Concept, Design, and Implementation of Novel Clinical Trials

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Making Cancer History®
How well did we do in developing cancer drugs?

Over half of the Phase III trials failed!

Figure 1 Phase transition probabilities for cancer compounds by period of first clinical testing. NDA/BLA, New Drug Application/Biologic License Application.

DiMasi, Clinical pharmacology & Therapeutics, 2013
Limitations of Traditional Clinical Trials

Design depends on good estimation of unknown parameters and assumptions:
- Treatment effect and its standard error (effect size)
- Accrual rate
- Patient heterogeneity
- Known and unknown prognostic and predictive markers

What if the design assumptions are wrong?
- Mid-trial correction?

Conduct is rigid
- No interim analyses – bad!
- Few, fixed interim analysis (number/time) helps but hard to accommodate unplanned interim analysis
- Typically, patients are equally randomized.
How Can We Do Better?

- Do more Phase I trials to determine the best dose, schedule, and route of administration.
- Do more Phase II trials
  - Single-arm or randomized Phase IIA screening trials.
  - Randomized Phase IIB trials to confirm the efficacy.
- Identify prognostic and predictive markers.
- Apply adaptive designs, e.g. adaptive enrichment, adaptive randomization, adaptive marker selection & validation, predictive probability for early stopping for futility and efficacy, etc.
- Do smaller, more focused Phase III trials.
- Continue to learn and to adapt.
3 Primary Goals for Clinical Trials

- Test the safety and efficacy of agents
- Identify prognostic and predictive markers
- Provide better treatments to patients enrolled in the trials
Traditional Designs

Adaptive Designs
What Are Adaptive Designs?
Trials that use interim data to guide the study conduct

- Adaptive dose finding and estimation
  - Continual reassessment method (CRM) in Phase I trials

- Adaptive decision making
  - Predictive probability in Phase II trials
  - Dropping bad treatments; add new treatments

- Adaptive patient assignment to treatment
  - Adaptive randomization in Phase II or Phase III trials

- Seamless phase I/II, II/III designs; combination studies

- Adaptive marker identification and validation

- Adaptive learning
  - Build a comprehensive knowledge database
  - Assign best treatment for each patient
  - Continuous updating of information; testing and validation of hypotheses
Why Adaptive?

- Clinical trial is a learning process.
- It makes sense to adjust the study conduct based on real-time learning during the trial.
- Can identify predictive marker(s) adaptively to enrich the study population.
- Use Bayesian paradigm for flexible and efficient designs and adaptive learning.
  - Adaptive design provides an ideal platform for learning.
    - "We learn as we go."
  - Validation is the key!
  - For both drugs and markers:
    - "Many are Called, But Few Are Chosen"

Lee and Chu, Bayesian Clinical Trials in Action. Statistics in Medicine, 2012.
Adaptive Dose Finding

Continual reassessment method (CRM)
- A model-based method for estimating the dose-toxicity curve
- Estimate MTD based on the available data
- Assign the next patient to the dose closest to the current estimate of the MTD
- Rapid dose escalation
- Simulations consistently show that the model-based method outperforms the 3+3 method in accurately identifying MTD
- 3+3 design only use the information in the current dose to decide the next dose. It is a myopic and inefficient design

Escalation with over-dose control (EWOC), Bayesian model averaging (BMA-CRM), Time-To-Event (TITE-CRM)

> 90 trials reported in the literature

Translation of innovative designs such as Bayesian adaptive designs into trials is a long and slow process (Rogatko, JCO 2007; Chevret, SIM 2011)
Video 1 – Continuous Reassessment Method
Adaptive Estimation of the Response Rate

Suppose we developed a new targeted agent MDA01.

What is the response rate in metastatic lung cancer patients?

The response rate ($\theta$) is an unknown parameter of interest.

Conduct a clinical trial to collect data.

