The robustness of global optimal designs
Joakim Nyberg and Andrew C. Hooker
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Results
As expected, the D-optimal designs (which use the optimal design in each SSE) is slightly better (bias and precision, fig. 3 and table1) than the robust criteria for both models. All the robust designs except ED perform well for the EXP model, while HCD and BAPI perform best for the EMAX model.

Figure 2. The RSE(%) from the SSE using the optimal designs from the different criteria. The RSE(%) for ED (with k=14) is not visible in the plot but goes up to a maximum of 226% for k=22. Note that the D-optimal designs are the only designs that are changing between f0 values.

Table 1.

The RSE(%) and absolute PE(%) for EXP and EMAX from the SSE. The values in the table are color scaled, i.e. a green value indicates a more precise or accurate value and a value going towards red indicated a less precise or accurate value.

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Conclusions
HCD performs very well and is fast to compute. However, likely to have problems if optimal information vs. the parameter distribution is non-monotonic.
BAPI performs in general very well with low bias but is slower than HCD.
ED-EFF performs good in general but very slow.
API performs good in general but worse than BAPI in the border of the parameter distribution.
ED not robust, overweights the most informative region.

References

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The robustness of global optimal designs

Background
A drawback with local optimal designs (OD), e.g. D-optimal, is that the parameters of the model are assumed known. This is a strong assumption and therefore robust (global) OD has been a suggested approach, i.e. without assuming that the parameters of the model are known but instead distributions of the parameters are known [1-5].

Objective
The objective is to compare different design criteria and to suggest an alternative criterion that overcomes some of the issues with other robust design criteria, such as overweighing certain parameter values.

Methods
Six different criteria were investigated; one local criterion D-optimal and five robust criteria ED-optimal (ED), API-optimal (API), HCD-optimal (HCD), ED-EFF-optimal (ED-EFF) and B-API-optimal (BAPI). The BAPI is designed to spread the support point over the whole design region by splitting the expectation over the parameter distribution into n<i> expectations over subsets of the parameter distribution (where n<i> is e.g. the number of support points).

Two models were investigated; A one-parameter fixed effect (4 samples between 0-100 ind), exp decay model (EXP) and a two-parameter mixed effect (3 doses between 0-& 100 ind). Emax model (EMAX) were f0 and w_f0 (exp IV of 30%) were the parameters to estimate. A uniform parameter distribution was assumed for EXP (D [22] and for EMAX, D [0,1,6.1]. 200 uniformly spread samples from the parameter distribution were used for the robust criteria and a D-optimal design was found for each sample. Multiple (n=1000) simulations and estimations (SSE) were used to check the performance of the designs. Figure 1 and 2 shows the optimal designs using the different criteria.

Figure 1. Optimal designs using different criteria. The red dots are the f0* for D-optimal designs with 200 different f0 values over the entire parameter uncertainty distribution. The dotted lines are the median of the f0 distribution (black) and the median of the D-optimal (FIM) (red). Note that all designs have 4 cluster points except BAPI and HCD (HCD has 2 cluster points). Standard D-optimal design at f0=12 is close to most of the robust criteria except ED which matches the D-optimal design at f0=4.

Figure 2. The shaded area represents the 95% prediction interval from the f0 parameter uncertainty distribution. The thin blue lines are the corresponding f0 values used in the SSE. The D-optimal design for the values used in SSE are present as well as the robust criteria designs. All the design points in the figure are clustered except the BAPI samples and the HCD sample. BAPI and HCD spread the design points as opposed to the other robust criteria which is similar to a D-optimal design for a specific f0 value.