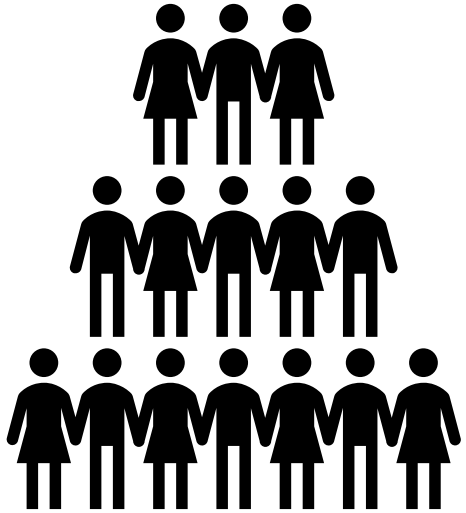
Biostatistician Roles in Drug Development

Marlina D. Nasution

ITS Dec 12-13, 2019



BIO BLURB

Marlina D. Nasution

The wand to Statistics

National TV life show series *"Belajar Matematika"*

Look who's in the TV!

A library of books

Enid Blyton and Tintin adventures: a must

JASA and Biometrics: saved for later

From birthday party to wedding:

~~You~~ (Statisticians/Mathematicians) are invited!

BIO BLURB

Marlina D. Nasution

- North Carolina State University, USA (Ph.D, MStat)
  Bogor Agricultural University (IPB), Indonesia (MS in Applied Statistics, BSc)
- Based in Research Triangle Park, Durham, NC, USA
- Currently, employed by Parexel International. Previously, with Family Health International, NCSU (Statistics department and CVM), IPB (Statistics department)
- 19+ years experience in clinical and pre-clinical trials. Therapeutic area experience across Oncology & Hematology, Cardiovascular, Immunology, Rare disease, Pulmonology, Infectious Disease, Dermatology, Endocrinology, Urology, Psychiatry/Trauma
- Attributes: Biostatistics, Biotech, Change Agent, Data Surveillance, Data Monitoring Committee, Duke-Industry Statistics Symposium, Mentoring, Training curriculum

Topics

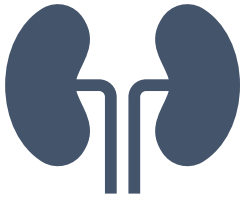
- Drug development
- Clinical research
- Clinical trial
- Biostatistician roles
- Trends changing and statistical considerations

- *"These are own views and do not necessarily represent views of my current employer, Parexel International"*

