A Bayesian Randomized Clinical Trial: A Decision Theoretic Sequential Design

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How about a clinical trial design that has the following features???

- Adaptive randomization.
- No patients are assigned to clearly inferior treatments.
- Early stopping for bad responses or for clearly superior treatments.
- For equivalent treatments we may have multiple winners.
- The relative gains of different responses and the toxicity of the treatments used are taken into consideration.
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Moreover, nice Operating Characteristics.

- Fully (extended*) Bayesian, using ideas of Bayesian robustness.

(*) There is an extended Bayesian theoretical framework where multiple utilities (and multiple priors) are considered as “imprecise” definitions of priors and utilities, see for example Rios-Insua, Martin, Proll, French, and Salhi (1997), and references therein.
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Randomization is, non the less, a good thing. We choose to randomize “to avoid biases due to lurking variables and time trends, or because constraints of the regulatory process and peer review require them to do so” etc. (Christen et al., 2004)

How can we justify randomization in a Bayesian setting?

If the expected utility $u^*(a)$ of an action $a$ is equal to the expected utility of another action $a'$, i.e. $u^*(a) = u^*(a')$, then we may choose either of them, and we might as well flip a coin to decide among these two, i.e. both decision are equally good (or equally bad!).
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In other words:

If there are more than one maxima for the expected utility we may randomly select the optimal decision among the maxima.
There are already adaptive clinical trails used today to reject obviously inferior procedures: For example, if the probability of “failure” of a treatment at some stage of the trial is greater than 0.85 with great probability, then stop randomizing patients to that treatment.

There are other Bayesian adaptive strategies in which weighted randomization is done according to the current (using all available data) posterior probability of success of each treatment, or even proportional to the current expected utility of each treatment. Therefore inferior treatments are sequentially and dynamically rejected from randomization (see Chang and Chow, 2005; Atkinson and Biswas, 2005; Cheung, Inoue, Wathen, and Thall, 2006; Zhou, Liu, Kim, Herbst, and Lee, 2008; Dawson and Lavori, 2008, for some recent references).

Full backward induction (dynamic programming) is not commonly used.
But we wanted to explore a formal, decision theoretical, sequential analysis for multiple arms clinical trials, using, at least approximately, dynamic programming.

In fact, we need to decide which treatments to include and which to remove from randomization, and therefore the correct setting should be a decision theoretical one.
In most settings, it is very rare to have two actions with the same expected utility. However, we may think that the utility function, for lack of time, controversy, etc., is not specified with complete “precision”. In that case we in fact have a set of utility functions.
Suppose we have $t = 1, 2, \ldots, T$ treatments and $r = 1, 2, \ldots, R$ responses, and a set $\mathcal{V}$ of possible utility functions.

For any $v \in \mathcal{V}$, the value $v(t, r)$ denotes the utility of applying treatment $t$ and obtaining response $r$. 
Admissible sets

Let

\[ T(v, t) = \sum_{r=1}^{T} v(t, r)P(r | I) \]

be the expected utility of treatment \( t \), given current information, for utility \( v \in \mathcal{V} \).

A core concept in our design is selecting a subset of admissible treatments, namely non dominated sets.
Non dominated sets

A treatment \( t \) is non dominated (see, for example, Rios-Insua et al., 1997) if there is no other treatment \( t' \) such that

\[
T(v, t') > T(v, t), \quad \text{for all } v \in V.
\]

If the set of alternatives is finite, then the set of non dominated treatments is non-empty.
Rule:
Randomize among non-dominated treatments (sets), only.
Sequential analysis

Fix a maximum number of patients to be enrolled in the trail; that is, a horizon $N$ (given the time and/or resources available), and suppose we have a utility function $v(t, r)$ as above.

Let $d_n = 1, n = 0, \ldots, N - 1$, indicate that the trial is stopped at stage $n$ and $d_n = 0$ otherwise. The utility function for the whole trial is defined as

$$u(d_n = 1, t_{n+1}, t_1 \ldots n, r_1 \ldots N+1, v) =$$

$$\frac{1}{N + 1} \sum_{i=1}^{n} v(t_i, r_i) + \frac{n - N}{N + 1} v(t_{n+1}, r). \quad (1)$$

(Adding all individual utilities, the usual utility in multiple arms bandits, see Orawo and Christen (2009) for a comprehensive explanation.)

Miss specification of $v(\in \mathcal{V})$ leads to a set of possible utilities of stopping.
Our design

At any stage $n = 0, 1, \ldots, N - 1$ we decide either to:

1. Take a new patient, choosing his/her treatment by randomizing from the admissible set (the current non-dominated set of treatments).
2. Stop the trail and decide upon the best treatment $t = 0, 1, \ldots, T$. In fact one decides on the final admissible (non dominated) set.