Estimate the unknown parameter $\theta$ from the data

- Point and Interval Estimation
- Hypothesis testing

- All inferences can be made from the posterior distribution of $\theta$
Video 2: Estimate the Response Rate

Response Status ($p = 0.3$)

Distribution of Response Status

Number of Patients

No Response 0
Response 0

Posterior Distribution of Response Rate

95% Confidence Interval of Response Rate

Density

Number of Patients
Phase IIA Design for A Single Treatment

- An efficacy screening trial
- Binary response endpoint with a response rate $p$
- For testing $H_0: p \leq p_0$ vs. $H_1: p \geq p_1$
- Find the sample size to control
  - Type I ($\alpha$) error
  - Type II ($\beta$) error

Frequentist Designs
- One-stage
- Two-stage
  - Gehan’s design
  - Simon’s optimal and minimax designs

Bayesian Design
- Predictive probability design for continuous monitoring
Predictive Probability Design - Adaptive Stopping

For testing $H_0: p \leq p_0$ vs. $H_1: p \geq p_1$

Predictive Probability (PP):
- The probability of a positive conclusion at the end of study should the current trend continue.

At any given time of the trial, try to predict whether the drug is likely to work or not
- If PP is very low, then, stop the trial for futility
- Otherwise, continue to the end of study
- No early stopping for efficacy

### Stopping Boundaries for $p_0=0.20$, $p_1=0.40$, $\alpha = \beta = 0.10$

<table>
<thead>
<tr>
<th>n</th>
<th>Simon’s Optimal</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rej Region</td>
<td>PET($p_0$)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td>0.55</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>2</td>
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<td>24</td>
<td>3</td>
<td>0.0815</td>
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<td>35</td>
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<td>9</td>
</tr>
<tr>
<td>36</td>
<td>10</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Prior for $p = \text{beta}(0.2, 0.8)$

- $\theta_L = 0.001$, $\theta_T = 0.900$
- $\alpha = 0.088$
- $\beta = 0.094$
- $E(N \mid p_0) = 27.67$
- $\text{PET}(p_0) = 0.86$

Simon’s Optimal:
- $\alpha = 0.095$
- $\beta = 0.097$
- $E(N \mid p_0) = 26.02$
- $\text{PET}(p_0) = 0.55$
Simon's MiniMax
Simon's Optimal
PP

Stopping Boundaries

Rejection Region in Number of Responses

Number of Patients
Stopping Boundaries

- Simon's MiniMax
- Simon's Optimal
- PP

Graph showing rejection region in number of responses against number of patients.
Adaptive Randomization

Traditional designs randomize patients equally to treatments via equal randomization (ER)
- Simple: 1:1 for two-arm trials; 1:1:1 for three-arm trials
- Consistent to the “clinically equipoise” principle.
- Maximize statistical power (collective ethics)

Outcome adaptive randomization (AR)
- Assigning more patients to the better arm based on the observed data; Treat patients better in the trial (individual ethics)
- Imbalance causes loss of statistical power
- Study accrual may be faster

AR has substantial benefit over ER when
- the efficacy difference between treatments is large
- Outside trial population is small, e.g., rare disease, and there is an effective treatment

Lee, Chen, and Yin, Worth adaptive? (CCR, 2012)
Video 3: Adaptive Randomization: $P_1 = 0.2$, $P_2 = 0.4$
Bayesian AR with Predictive Probability

- Start with ER for initial learning
- Switch to AR to assign more patients to the better treatment
- Test treatment efficacy by computing the predictive probability
  - If PP is very large, stop the trial for efficacy
  - If PP is very small, stop the trial for futility
- Continue until reaching early stopping criteria or $N_{max}$
- Make a final decision on treatment efficacy

Berry DA. Adaptive Clinical Trials: The Promise and the Caution. JCO 2011
Yin, Chen, and Lee. Phase II trial design with Bayesian adaptive randomization and predictive probability. Applied Statistics (JRSS-C), 2012
Video 4: Adaptive Randomization /w Predictive Probability

Design Parameters

- $N_{\text{max}} = 160$
- $\delta = 0.05$
- $\theta_T = 0.85$
- $\theta_U = 0.99$
- $\theta_L = 0.05$

ER Stage: 40 Patients
AR and Early Stopping
Starts after 40 Patients
PP - P(|p_1 - p_2| > \delta) > \theta_T
Stop if PP > $\theta_U$ or
PP < $\theta_L$

