

Incorporating EHR Data as a New Tool for Adaptive Clinical Trial Design

作为一种新的自适应临床试验设计工具结合电子
医疗记录数据

Philadelphia August 14, 2012

R. Stephen Porter, Pharm.D, FCP

Chairman CEO, and Director & Co-Founder

VDDI Pharmaceuticals ; USA and Dragon Bio-Consultants, Ltd.
Hong Kong, SAR

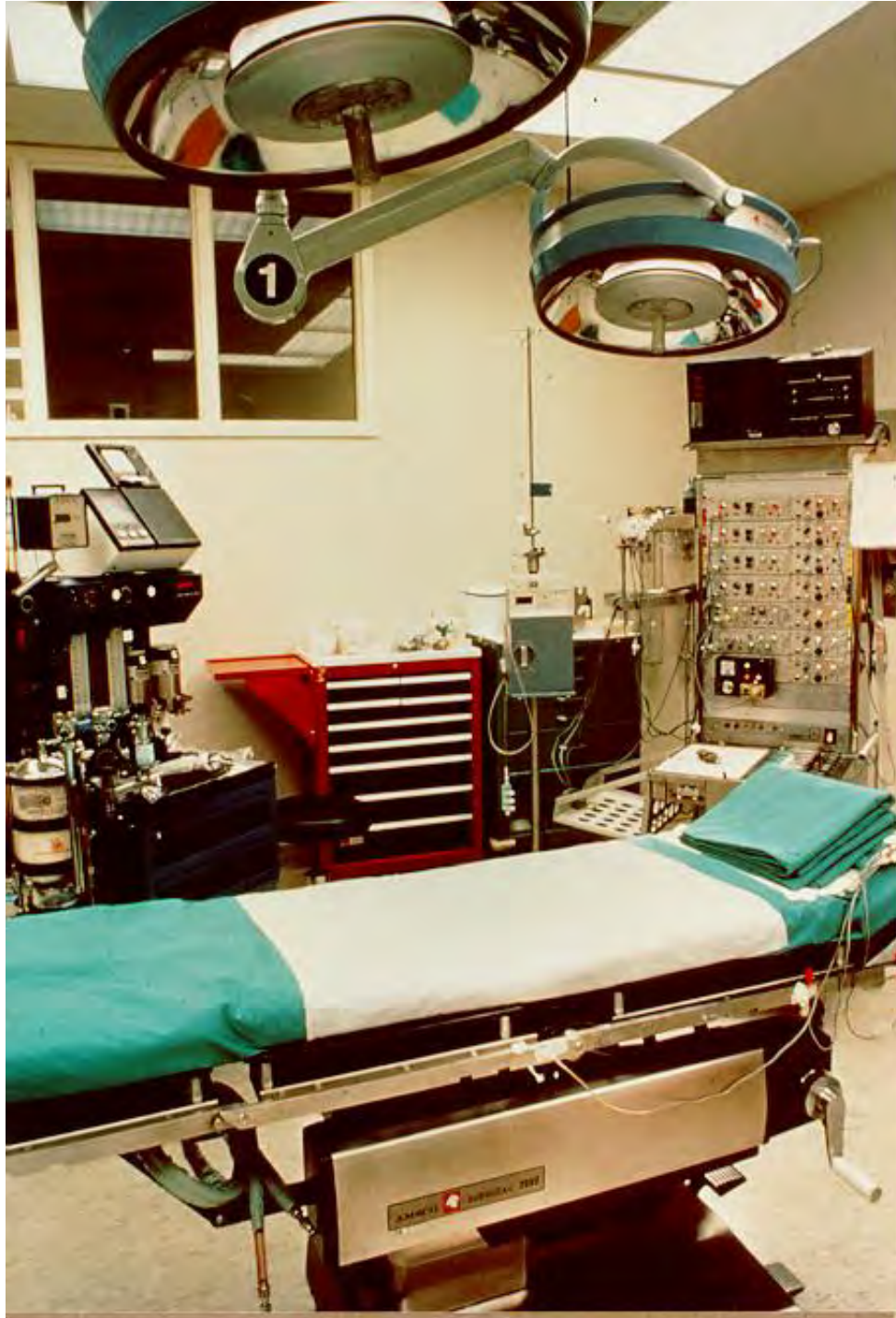


Outline

- Medicine and Personalized Care
- HER what is it?
- What is adaptive design?
 - Type of adaptive designs
- Possible benefits
- Battle I-spy Examples
- Xemilofiban
- Conclusions