Drug Development

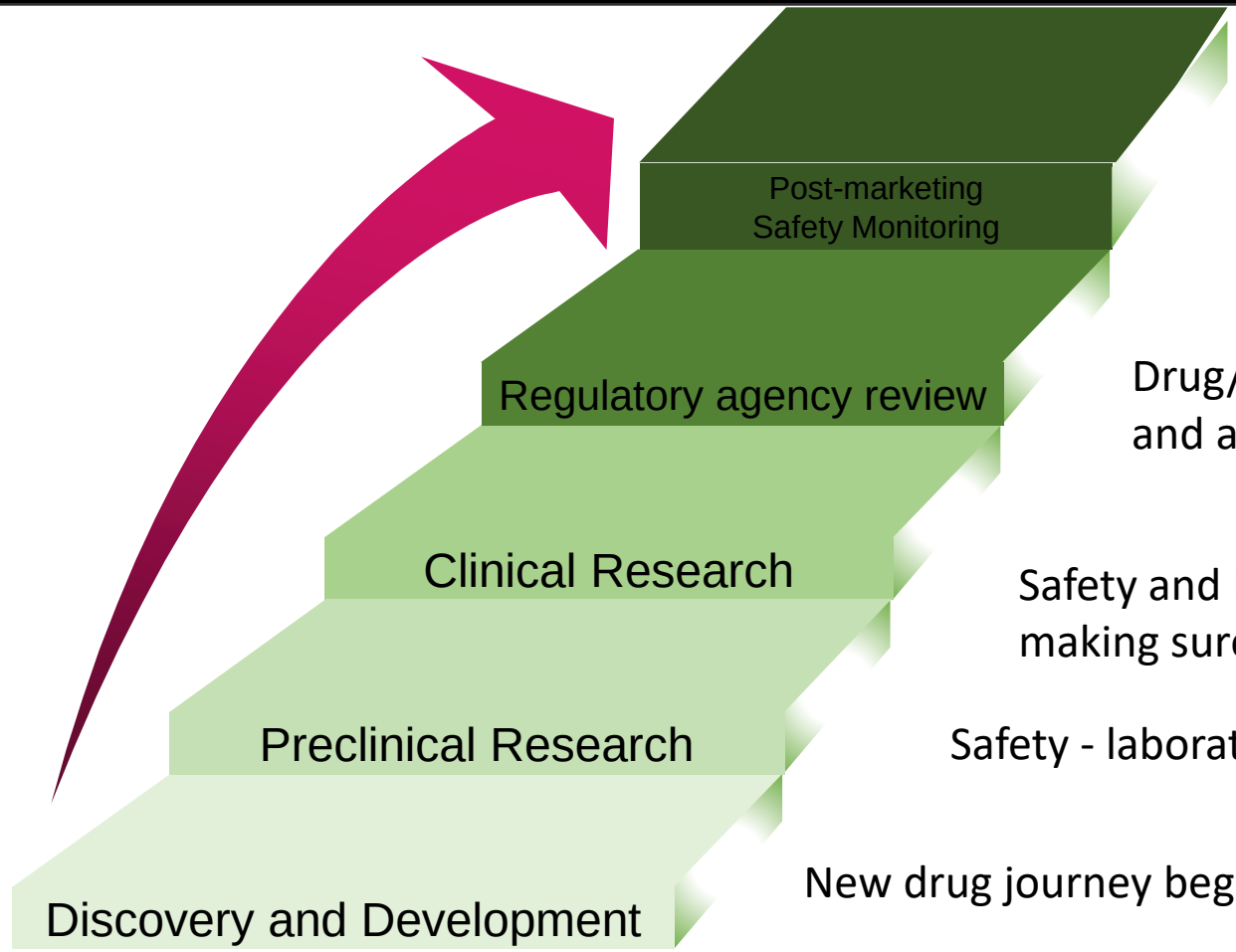
What is Drug Development?

The process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery



- Preclinical research on microorganisms and animals,
- Filing an IND for regulatory to initiate clinical trials on humans, and
- Obtaining regulatory approval with an NDA to market the drug

Drug Development Process



Regular agency monitoring post drug/device marketing

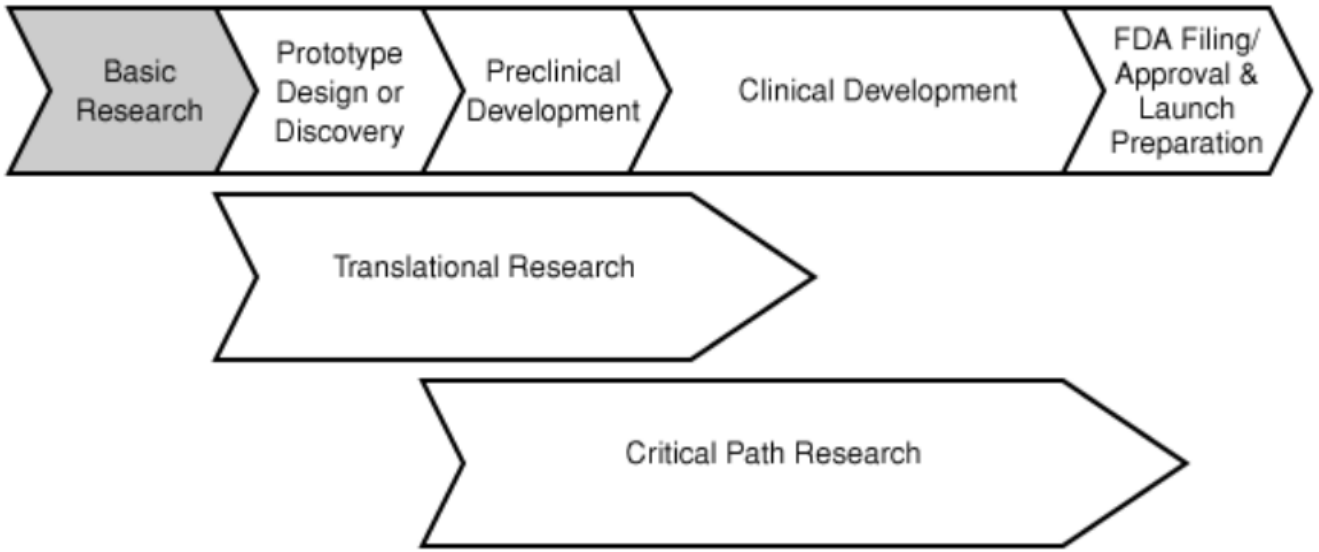
Drug/device submission through regulatory agency review and approval (USA – FDA)

