scores in the period from actual death until the end of treatment. -> Does not occur in the real world.
Principal stratum strategy	Populations in which no ICEs occur are identified and evaluated. Actual death is known to be unlikely to occur in populations with high baseline EQ-5D-5L scores. Therefore, EQ-5D-5L scores are evaluated only in these populations.