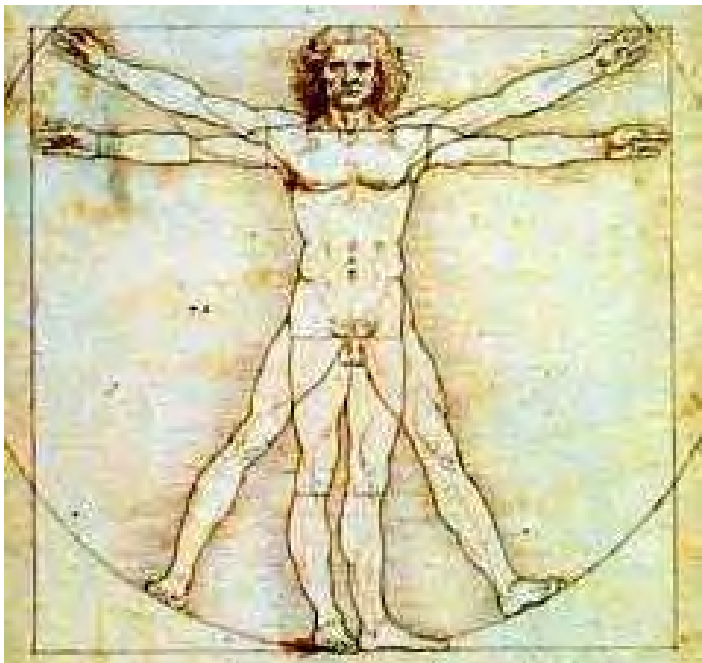






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Revolution in Personalized Medicine



Then



Now



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The Future of Medicine: Molecular Diagnostics and DxRx Concepts

- Overall Strategic Health Trends
- Healthcare Paradigm Shift
- More Molecular Testing in the Future
- Genetic Testing-Personalized Medicine
- Genetic Testing as a Prelim to Cancer Therapy
- DxRx role in disruptive technology
- Animal Models Bridging to Clinical and beyond to market



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The Case for Personalized Medicine

- There are approximately 350 biologics in phase III
 - >2,000 other treatments are in early development
- Blue Cross Blue Shield plans reported:
 - Spending on specialty Pharma products ↑ 35%
 - Specialty Pharma = ~25% of all outpatient pharmacy spending in 2008
- As cost of some **treatments exceed \$10-20,000** per month, affordability and access are key considerations
- Need solutions to ↑ quality & outcomes 羊 some products offer only marginal benefits or no benefits to certain patients
- Personalized medicine is one such solution



Watkins JB et al. Health Affairs 2007;25(5):1347-52; Mullins CD et al. Health Aff 2006;25(5):1332-9; Stern D, Reissman D. J Manag Care Pharm. 2006;12(9):736-44.
Fish L. Amer J Manag Care 2006;12(6):159-161.

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Current Role of Biomarkers in Drug Selection & Use

- A recent Medco study of FDA-approved drug labels found that:
 - 121 drug labels contained pharmacogenomic information
 - 69 contained human genomic biomarkers
 - 52 contained microbial biomarkers relevant to human treatment
- 24.3% of 36.1 million patients processed by Medco took *one or more drugs* with pharmacogenomic information in the label
- The importance of biomarkers in treatment selection and patient management is only anticipated to increase in the coming years