Safety and Efficacy – drugs are tested on volunteer/patient making sure they are safe and effective

Safety - laboratory and animal testing

New drug journey begin in laboratory!

Critical Path



- Basic research is aimed to understand biology and disease processes. It provides the foundation for product development as well as translational and critical path research.
- In drug development the "discovery" process seeks to select or create a molecule with specific desired biological activities.
- Translational research – to move basic discoveries from concept into clinical evaluation and is often focused on specific disease entities or therapeutic concepts.
- Critical path research – to improve the product development process itself by establishing new evaluation tools. It begins when candidate products are selected for development.

…in Indonesia?

Badan Pengawas Obat dan Makanan (BPOM)

The National Agency of Drug and Food Control of Republic of Indonesia or NADFC or Badan POM is a government agency of Indonesia, BPOM is responsible for protecting public health through the control and supervision of prescription and over-the-counter pharmaceutical drugs, vaccines, biopharmaceuticals, dietary supplements, food safety and cosmetics.

Badan POM (2018): "*Cara Pembuatan Obat yang Baik yang selanjutnya disingkat CPOB adalah cara pembuatan obat dan/atau bahan obat yang bertujuan untuk memastikan agar mutu obat dan/atau bahan obat yang dihasilkan sesuai dengan persyaratan dan tujuan penggunaan*"

Clinical Research

Clinical Research

- A branch of medical/healthcare science
- To collect evidence for new drugs to establish as a treatment
- Determines the safety and effectiveness of drugs intended for human use.
- Drugs as prevention, treatment, diagnosis or for relieving symptoms of a disease.
- Its ultimate goal – improve quality of live for human in particular, patients

Why Clinical Research?

New drugs to market

Combined standard treatments

New devices to market

New techniques, e.g. for screening/diagnosing diseases

New methods for surgery

New approach for new therapy

Clinical Trial

Clinical Trial

Experiments or observations done in clinical research

Prospective biomedical or behavioral research studies on human participants (healthy volunteers or patients)

Design to answer specific questions about biomedical or behavioral interventions

New treatments (e.g. novel vaccines, drugs, dietary choices, dietary supplements and medical devices)

Known treatments/interventions that warrant further study and comparison

Generate data on safety and efficacy

Conducted only after they have received health authority/ethics committee approval in the country where approval of the therapy is south

Health authorities are responsible for vetting the risk-benefit ratio of the trial that trial may be conducted

not approval for safety/effectiveness of the therapy

To evaluate effectiveness and safety of medications, medical devices, biologics,..

Clinical Trial Types

Based on its purpose,

- prevention trial, screening trial, diagnosis trial, treatment trial and on..