Efficacy Stopping Boundary
Futility Stopping Boundary

$p_1 = 0.2, p_2 = 0.4, \text{Prior} = \text{Beta}(2,2), N_{\text{max}} = 160, \text{ARpower} = 1, \text{ARmin} = 0.1$
Promise & Challenge of Combination Therapy

Promise

– Overcome drug resistance induced by single agents.
– Block the potential by-pass mechanisms in signaling pathways and induce synthetic lethality
– Increase efficacy without increasing toxicity

Challenge

– 2 drugs, 3 drugs, 4 drugs, …?
– Select dose of each drugs
– Schedule
  - Simultaneous; Sequential (which sequence?); Intermittent (how?)
– Biomarkers
  - Selection: discovery and validation
  - Main effect: additive? Non-linear?
  - Interaction effect: treatment x marker; marker x marker

Complexity exponentiates for combination studies!
Phase I/II Parallel Design for Combinations

Choose dose grid for single/combination treatments.

Simultaneously evaluate toxicity and efficacy. Define doses with acceptable toxicity as “admissible doses.”

Start at the lowest dose. Then, move up the grid if the current doses are admissible.

Adaptively randomize patients into all admissible doses in proportion to the efficacy at each dose. Hence, more patients can be treated at more effective doses.

Allow early stopping when the trial results cross the pre-determined safety, efficacy, or futility boundaries.

Identify predictive biomarkers

Adapted from Huang, Biswas, Oki, Issa, Berry. Biometrics 2007;63(2):429-36.
Start with dose (1,1) and check whether it is admissible or not.

Dose (1,1) is admissible.
Drug B Doses

Drug A Doses

Escalate to doses (1,2) and (2,1)
Doses (1,1), (1,2) and (2,1) are all admissible.
Drug B Doses

Drug A Doses

Escalate to doses (1,3), (3,1), and (2,2)
Doses (1,3) is too toxic but doses (2,2) and (3,1) are admissible.
Skip dose (2,3)
Escalate to dose (3,2)
Drug B Doses

Drug A Doses

Dose (3,2) is too toxic
All admissible doses are identified.
Adaptive randomizing pts into admissible doses

Predictive markers are evaluated
Seamless Phase II/III Design

- Start with a randomized Phase II trial with an active control (standard treatment) and several experimental arms with different treatments and/or doses
- Use a short-term endpoint in the Phase II part, e.g., ORR to inform the long-term endpoint, e.g. OS.
- Drop inefficacious arms
- Suspend accrual in the marker subgroups with inferior outcomes
- If at least one experimental arm is promising, roll into Phase III with one standard treatment and one or more selected experimental treatments. Use longer-term endpoint, e.g. OS.
- Information collected in the Phase II part is used in Phase III. No “white space” in trial conduct.

Inoue et al, Biometrics 2002; Bretz et al, Biometrical J 2006; Stallard, SIM 2010
Seamless Phase II-III Design

Berry, Nature Review Clinical Oncology, 2012
Seamless Phase II-III Design

Berry, Nature Review Clinical Oncology, 2012
Seamless Phase II-III Design

Berry, Nature Review Clinical Oncology, 2012
Biomarker Based Designs

- Efficient target design
- Marker stratified design
- Adaptive enrichment design
- Bayesian adaptive randomized design
  - Outcome adaptive randomization
  - Early stopping for futility and/or efficacy
- BATTLE-1 and BATTLE-2 trials
  - Biomarker training (discovery), testing, and validation
- Multiple randomized phase II studies → a small, more focus randomized phase III study
- N-of-All design – Adaptive learning
1. Screen out Marker (−) patients and only focus on Marker + patients
2. Can answer the question: Does targeted therapy work in Marker (+)? (A vs. B)
Marker Stratified Design

Can Answer 4 Questions:
1. Does targeted therapy work in Marker (−)? (A vs. B)
2. Does targeted therapy work in Marker (+)? (C vs. D)
3. Is marker prognostic? (A vs. C)
4. Is marker predictive (MK x TX Interaction)? (A/B vs. C/D)
Adaptive Enrichment Design

Stage 1: Test whether targeted therapy work for Marker (−) / (+) patients

Wang and Hung, Contemporary Clinical Trials, 2013
Simon and Simon: Biostatistics, 2013
Adaptive Enrichment Design

Stage 2: If not working in Marker (−) patients, terminate the subgroup.
Similar to Marker Stratify Design but instead of using ER, apply AR to assign more patients with more effective treatments.