Source: Frueh F. et al Pharmacotherapy 28(8): 2008

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Personalized Medicine

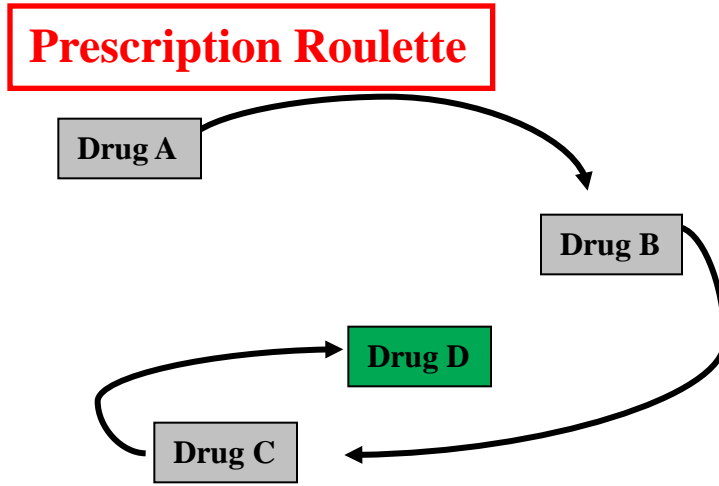
- Gleevec(Novartis) -pH+ CML kinase inhibitor
- Iressa(AstraZeneca) –EGFR tyrosine kinase inhibitor
- Tarceva(Genentech/OSI) –HER1/EGFR inhibitor
- Erbitux(ImClone/BMS) –HER1/EGFR inhibitor
- Avastin(Genentech) –VEGF/VEGFR inhibitor
- Herceptin(Genentech) –HER2 inhibitor
- BilDil(NitroMed) -heart failure in African American patients
- Other “Semi Targeted” Treatments (approved or late stage trials)
- Nexavar(Bayer/Onyx) –multi-kinase inhibitor
- Tykerb(GSK) -ErbB-2/EGFR inhibitor
- Enzastaurin(Lilly) -PKC-Beta, AKT/P13 inhibitor
- Favrilite–Favldfor non-Hodgkin’s lymphoma
- Genitope–MyVaxfor non-Hodgkin’s lymphoma
- PGx Predict: warfarin
- Strattera (ADHD Metabolism P450 2D6)
- 6-MP (leukemia , metabolism TPM)



Targeted prescription of medicines

Today

“One-size fits all” Prescription

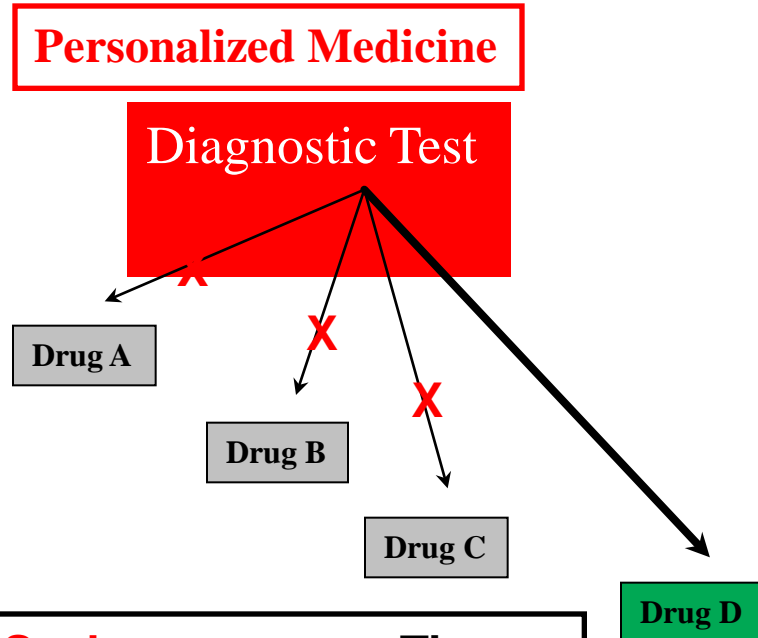


Cost: Time
Money
Well-Being



Future

Rational “targeted” prescription



Savings: Time
Money
Illness

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Drug Attrition

TABLE ONE

Reasons for drug attrition and how adaptive trials can change the picture.