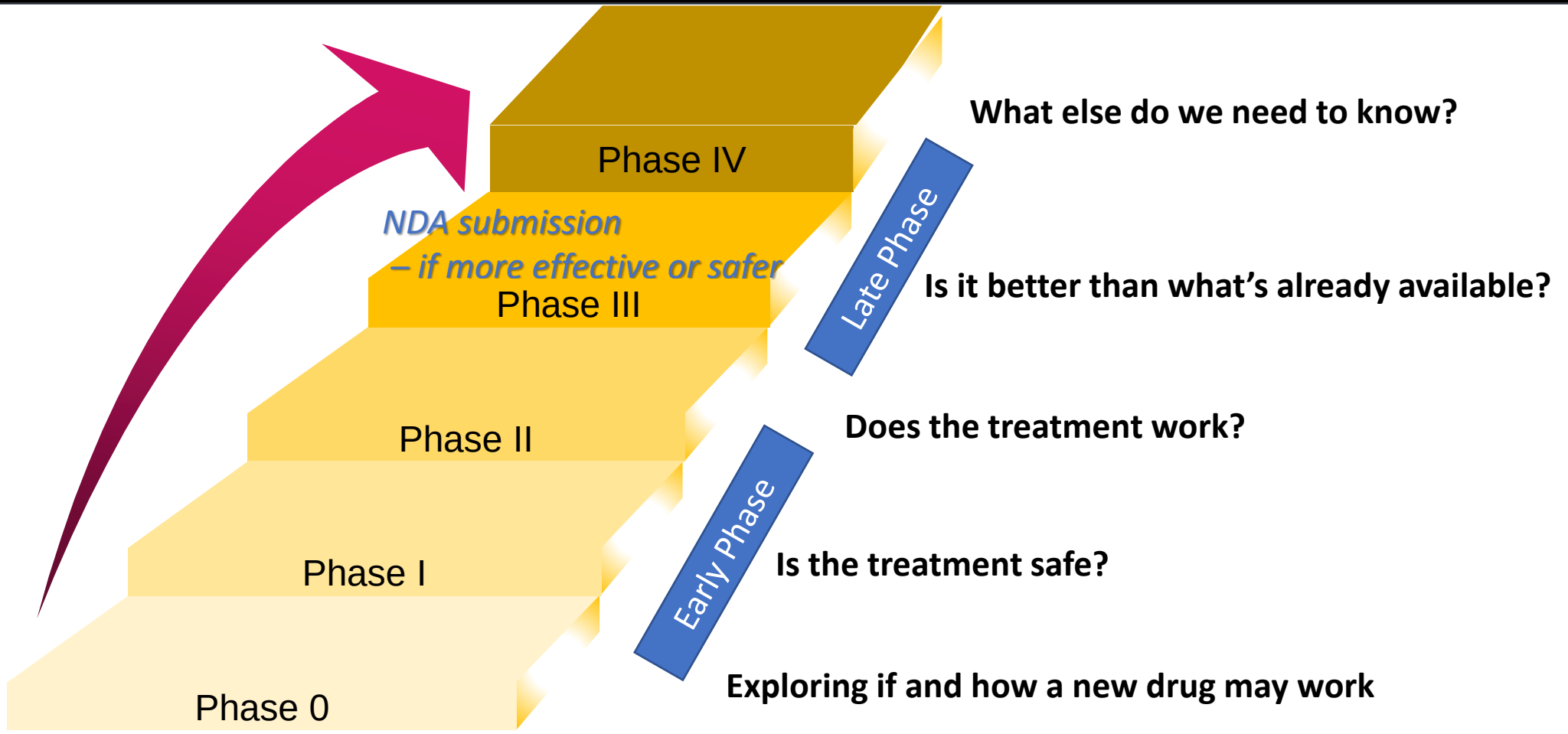
Intervention vs. non-intervention trials

- Non-intervention ~ Observational
- Most recently, low-intervention trials (Fournie, Siebenaler and Wiederkehr, 2016)

Intervention trials

- Three criteria to meet (Fournie, Siebenaler and Wiederkehr (2016)):
  - Assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice (i.e., the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder) of the member state concerned.
  - The decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study.
  - Diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.
- A table of decision tree to guide whether a trial is an intervention or non-intervention trial (Vol 10 – Guidance Document Applying for Clinical Trials, Q&A, Version 11.0)

Clinical Trial Phases



Phase 0: Exploring if and how a new drug may work

- To help speed up and streamline the drug approval process
- Expediting clinical evaluation by integrating qualified pharmacodynamic biomarker assays into first-in-human cancer clinical trials of molecularly targeted agents
- Exploratory
- A few small doses of a new drug in a few patients (< 15 patients)
- Short time duration of drug administered
- Preliminary data on PD/PK
- No data on safety and efficacy,

Phase I: Is the treatment safe?