Lee JJ, Gu X, Liu S. Bayesian adaptive randomization designs for targeted agent development. Clinical Trials, 2010;7:584-596
BATTLE (Biomarker-based Approaches of Targeted Therapy for Lung Cancer Elimination)

- **Patient Population:** Stage IV recurrent non-small cell lung cancer (NSCLC)
- **Primary Endpoint:** 8-week disease control rate (DCR)
- **4 Targeted treatments, 11 Biomarkers**
- **200 evaluable patients**

**Goal:**
- Test treatment efficacy
- Test biomarker effect and their predictive roles to treatment
- Treat patients better in the trial based on their biomarkers

BATTLE Schema

Umbrella Protocol

Core Biopsy

EGFR VEGF KRAS/BRAF RXR/CyclinD1

Randomization:
Equal → Adaptive

Primary end point: 8 week Disease Control (DC)
Study Accrual and Randomization

AR kicked in
ER~40%; AR~60%

Patients Enrolled

Time (months)

Est. reg
Cum. reg
Est. rand
Cum. rand

341
255
Schematic Diagram to run the web based “BATTLE” application

Registration

Biopsy

Biomarker Information (Determine MarkerGroup)

Adaptive Randomization Assign Treatment

Clinical Visits

Evaluate at 8 Week And determine Response

Patient Follow Up Visits

Off Study Information

Web Interface

Medical History

Lab Tests

Adaptive Randomization (R Code, Web Svc)

Adverse Events

Tumor Measurements

Physical Exams

Diagnostic Procedures

Concomitant Medications

Sample Collection

Drug Compliance

CORe

SQL 2005 Database

Reports
Randomization Process

1. Patient consented and registered in database
2. Information sent to surgical team for biopsy
3. Biopsy sent to Thoracic Molecular Path Lab
4. Biomarker results entered into database
5. Randomization of patient to trial
6. Research nurse notified automatically
7. Patient consented to appropriate trial
Video 5: Adaptive Randomization in BATTLE Trial
# BATTLE Results: Disease Control in % (n)

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Marker Groups</th>
<th>EGFR</th>
<th>KRAS</th>
<th>VEGF</th>
<th>RXR/CycD1</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td></td>
<td>35% (17)</td>
<td>14% (7)</td>
<td>40% (25)</td>
<td>0% (1)</td>
<td>38% (8)</td>
<td>34% (58)</td>
</tr>
<tr>
<td>Vandetanib</td>
<td></td>
<td>41% (27)</td>
<td>0% (3)</td>
<td>38% (16)</td>
<td>NA (0)</td>
<td>0% (6)</td>
<td>33% (52)</td>
</tr>
<tr>
<td>Erlotinib + Bexarotene</td>
<td></td>
<td>55% (20)</td>
<td>33% (3)</td>
<td>0% (3)</td>
<td>100% (1)</td>
<td>56% (9)</td>
<td>50% (36)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td></td>
<td>39% (23)</td>
<td>79% (14)</td>
<td>64% (39)</td>
<td>25% (4)</td>
<td>61% (18)</td>
<td>58% (98)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>43% (87)</td>
<td>48% (27)</td>
<td>49% (83)</td>
<td>33% (6)</td>
<td>46% (41)</td>
<td>46% (244)</td>
</tr>
</tbody>
</table>

AACR Presentation: [Link](http://app2.capitalreach.com/esp1204/servlet/tc?cn=aacr&c=10165&s=20435&e=12587&&m=1&br=80&audio=false)
**Individual Biomarkers for Response and Resistance to Targeted Treatment: Exploratory Analysis**