Reasons for attrition	Phase III Attrition Rate	Comments
ECONOMIC REASONS		
Efficacy uncompetitive	18%	42%
Safety uncompetitive	11%	
Lacks "strategic fit"	3%	
Market too small	8%	
Manufacturing cost too high	2%	
APPROVABILITY REASONS		
Inadequate efficacy for FDA approval	18%	45%
Inadequate safety for FDA approval	13%	
PK/bioavailability issues	3%	
Compound was backup	8%	
Chemistry/control issue	3%	
OTHER	13%	13%

Source: Cytel Inc.



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US at an 'Inflection Point' for Targeted Therapies

Woodcock said that FDA expects that the increased use of drug and diagnostic combinations as well as "adaptive trial designs to evaluate the multiple drug and diagnostic pairings and to ensure ethical treatment [of] enrolled subjects, and increasing attention to the use of novel biomarkers" will move R&D forward.



PhRMA/FDA conference on Adaptive Design: Opportunities, Challenges and Scope in Drug Development

- Nov 13/14th, 2006
 - Marriott Bethesda North Hotel & Conference Center
North Bethesda, MD 20852

- Program committee

Dennis Erb	Merck	Greg Campbell	FDA CDRH
Brenda Gaydos	Eli Lilly	Shirley Murphy	FDA CDER
Michael Krams	Wyeth, Co-Chair	Robert O'Neill	FDA CDER
Walt Offen	Eli Lilly, Co-Chair	Robert Powell	FDA CDER
Frank Shen	BMS	Marc Walton	FDA CDER
Luc Truyen	J&J	Sue Jane Wang	FDA CDER



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Adaptive Trail Design

Adaptive trial design is a hot issue in the drug development community. Adaptive conferences and web seminars abound, and suddenly, every consultant or vendor to the industry has become an adaptive expert. The FDA, SFDA, and EMEA are also much more receptive to adaptive trials than they were a few years ago.

However, the picture is a shade different from what the industry had expected. Originally, much of the focus was on adaptive phase III trials as well as on seamless phase II/III trials. Those are, indeed, successfully and selectively being implemented today. But the real action is in phase II dose-finding trials and even in Phase I trials for safety.



Adaptive Trial Design

The best way to make expensive phase III trials **more successful** is to do more thorough work in Phases I and II. This is clear from the study commissioned by PhRMA some years ago of why drugs fail at various stages of clinical development (see table one). As David Brennan, the CEO of AstraZeneca, is reported to say repeatedly within his company, “Once in my life, I hope we will get the dose right.” **Getting the dose right** through well-designed phase I and phase II trials is the best way to maximize success in phase III, which then leads to a higher rate of NDAs.



What is it and what do we want from it?

- It is called many names – AMR, CPR, EMR, EPR, CBPR, PRMI, EHR, PHR, EHCR, ICRS
- ISO defines it by referring to its multiple definitions by others.
- For some it is just the data repository, for others it includes the functionality.
- For some, it has a disease orientation; i.e., the diabetes' record.
- For others, it is the place: the inpatient record.
- For others, it is the view: the personal health record.
- For others, it is the purpose: the billing record.



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What does the EHR contain?

- Data
 - Patient-centered
 - Comprehensive
 - Aggregated
 - Organized
 - High data integrity
 - Timely
 - Structured, semantically understandable
 - Sharable
 - Accountable
 - Secure and private



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What does the EHR provide?