At stage $N$ we start the algorithm at step 2.
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At stage $N$ we start the algorithm at step 2.
When stopping, the optimal decision $t_{n+1}$ is found by maximizing the expected utility

$$U_n(d_n = 1, t_{n+1}, t_1...n, r_1...n, \nu) =$$

$$E\{u(d_n = 1, t_{n+1}, r_{n+1}...N+1, t_1...n, r_1...n, \nu) \mid t_1...n, r_1...n\}. \quad (2)$$

The expected utility of continuing

$$U_n(d_n = 0, t_{n+1}, t_1...n, r_1...n, \nu)$$

may be found using backward induction.
When $T \leq 2$ and $R = 2$ we may calculate $U_n(d_n = 0, \ldots)$ above exactly, using ideas of Christen and Nakamura (2003) and Brockwell and Kadane (2003) and the implementation is explained in Wathen and Christen (2006), JCGS.

For other values of $T$ and $R$, in the original paper we proposed using a 2-step lookahead approximation. A simple program in R (called $tr$), using this approximation, can be used to graphically illustrate how the trail design works.
Implementation

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Algorithm for randomization:

1. For all $v \in \mathcal{V}$, calculate $U_n(d_n, t_{n+1}, t_1...n, r_1...n, v)$ using backward induction.

2. If stopping, $d_n = 1$, dominates, i.e.,

$$\max_{t_{n+1}=0,1,...,T} U_n(d_n = 1, t_{n+1}, t_1...n, r_1...n, v) \geq \max_{t_{n+1}=1,2,...,T} U_n(d_n = 0, t_{n+1}, t_1...n, r_1...n, v) \quad (3)$$

for all $v \in \mathcal{V}$, then stop the trial. Otherwise, randomize the next patient among the non-dominated set of treatments – according to $U_n(d_n = 0, t_{n+1}, t_1...n, r_1...n, v)$.

3. When the trial stops report the non dominated set $A^*$ of treatments – according to $U_n(d_n = 1, t_{n+1}, t_1...n, r_1...n, v)$. 

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Many of them use adaptive randomization, our does ... Scary.

Not many use utility function or utility maximization, our does ... SCARY.

Backward Induction is seldom used (analytically and computationally very complex), our uses BI ... SPOOKY!

More over we use multiple utilities, use non-dominated sets, approximate BI, etc. That is G.W. Bush returning to office!
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New Implementation

- I coded the new “one-arm” approximation of Orawo and Christen (2009) to approximate backward induction of a multiple arm trial with binary response ($R = 2$) in a time of order $N^2$.

- I use the above approximation to create a Python (a Python module called ADeBay) program to run the trial, find the next non-dominated set, and perform Operating Characteristics (see below).

- Both the R and Python softwares may be downloaded from my web page: http://www.cimat.mx/~jac/software.html. No prior knowledge of either R nor Python is needed to run the corresponding program.
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1. $a_r = \text{life expectancy (in weeks, months, etc.)}$ and
2. $p_t = \text{quality of life, number in } [0, 1]$.

This, for an abstract patient, with the eligibility characteristics of the trial. $a_r$ and $p_t$ are allowed to vary within ranges, to generate the utility set $\mathcal{V}$. 
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Let $t = 0$ mean no-treatment. A utility function to be considered for one single patient is

$$v(t, r) = 100 \frac{p_t a_r - p_0 a_0}{p_0 a_0}.$$ 

Note that $p_t a_r$ may be regarded as a QALY (Quality Adjusted Life Years), thus the utility is the percentage differential in QALY’s.

A specific trial is considered in the paper, using feedback from the physician to establish the utilities. Also, the “Operating Characteristics” are studied for that specific trial.
Note that the proposed randomization scheme is adaptive and thus treatments may be dropped, and even taken again, to be randomize, along the trial.