To find the highest dose of the new treatment that can be given safely without serious side effects

Testing on safety, tolerability, PK/PD

Small group of healthy volunteers or patients (up to a few dozen)

Short duration

Dose ranging/escalation (SAD, MAD)

No placebo

Phase II: Does the treatment work?

If a new treatment is found to be reasonably safe in phase I clinical trials, it can then be tested in a phase II clinical trial to find out if it works

Usually, a group of 25 to 100 patients with the same type of indication treated using the dose and method found to be the safest and most effective in phase I

Some phase II studies randomly assign subjects to different treatment groups (much like what's done in phase III trials). These groups may get different doses or get the treatment in different ways to see which provides the best balance of safety and effectiveness.

No placebo (sham or inactive treatments) is used.

Exploratory trial

optimum dose finding

Phase IIA – dose requirement assessment, Phase IIb – study efficacy

Phase III: Is the treatment better than what's available?

Most phase III clinical trials have a large number of patients, at least several hundred

Often done in many places across the country or worldwide

Tend to last longer than Phase I and II

Placebos may be used in some phase III studies, but they're never used alone if there's a treatment available that works.

Confirmatory trial, generally pivot

Efficacy as primary objective

Phase IIIA – get sufficient & significant data, Phase IIIb – allow patients to continue treatments, label expansion, collect additional safety data

As with other studies, patients in phase III clinical trials are watched closely for side effects, and treatment is stopped if they're too bad.

Phase IV: What else do we need to know?

Phase IV studies look at drugs that have already been approved by the FDA (Post-marketing)

May involve thousands of people

The drugs are available for doctors to prescribe for patients, but phase IV studies might still be needed to answer important questions

Surveillance for human safety in real life – e.g. drug behavior and action if missing or over-dose

May also look at other aspects of the treatment, such as quality of life or cost effectiveness

Typically the safest type of clinical trial because the treatment has already been studied a lot and might have already been used in many people. Phase IV studies look at safety over time

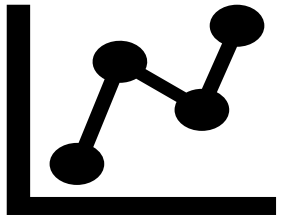
Good Clinical Practice

- An international ethical and scientific quality standard
  - for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects
- Guidance document for companies that conduct clinical trials
  - developed by the International Conference on Harmonisation (ICH)
- Intended:
  - to provide assurance that the rights, safety and well-being of clinical trial subjects are protected
  - to assure that the research yields quality scientific data
- GCP principles for clinical trials:
  - CTs should be according to ethical principles, sound scientific evidence and clear detailed protocols.
  - Benefits should outweigh the risks
  - Obtain participant informed consent and maintain their confidentiality
    - The rights, safety and well-being of trial participants are of paramount importance
  - The care must be given by adequately qualified and experienced personnels
  - Records should be easily accessible and retrievable for accurate reporting, verification and interpretation
  - Investigational products should be manufactured per Good Manufacturing Practice

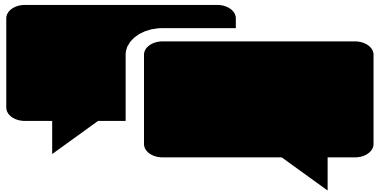
(Bio)statistics in Clinical Research

Connect the Two

Statistics



abstract



Two-way translation

Clinical Process

real world

Measurement Scaling

Represents measurement as scales

Being treated as variables in the analysis

Guides the choice among statistical procedures

Scaling:

Nominal, e.g. a disease is present or absent

Ordinal, e.g. disease stage, tumor grade

Interval

- **Discreet, e.g. number of children in a household**
- **Continuous, e.g. blood pressure, weight, height**

Summarize Measurement Scaling

- Descriptive statistics
  - Summarize characteristics of the study and control groups in randomized trials
    - Single variable
    - Multiple variables

Measurement Timing

- Long-term clinical events and processes vs. acute clinical events and processes
- Unable to measure the entire course of the events we are studying
- Set a limited study timeframe
- Right censoring - when a study is investigating a process that has reached a conclusion in some, but not all of the subjects when the study ends hence
- censoring information about that outcome
- Time-to-event – survival analysis and life-table
  - Kaplan-Meier - non-parametric
  - Cox proportional hazard model – parametric
  - Tumor assessment endpoints: Overall Survival, Progression Free Survival, Time to Progression, Time to Failure, Disease Free Survival

Tumor assessment endpoints (FDA Guidance, 2018)

Table 2. Advantages and Disadvantages of Important Cancer Approval Endpoints

Endpoint	Advantages	Disadvantages
Overall Survival	• Easily and precisely measured • Generally based on objective and quantitative assessment	• May be affected by switch-over of control to treatment or subsequent therapies • Needs longer follow-up • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	• Generally assessed earlier and with smaller sample size compared with survival studies	• Blinding is important for assessing the endpoint • Potentially subject to assessment bias, particularly in open-label studies • Lack of validated instruments in many disease areas • Definitions vary among studies • Balanced timing of assessments among treatment arms is critical
Disease-Free Survival or Event-Free Survival	• Generally assessed earlier and with smaller sample size compared with survival studies • Generally based on objective and quantitative assessment	• Potentially subject to assessment bias, particularly in open-label studies • Definitions vary among studies • Balanced timing of assessments among treatment arms is critical • Includes noncancer deaths
Objective Response Rate	• Generally assessed earlier and with smaller sample size compared with survival studies • Effect on tumor attributable to drug(s), not natural history • Generally based on objective and quantitative assessment	• Definitions vary among studies • Frequent radiological or other assessments • May not always correlate with survival
Complete Response	• Generally assessed earlier and with smaller sample size compared with survival studies • Effect on tumor attributable to drug(s), not natural history • Generally based on objective and quantitative assessment	• Definitions vary among studies • Frequent radiological or other assessments • May not always correlate with survival
Progression-Free Survival or Time to Progression	• Generally assessed earlier and with smaller sample size compared with survival studies • Measurement of stable disease included • Generally based on objective and quantitative assessment	• Potentially subject to assessment bias, particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Balanced timing of assessments among treatment arms is critical • May not always correlate with survival

Result likelihood and stability

- Clinical decision: from initial sample to general
  - E.g. lab measurement following a surgery
  - How likely will other patients experience the same?
- The urgency of statistical inference
- Test of statistical significance
  - Point statement
  - Range of estimation
- Bayesian techniques: Calculate predictive value of a diagnostic finding given prior belief of the finding’s sensitivity and specificity and the prevalence of disease

Independent vs. Paired Measurement

- Tests of statistical significance are different between the two:
  - Any difference (one or two directions) – independent samples
  - Second set of sample as the precise prediction of first set – paired samples
- Paired analyses needed when the selection of samples is matched
  - Matching – to maximize comparability of the samples on all factors other than the factor whose influence is being compared
    - Cohort study – risk factor
    - Case-control design – clinical outcome

Adjustment for multiple outcomes

- Classical test of statistical significance is based on a single examination of the relationship investigated.
- Often, multiple comparisons are made
- Data safety monitoring/Interim analysis
  - Review data at pre-specified intervals
- Most conservative approach for adjustment:
  - Bonferroni ~ target p-value divided by the number of comparisons made
  - Final statistical significance for all comparisons combined do not exceed target p-value