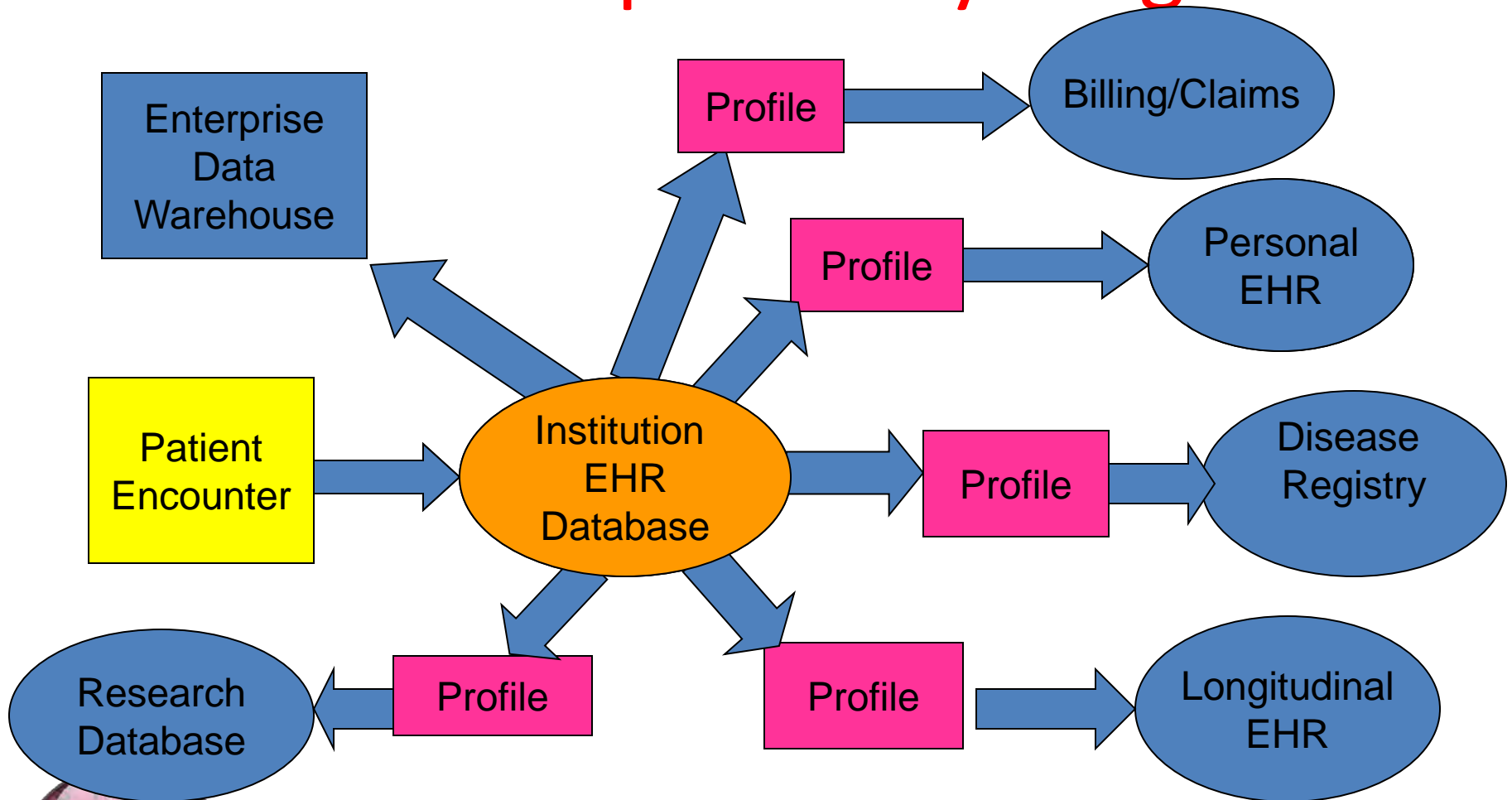
- Information for ...
 - Patient care
 - Prevention of medical errors
 - Improved quality of care
 - Consistency in care
 - Cost effective care
 - Shared understanding of health and health care among patient and provider
 - Health surveillance and biodefense
 - Workflow management
 - Research
 - Epidemiology
 - Billing



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EHR Interoperability Diagram



Profiles contain business rules

With what does the EHR interact?

- Knowledge
 - Clinical trials
 - Decision support; DxRx
 - Disease demographics
 - Outcomes Biomarker integration
 - Quality indicators
 - Evidence based medicine



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What does an effective EHR permit?

- Wisdom
 - New models for health and health care
 - More cost effective care
 - Better understanding of disease and disease processes
 - Better relationship among stakeholders
 - A happier, healthier world



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What is adaptive design?