We present a simulation using the R software \textit{tr}.
Illustration using tr...
Illustration using tr

Real Utilities

n = 3 Stop

n = 3 Continue
Illustration using tr

Real Utilities

n = 6 Stop

n = 6 Continue
Illustration using tr

Real Utilities

n = 7 Stop

n = 7 Continue
Illustration using tr

Real Utilities

Utilities

n = 8 Stop

Utilities

n = 8 Continue

Utilities
Illustration using tr

Real Utilities

n = 9 Stop

n = 9 Continue
Illustration using tr

Real Utilities

\[ \text{Utilities} \]

\[ 0.99512, 1.07460, 1.15381, 1.20320, 1.31250 \]

\[ 0, 1, 2, 3 \]

\[ \text{Treatments} \]

\[ n=10 \text{ Stop} \]

\[ \text{Utilities} \]

\[ 0.99096, 1.04770, 1.10470, 1.16180, 1.21880 \]

\[ 0, 1, 2, 3 \]

\[ \text{Treatments} \]

\[ n=10 \text{ Continue} \]

\[ \text{Utilities} \]

\[ 0.99096, 1.04770, 1.10470, 1.16180, 1.21880 \]

\[ 1, 2, 3 \]

\[ \text{Treatments} \]
Illustration using tr

Real Utilities

n= 11 Stop

n= 11 Continue
Illustration using tr

Real Utilities

n = 13 Stop

n = 13 Continue
Illustration using tr
Illustration using tr

Real Utilities

n = 15 Stop

n = 15 Continue

Utilities

Treatments
Illustration using tr

Real Utilities

n= 16 Stop

n= 16 Continue

Utilities

Utilities

Utilities

Treatments

Treatments

Treatments

0.99512
1.07460
1.15380
1.23320
1.31250

1.0021
1.0883
1.1745
1.2607
1.3469

1.0021
1.0883
1.1745
1.2607
1.3469

0
1
2
3

0
1
2
3

0
1
2
3

Christen et al. (CIMAT/MDACC) ADeBay BayesBioStatC 2009, MADCC
Illustration using tr

Real Utilities

\[ \begin{align*}
\text{Utilities} & : 1.2356, 1.2358, 1.2359, 1.2360, 1.2361 \\
\text{Treatments} & : 0, 1, 2, 3
\end{align*} \]

n = 17 Stop

\[ \begin{align*}
\text{Utilities} & : 1.2762, 1.2763, 1.2764, 1.2765, 1.2766 \\
\text{Treatments} & : 0, 1, 2, 3
\end{align*} \]

n = 17 Continue

\[ \begin{align*}
\text{Utilities} & : 1.2762, 1.2763, 1.2764, 1.2765, 1.2766 \\
\text{Treatments} & : 1, 2, 3
\end{align*} \]
Illustration using tr Christen et al. (CIMAT/MDACC)
Illustration using tr

Real Utilities

n= 19 Stop

n= 19 Continue

Utilities

Treatments
Illustration using tr
Illustration using tr

Real Utilities

Utilities

0.99512 1.07460 1.15380 1.20320 1.31250

n = 22 Stop

Utilities

0.99991 1.07000 1.14650 1.21090 1.28130

n = 22 Continue

Utilities

0.99991 1.07000 1.14650 1.21090 1.28130
Illustration using tr

Real Utilities

n= 23 Stop

n= 23 Continue

Utilities

0.99512 1.07460 1.15381 1.20320 1.31050

0.99918 1.06910 1.13890 1.20860 1.27670

0.99918 1.06910 1.13890 1.20860 1.27670

Treatments

Treatments

Treatments
Illustration using tr

Real Utilities

n = 24 Stop

n = 24 Continue
Illustration using tr: STOP!

Real Utilities

n = 25 Stop

n = 25 Continue
We ran an example using ADeBay with the following input:

Life expectancy (in months for example), $a_r$’s above:

<table>
<thead>
<tr>
<th>Rep.</th>
<th>$r$</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1.0</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>4.0</td>
<td>30.0</td>
<td></td>
</tr>
</tbody>
</table>

Toxicity discount factors, $p_t$’s above:

<table>
<thead>
<tr>
<th>Trt.</th>
<th>$t$</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.0</td>
<td>0.9</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>
Example using Python ADeBay

Output produced by the program. The program took approximately 1 hour to run in a 2.2 GHz Intel Core 2 Duo, running under Mac OS (MacBook Pro laptop), with 2 GB of Memory.

**** Operating Characteristics, ****
Number of iterations: 100, trial length: 30
Trt True Prob. Mean n (std. dev) %RS

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.0</td>
<td>4.0</td>
<td>2.4</td>
<td>0.0</td>
</tr>
<tr>
<td>1</td>
<td>50.0</td>
<td>12.2</td>
<td>6.0</td>
<td>58.0</td>
</tr>
<tr>
<td>2</td>
<td>58.0</td>
<td>7.6</td>
<td>6.3</td>
<td>42.0</td>
</tr>
</tbody>
</table>

Mean number of patients enrolled: 23.7 (3.6)
Perc. of trials stopped early: 97.0
Perc. of times the final non-dom. set is included in the true non-dom. set: 100.0

(Several more information is available besides this output.)
¡GRACIAS!
References


References


References


References


