Conflicts of interest
The project was funded by the University of Southern Denmark. None of the authors have conflicts of interest to disclose.

Background & Objectives
The magnitude of risk for adverse drug reactions may be communicated by a measure of “exposure needed for one additional patient to be harmed” (ENH). The ENH expresses the number of person years of exposure that on the average would be required to provide one additional outcome, given the calculated ORs and other study output. We present four ENH measures, based on four different counterfactual contrasts, as illustrated by the known association between NSAID use and peptic ulcer bleeding.

Methods
Data were derived from a case-control dataset on NSAID and severe peptic ulcer bleeding, collected in Funen County 1995-2006. We incorporated prescription and census data to account for the source population’s drug use and demography. Four measures of ENH were calculated:

- **Basic ENH** (the entire source population treated vs none treated)
  \[ \text{NNTH} = \frac{1}{\text{OR} - 1} \cdot \text{UER} \]
  Where UER is the incidence rate of the outcome among unexposed in the source population, and OR the odds ratio associating exposure with the outcome

- **Age-restricted ENH** (the entire source population above e.g., 50 vs none above 50 treated)
  The equation is applied only to the source population and case material above 50 year of age

- **Standardised ENH** (a population of similar age and gender distribution as those actually treated vs same subjects not treated)
  The equation is applied to a standardized data set.

- **Naturalistic ENH** (those actually treated vs same subjects not treated)
  \[ \text{Naturalistic ENH} = \frac{\text{PT}^\text{at}}{(\text{OR} - 1 \cdot \text{UER}) \cdot \text{nex}} \]
  Where PT^at denotes the cumulative amount of exposed person-time in the source population and n_ex is the number of exposed cases in the data set.

The input required to calculate each of these measures is shown in table 1.

Results
The four methods resulted in widely different ENH-values, ranging from 131 personyears of exposure to 619 personyears of exposure (Table 1). The value of the age-restricted ENH depended strongly on the chosen age-limit (Figure 1).

Conclusions and Discussion
The differing counterfactual contrasts underlying the ENH result in widely different estimates. These differences are best understood by considering the clinical aspects of NSAID-related peptic ulcer bleeding; strong age dependency of NSAID use, strong age dependency in the incidence rate of outcome, little age dependency of the odds ratio and channeling of NSAID use to persons with high tolerance for a given age. The ultimate choice of ENH measure will depend on clinical or epidemiological considerations and on availability of data.