- There is no universal definition.
 - Adaptive randomization, group sequential, and sample size re-estimation, etc.
 - PhRMA (2006)
 - FDA (2010)
- Adaptive design is also known as
 - Flexible design (EMA, 2002, 2006)
 - Attractive design (Uchida, 2006)
- Rolling Thunder design



PhRMA's definition

- Characteristics
 - Adaptation is a design feature.
 - Changes are made *by design* not on an *ad hoc* basis.
- Comments
 - It does not reflect real practice.
 - It may not be flexible as it means to be.



FDA's definition

US FDA Guidance for Industry – Adaptive Design
Clinical Trials for Drugs and Biologics Feb, 2010

An adaptive design clinical study is defined as a study that includes a *prospectively* planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study



FDA Guidance

- Compared to non-adaptive studies, adaptive design approaches may lead to a study that:
 - (1) more efficiently provides the same information,
 - (2) increases the likelihood of success on the study objective, or
 - (3) yields improved understanding of the treatment's effect (e.g., better estimates of the dose-response relationship or subgroup effects, which may also lead to more efficient subsequent studies).



FDA's definition

- Characteristics
 - Adaptation is a *prospectively* planned opportunity.
 - Changes are made *based on analysis of data* (usually interim data).
 - Does not include medical devices?
- Comments
 - It classifies adaptive designs into *well-understood* and *less well-understood* designs
 - It does not reflect real practice (protocol amendments)
 - It is not a guidance but a document of caution



Why Adaptive Treatment Strategies?

High heterogeneity in response to any one treatment

- What works for one person may not work for another
- What works now for a person may not work later
- Improvement often marred by relapse
- Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient
- Lack of adherence or excessive burden is common



Adaptation

- An adaptation is defined as a change or modification made to a clinical trial before and during the conduct of the study.
- Examples include
 - Relax inclusion/exclusion criteria
 - Change study endpoints
 - Modify dose and treatment durationetc.



Adaptive designs

- Adaptive randomization design
- Adaptive group sequential design
- N-adjustable design
- Drop-the-loser design
- Adaptive dose-escalation design
- Biomarker-adaptive design
- Adaptive treatment-switching design
- Adaptive-hypotheses design
- Adaptive seamless phase II/III trial design
- Any combinations of the above (multiple adaptive design)



Seamless Design

A seamless trial design is referred to a program that addresses within a **single trial** objectives that are normally achieved through **separate trials** of clinical development



Adaptive Seamless Trial Design

- Characteristics
 - Combine two separate trials into a single trial
 - The single trial consists of two phases
 - Learning phase
 - Confirmatory phase
 - Opportunity for adaptation based on accrued data at the end of learning phase



Advantages Of Adaptive Seamless Design

- Opportunities for saving
 - Stopping early for futility
 - Stopping early for efficacy
- Efficiency
 - Can reduce lead time between the learning and confirmatory phases
- Combined analysis
 - Data collected at the learning phase are combined with those data obtained at the confirmatory phase for final analysis



Comparison Of Type I Errors

- Let α_{II} and α_{III} be the type I error for phase II and phase III studies, respectively. Then the alpha for the traditional approach is given by
 - $\alpha = \alpha_{II} \alpha_{III}$ if one phase III study is required
 - $\alpha = \alpha_{II} \alpha_{III} \alpha_{III}$ if two phase III studies are required
- In an adaptive seamless phase II/III design, the actual alpha is $\alpha = \alpha_{III}$
 - The alpha for a seamless design is actually $1/\alpha_{II}$ times larger than the traditional design

Shein-Chung Chow, Duke U, Durham, NC, USA
Qingshu Lu, U of Science and Technology of China
Siu-Keung Tse, City U of Hong Kong, Hong Kong