<table>
<thead>
<tr>
<th>Drug Treatment</th>
<th>Biomarker</th>
<th>P–value</th>
<th>DC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td><em>EGFR</em> mutation</td>
<td>0.04</td>
<td>Improved</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>High VEGFR-2 expression</td>
<td>0.05</td>
<td>Improved</td>
</tr>
<tr>
<td>Erlotinib + Bexarotene</td>
<td>High Cyclin D1 expression</td>
<td>0.001</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td><em>EGFR</em> FISH Amp</td>
<td>0.006</td>
<td>Improved</td>
</tr>
<tr>
<td>Sorafenib</td>
<td><em>EGFR</em> mutation</td>
<td>0.012</td>
<td>Worse</td>
</tr>
<tr>
<td></td>
<td><em>EGFR</em> high polysomy</td>
<td>0.048</td>
<td>Worse</td>
</tr>
</tbody>
</table>
Lessons Learned from BATTLE-1?

- Biomarker-based adaptive design is doable! It is well received by clinicians and patients.
- Prospective tissues collection & biomarkers analysis provide a wealth of information
- Treatment effect & predictive markers are efficiently assessed.
- Pre-selecting and grouping markers are not good ideas. We don’t know what are the best predictive markers at get-go.
- AR should kick in earlier & be closely monitored.

- AR works well only when we have good drugs and good predictive markers.

BATTLE-2 Schema

**Principles**
- Better specific drugs
- Better specific targets
- No biomarker grouping
- Selection, integration and validation of novel predictive biomarkers

**Protocol enrollment**
- Biopsy performed

**Stage 1 (N=200):**
- Adaptive Randomization
- KRAS mutation

**Stage 2 (N=200):**
- Refined Adaptive Randomization
- "Best" discovery markers/signatures

- Erlotinib
- Erlotinib+AKTi
- MEKi+AKTi
- Sorafenib

Open:
- MDA - June 2011
- Yale - August 2012
- 200 Randomized, 12/2013

Primary endpoint: 8-week disease control
- N = 400
**Training**

1. Signatures from Literature
   - Cell Lines (MTT-GI50, Four Arms)
   - BATTLE1 (Erlotinib, Sorafenib)
   - Test Predictions
     - Does it work?
       - No → Discard
       - Yes → Add to List of Candidates

2. Public Datasets
   - Discover new signatures (EMT, 5-gene, etc)
   - Test Distributions
     - Does it work?
       - No → Discard
       - Yes → Add to List of Candidates

**Testing**

- BATTLE2, Stage 1
- Test Predictions
  - Does it work?
    - No → Discard
    - Yes → Form Composite Markers

**Validation**

- BATTLE2, Stage 2
- Use for Adaptive Randomization

**Biomarker Selection**

Courtesy of Kevin Coombes
Statistical Design

- **Main goals**
  - Test treatment efficacy
  - Identify prognostic and predictive markers
  - Provide better treatment for patients enrolled in the trial based on their marker status

- **Bayesian logistic regression model for 8-week DCR**
  \[
  \text{logit}(p_j) = \mu_0 + \alpha_j T_j + \sum_{k=1}^{K} \beta_k M_k + \sum_{k=1}^{K} \gamma_{jk} T_j M_k + \left( \alpha'_j T_j Z + \sum_{k=1}^{K} \gamma'_{jk} T_j M_k Z \right)
  \]

- **Adaptive randomization**
  - The prob. of a patient being randomized to Arm \(j\) is
  \[
  \Pr(p_j > p_{j'}, j' \in \{1, 2, 3, 4 \mid j' \neq j\})
  \]
Statistical Design (cont.)

