Optimal PK sampling under constraint imposed in later phase clinical trials

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Introduction

Given good prior information on the expected drug concentration-time relationship, theory for computing D-optimal designs is available. Such designs give sampling times that maximise PK information collected during a clinical trial. The assumption is that subjects have blood samples taken at the same fixed times post dose. However, fixed sampling times for each subject rarely happen in later phase clinical trials so designs obtained using mathematical theory may not be optimal given such constraint. The purpose of this presentation is to describe a method using simulation that aims to maximise the PK information collected given the practical constraints of later phase clinical trials.

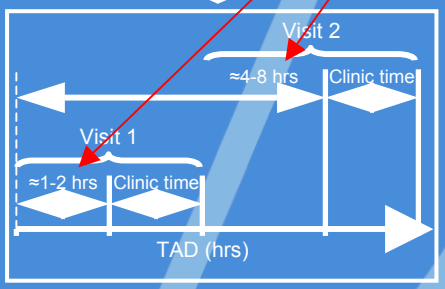
Later phase clinical trial constraints

With successful Phase 1 we should know the PK model. May be first time drug in target population so still much to learn. Constraints:

- PK data collection not primary objective
- Sparse sampling (*e.g.* 2 x 2 samples)
- Some restraint to sampling times
- Compliance

Example protocol

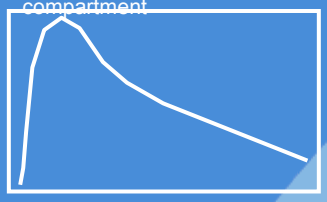
- During **2 visits, 2 blood samples** taken
- Samples **as far apart as possible,** *e.g.* first sample obtained **upon arrival**, second **immediately prior to leaving** the clinic
- Recommended:
  - -Visit 1 subject take dose between **1** & **2** hrs prior to clinic appointment
  - -Visit 2 subject take dose between **4** & **8** hrs prior to clinic appointment



- Random component to when samples are collected (*e.g.* due to visit windows, clinic time)
- Subjects will all have different sampling times
- Need something that incorporates random component
- We've used simulation

Simulation

1. Need a model – first order absorption, one compartment



2. Create sampling windows (see example protocol):

Visit 1 subject take dose between **S1** & **F1** hrs prior to clinic appointment
Visit 2 subject take dose between **S2** & **F2** hrs prior to clinic appointment

Sampling window constraints:

- **S1**: 0-1 hrs by 0.5 hr increments
- **F1**: 3-5 hrs by 0.5 hr increments
- **S2**: 3-18 hrs by 1 hr increments
- **F2**: 5-18 hrs by 1 hr increments

Example sampling windows

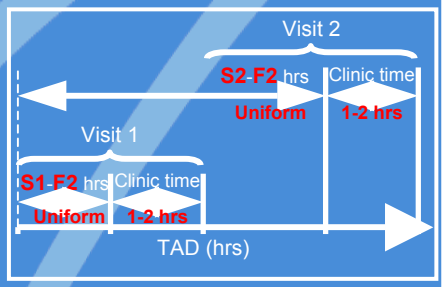
S1	F1	S2	F2
0.0	3.0	3.0	5.0
0.5	3.0	3.0	5.0
1.0	4.0	3.0	6.0
0.5	5.0	3.0	8.0
0.0	4.5	4.0	9.0
1.0	3.5	3.0	12.0
0.5	4.5	12.0	15.0

1600 possible sampling windows!

3. Pick sampling window

3.1 Simulate 100 subjects (1 dose)

3.2 For each subject simulate sampling times constrained by selected sampling window:



3.3 Estimate PK concentration

3.4 Model/fit data (NLME)

3.5 Estimate efficiency (**E**) of sampling window (**E**=1/det(covar matrix))

4 Repeat step 3 on all sampling windows

5 Select best 25% of windows and re-run 10 times:

S1	F1	S2	F2	E
0.0	3.0	12.0	14.0	**3107**
0.0	3.0	10.0	18.0	**3096**
0.0	3.0	11.0	13.0	**2930**
0.0	3.0	11.0	18.0	**2927**
0.0	3.0	15.0	18.0	**2918**

5.1 **F1** at boundary (3.0), so investigated earlier values (0.5–2.5 hrs)

S1	F1	S2	F2	E
0.0	1.0	12.0	14.0	**4626**
0.0	1.5	12.0	14.0	**4308**

Results

Given sampling window constraint, simulation identified four specified protocol parameters (**S1**=0.0, **F1**=1.0, **S2**=12.0 & **F2**=14.0) which would maximise the PK information collected. For comparison, the 4 fixed sampling time points estimated using a D-optimal design were 0.5, 3.2, 15.5 & 16.5 hours (PFIM_OPT [1]). These fixed time points were simulated as above (without random sampling); average **E** was **7520**. This value, although not strictly comparable, represents the maximum information attainable and can used as a standard to compare. The constraint of sampling windows loses efficiency (**4626** v **7520**). This loss is inevitable but we show a method by which it can be minimised.

Conclusion

Simulation discriminates between possible sampling windows giving technique to help maximise PK information collected during later phase clinical trials. The flexibility that simulation affords also allows the solution to be more realistic by further incorporating data collected from previous clinical trials (*e.g.* compliance, clinic time). A full search of all possible sampling windows represents a cost in both time and resource. It is recommended that a combination of both optimal theory and simulation is the best compromise as it will lead to both a faster and more applicable design solution.

References

[1] Retout & Mentré (2003). Optimisation of individual and population designs using Splus. *J. Pharmacokinet. Pharmacodyn.*, 30(6): 417-443.