Comparison of powers

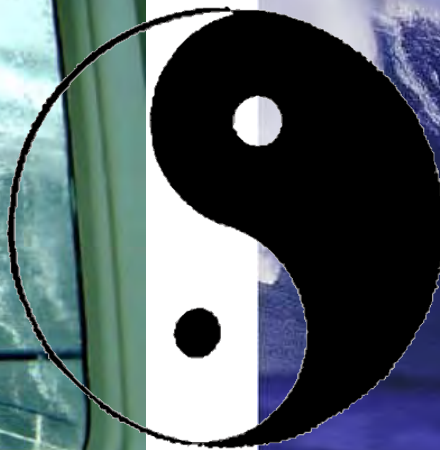
- Let $Power_{II}$ and $Power_{III}$ be the power for phase II and phase III studies, respectively. Then the power for the traditional approach is given by
 - $Power = Power_{II} * Power_{III}$
if one phase III study is required
 - $Power = Power_{II} * Power_{III} * Power_{III}$
if two phase III studies are required
- In an adaptive seamless phase II/III design, the power is
 - The power for a seamless design is actually $1/Power_{II}$ times larger than the traditional design $Power = Power_{III}$



Shein-Chung Chow, Duke U, Durham, NC, USA
Qingshu Lu, U of Science and Technology of China
Siu-Keung Tse, City U of Hong Kong, Hong Kong



Perfect Storm or Perfect Wave



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BATTLE



- BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination)
- "Ultimately, we would like to be able to screen patients for tumor characteristics and give them appropriate therapies up front."
- "These molecular signatures, known as biomarkers, are a product of mutations and other cell abnormalities responsible for the cancer,"
- **Dr. Edward S. Kim**, Associate Professor in the Department of Thoracic/Head and Neck Medical Oncology and principal investigator



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BATTLE



- Non-small cell lung cancer (**NSCLC**), like so many other malignancies, does **not** represent a **molecularly homogeneous** group of tumors. Rather, NSCLC exhibits a wide range of mutations that should make it possible to choose treatment based on an individual tumor's molecular characteristics.
- showed for the first time that **real-time biopsies** of NSCLCs reveal molecular signatures that may be able to predict which targeted therapies are most likely to work.



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I-spy Trial Offers Key Insights Into Locally Advanced Breast Cancer



Laura
Esserman, MD

Study by Cheryl Lin, MD, postdoctoral research fellow in surgery, contains a critical message, says Esserman. “

- For these faster growing cancers, patients with **interval cancers**’ should explore the potential of standard chemotherapy and/or clinical studies that
 - add novel agents in addition to standard therapy in advance of surgery (so called **neoadjuvant** chemotherapy), which is increasingly the standard of care in this set of patients.
 - **molecular profiles** of locally advanced breast cancer tumors predicted the response of the tumors to chemotherapy drugs given in advance of surgery.



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I-spy Trial Offers Key Insights Into Locally Advanced Breast Cancer



“Response to therapy and outcome can be predicted by many biomarkers. The I-SPY data set provides a platform to study marker signatures to tailor therapy and demonstrates the power of the neoadjuvant setting.”

Laura
Esserman, MD



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Why IV & Oral GP IIb/IIIa Inhibitors have under performed

- Improper dose: low platelet inhibition, PK issues
- Improper timing: need pretreatment
- Too expensive: IV
- Inconsistent variable concomitant therapy: Plavix, LMWH, ASA
- Poor patient selection: too broad (Troponin I levels, diabetics)
- Improper duration 12-48 hr vs. 6 months: paradoxically prothrombotic
- Competition: Plavix, AngioMax
- 50,000 patients and \$2 Billion on PO development
- Inflammation: soluble CD40; role of leukocytes



Xemilofiban

- Primary indication – Peri- treatment for Percutaneous Coronary Intervention (PCI) with stent procedures
- Will be only oral IIb/IIIa product – “class effect”
- Has short half-life (surgeons view as distinct advantage)
- Has IV loading dose capabilities
- Oral route could capture the AMI market



Xemilofiban

- Fiban Research 1989-1999
 - G.D. Searle
 - Pharmacia
 - Pfizer
- \$860 M total development cost



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PROPRIETARY



Regulatory Status SFDA Guidance

- Repeat Phase I study 20 normal volunteers for repeat PK/PD;
- 5-800 patient combined phase II/III trial prior to China market;
- Phase IV post marketing surveillance; and
- Sponsoring domestic company.