Early futility stopping rule
- Evaluated starts from 71\textsuperscript{th} patient to the end of trial
- Stop the trial only if all three experimental arms are not better than the control arm with a high probability

Markers Selection
- A panel of putative prognostic and predictive markers will be analyzed in Stage 1
- Extensive model apply the two-step LASSO
  1st step: Group selection of either prognostic or predictive markers to any treatments
  2nd step: Step-down test with adaptive LASSO to refine the selection

Define “success” for treatment \( j \) in marker \( k \) if
- For erlotinib-naïve patients: \( \Pr(\alpha_j + \gamma_{jk} > 0) > \theta \)
- For erlotinib-resistant patients: \( \Pr(\alpha_j + \alpha_j' + \gamma_{jk} + \gamma_{jk}' > 0) > \theta \)
- \( \theta \) is chosen to control type I error to 10%
Step 1: Group LASSO

For each marker $k$, let $\mathbf{\eta}_k = (\beta_k, \gamma_{2k}, \gamma_{3k}, \gamma_{4k}, \gamma'_{2k}, \gamma'_{3k}, \gamma'_{4k})$

\[
\mathbf{\eta}_k \sim N_{m_k}(0, \tau_k^2 I_k)
\]

**Priors**

\[
\begin{align*}
\tau_k^2 &\sim \text{InvGamma}\left(\frac{m_k+1}{2}, \frac{\lambda_k^2}{2}\right) \\
\lambda &\sim \text{Gamma}(a, b)
\end{align*}
\]

Letting $\mathbf{\tilde{\eta}}_k$ be a posterior random sample of $\mathbf{\eta}_k$, and $\mathbf{\bar{\eta}}_k = (\bar{\beta}_k, \bar{\gamma}_{2k}, \bar{\gamma}_{3k}, \bar{\gamma}_{4k}, \bar{\gamma}'_{2k}, \bar{\gamma}'_{3k}, \bar{\gamma}'_{4k})$ be its posterior mean, compute the distance between the posterior sample and the zero vector:

\[
T_k = (\mathbf{\tilde{\eta}}_k - \mathbf{0})^T \mathbf{W}_k^{-1} (\mathbf{\tilde{\eta}}_k - \mathbf{0}), \text{ where } \mathbf{W}_k^{-1} \text{ is the sample variance–covariance matrix.}
\]

Let $\tilde{T}_q$ be the $q^{th}$ empirical quantile of $T_k$. For a given $q$, select the $k^{th}$ marker if $\mathbf{\bar{\eta}}_k^T \mathbf{W}_k^{-1} \mathbf{\bar{\eta}}_k > \tilde{T}_q$.

Choose $(a = 1, b = 10, q = 30\%)$ for selecting $T_k$

Park, T., Casella, G. The Bayesian Lasso. JASA 103, 681--686 (2008)


Step 2: Adaptive LASSO

Let $\Omega$ be the set of markers selected in the first step, the prior distribution for $\{\theta_k : k \in \Omega\}$ in the adaptive lasso is

$$\pi(\theta_k | \lambda) \propto \exp\left(-\lambda \frac{|\theta_k|}{|\tilde{\theta}_k^{LS}|}\right),$$

where $\theta_k$ is a generic representation of either the marker main effect or the marker–treatment interaction and $\tilde{\theta}_k^{LS}$ is the least squares estimation of the parameter.

A variable will be selected if the 80% empirical posterior credible interval does not cover zero. The selections of the credible interval in this second step and the $\tilde{T}_q$ in the first step can be adjusted to achieve a desirable false-positive rate and true-positive rate of the variable selection in the null case and alternative case separately.

N-of-ALL Design (Adaptive Learning)

- Build a comprehensive knowledge database with
  - Consistent and accurate curating of patient demographics, clinical characteristics, treatments, and outcomes
  - Frequent and timely updates

- Apply statistical analysis to identify the effective marker-treatment pairs
  - Classification, machine learning
  - Prediction, validation

- Refine the model based on the updated outcome
  - Real time learning; Continuous learning

- E.g.: MD Anderson’s APOLLO/IBM-Watson project
  - A cognitive computing system piloted in leukemia
  - An “adaptive learning environment” as part of its Moon Shots program.
Example: IBM Watson

- Name after IBM’s Thomas J. Watson
- Watson is a question answering (QA) computing system applying advanced natural language processing, information retrieval, knowledge representation, automated reasoning, and machine learning technologies to the field of open domain question answering.
  - It is optimized, integrating massively parallel POWER7 processors and IBM's DeepQA technology, which generates hypotheses, gather massive evidence, and analyze data.
  - Composed of a cluster of 90 IBM Power 750 servers, each of which uses a 3.5 GHz POWER7 eight core processor, with four threads per core. In total, the system has 2,880 POWER7 processor cores and has 16 terabytes of RAM.
- In 2011, Watson competed on Jeopardy! against former winners Brad Rutter and Ken Jennings. Watson received the first prize of $1 million.
Oncology Expert Advisor (OEA)

MD Anderson’s APOLLO/IBM-Watson project

- A cognitive computing system piloted in leukemia
- By pulling together, analyzing, and synthesizing vast amounts of information from patient and research databases, the goal of OEA is to help care teams identify and fine-tune the best possible cancer treatments

Watson technology drives “adaptive learning environment” as part of its Moon Shots program.

- Enable iterative and continued learning between clinical care and research
- Streamline and standardize the longitudinal collection, ingestion and integration of patient’s medical and clinical history, laboratory data as well as research data.
- The complex data is linked and made available for deep analyses by advanced analytics to extract novel insights to improve effectiveness of care and better patient outcomes.
Software Tools

https://biostatistics.mdanderson.org/SoftwareDownload/

Over 80 programs freely available
Tools for Conducting Bayesian / Adaptive Trials at MDA

Clinical Trial Conduct (CTC) Website

Secured web application for conducting Bayesian clinical trials

Can be used to

– Register patients
– Log in key information for randomization
  – Baseline characteristics
  – Outcome (toxicity, efficacy)
– Randomize patients
  – Connect to statistical software via web services
– Capture endpoints for interim analysis
New Trial Request Form

Clinical Trial Conduct
New Request Form

The request form contains the following items, and the highlighted one is what you are currently working on. You should always start with the first item.

1. General Information (Use the information in PDOL to fill out this page.)
2. Design
3. Centers
4. Users
5. Data Monitoring (only applies to Adaptive Randomization and OneArmTTE trials)

Trial General Information (from PDOL)

Protocol ID
Principal Investigator Last Name
Principal Investigator First Name
Statistical Collaborator Last Name
Statistical Collaborator First Name
IRB Approved
Anticipated Activation Date (mm/dd/yyyy)
Trial Method
Short Title
Full Title
Multiple Center
Request Form Status
Trial Information and Administration

Clinical Trial Conduct
2008-0661 (active)

Trial General Information

Protocol Id*: 2008-0661
Trial Method*: EFTox
Trial Name: Lenalidomide and High-Dose Melphalan
PI Name: Qaziibash, Muzaifar H.
Trial Description: Phase I/II Study of the Combination of Lenalidomide with High-Dose Melphalan for Autologous Transplant in Patients with Multiple Myeloma
Multiple Center*: No
Trial Status: active

Update
# Monitoring Efficacy and Toxicity

## Clinical Trial Conduct

**2008-0661 (active)**

Nan Chen (nChen2) logged in | Log Off | User's Guide

### Enroll Patient and/or Get Next Treatment

<table>
<thead>
<tr>
<th>Edit</th>
<th>Row #</th>
<th>Patient ID</th>
<th>Center Code</th>
<th>Treatment (mg daily)</th>
<th>Toxicity</th>
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### Clinical Trial Conduct (CTC) Website
(from Jan 2012 to Dec 2013)

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<td>Pocock-Simon Design</td>
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</table>

- **Total active trials during 2012-2013**: 87
- **Total patients enrolled in 2012-2013**: ~3,000
Adaptive design continues to learn about the new agents’ activities and provide best treatments to patients in real time.

- Adaptive dose finding, estimation, treatment assignment, biomarker identification and validation, stopping for futility and/or efficacy, combination studies, seamless designs

Adaptive learning is an ambitious and appealing concept. Need data to train and refine the algorithm and demonstrate how well it works.

Adaptive designs can assist biomarker discovery and validation to match patients with treatments.

Need more tools for study design, conduct & analysis.

Biomarker-based adaptive designs can increase the study efficiency, allow flexibility in study conduct, and provide better treatment to study patients to

- Speed up drug development
- Step towards personalized medicine