Phase II PK/PD Study

Design:

- Placebo-controlled, dose-escalating trial
- Patients eligible for PCI with or without stent
- Randomization 12 active:3 placebo



Phase II PK/PD Study

Primary Objective:

To determine the loading and maintenance doses of Xemilofiban which, in combination with standard of care (ASA, antithrombin, clopidogrel), produces greater than 80% inhibition of platelet aggregation (using optical aggregometry) in 100% of patients during the PCI, and up to 8 hours after dosing.



Phase II PK/PD Study

Secondary Objectives:

- Receptor occupancy (flow cytometry)
- Plasma concentrations of active drug PK/PD correlations
- Track clinical events (MACE)
- Track biochemical markers (CK_{MB}, CRP, sCD40L, troponin 72 hr)
- Proportion of patients who require rescue therapy
- Safety (bleeding, thrombocytopenia)



Dosing Strata

Group 1: BMI < 30 kg/ m² - 30 mg loading dose, 20 mg TID vs. placebo

N=15 BMI >30 kg/ m² - 40 mg loading dose, 20 mg TID vs. placebo

Group 2: BMI < 30 kg/ m² - 40 mg loading dose, 20 mg TID vs. placebo

N=15 BMI >30 kg/ m² - 50 mg loading dose, 20 mg TID vs. placebo

Interim analysis make appropriate adjustments



Dosing Strata

Group 3: BMI < 30 kg/ m² - 30 mg loading dose, 20 mg QID
vs. placebo

N=15 BMI >30 kg/ m² - 40 mg loading dose, 20 mg QID vs. placebo

Group 4: BMI < 30 kg/ m² - 40 mg loading dose, 20 mg QID vs. placebo

N=15 BMI >30 kg/ m² - 50 mg loading dose, 20 mg QID vs. placebo

Group 5: BMI < 30 kg/ m² - 3 mg IV loading dose, 20 mg QID vs. placebo

N=15 BMI >30 kg/ m² - 4 mg IV loading dose, 20 mg QID vs. placebo

Group 6: BMI < 30 kg/ m² - 5 mg IV loading dose, 20 mg QID vs. placebo

N=15 BMI >30 kg/ m² - 6 mg IV loading dose, 20 mg QID vs. placebo

Interim analysis to make appropriate adjustments to dosing



Dosing Strata

Group 7: BMI < 30 kg/m² - 5 mg IV loading dose, 20 mg
placebo

QID vs.

N=15 BMI >30 kg/m² - 6 mg IV loading dose, 20 mg
QID vs. placebo



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PROPRIETARY



Conclusions

- Adaptive design methods reflect **real clinical practice** in clinical development.
- Adaptive design methods are very attractive due to their flexibility and are very useful especially in **early clinical development**.
- From the statistical point of view, the use of adaptive methods in clinical trials makes current **good statistics practice** even more complicated.
- The validity of the use of adaptive design methods is **not well established** and fully understood.
- **Guidelines** regarding the use of adaptive design methods must be developed so that appropriate statistical methods and statistical software packages can be developed accordingly.
- **Regulatory** guidelines can not only prevent possible misuse and/or abuse of adaptive design methods in clinical trials, but also **maintain the validity and integrity** of the trial.



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Contact

R. Stephen Porter, Pharm.D., FCP, MRCP

VDDI Pharmaceuticals

Chairman, President and CEO

115 Penn Warren Drive

Suite 300-389

Brentwood, TN 37027

(615)445-5761 (cell)

+86.15021242314 (Cell China)

virtualdoc@gmail.com

<http://www.virtualdrugdevelopment.com>

R. Stephen Porter, Director and Founder

Dragon Bio-Consultants, Ltd.

Suite 1802-03, 18/F, Olympia Plaza

255 King's Road, Fortress Hill

North Point, Hong Kong SAR

HK Registered Company No.: 1429099

SKYPE: virtualdoc77

+86.15021242314 (Cell China)

+1(615)445-5761 (Cell USA)

<http://www.dragonbio-consultants.com/>



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