Statistical Power and Negative Studies

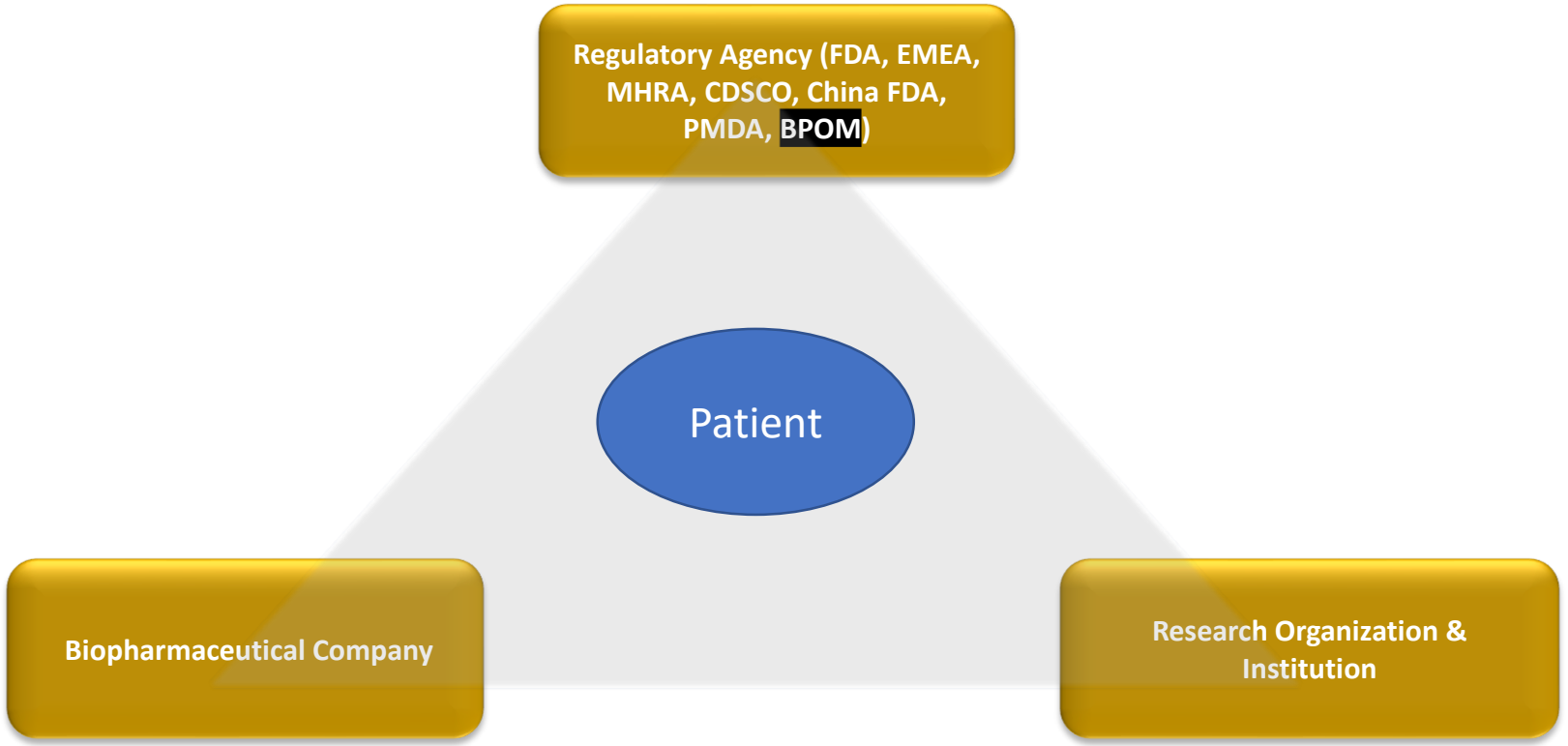
- When study results fail to show statistically significant results
  - Under power studies
- Sample size must be large enough for a study to have a reasonable chance of finding the association per study hypothesis
- Many statistical power methods have been established based on:
  - Planned analysis
  - Sample size
  - Population assumptions
- the importance of select the proper method
- The importance of planning
  - Conduct of pilot studies

Biostatistician roles

Study Life Cycle

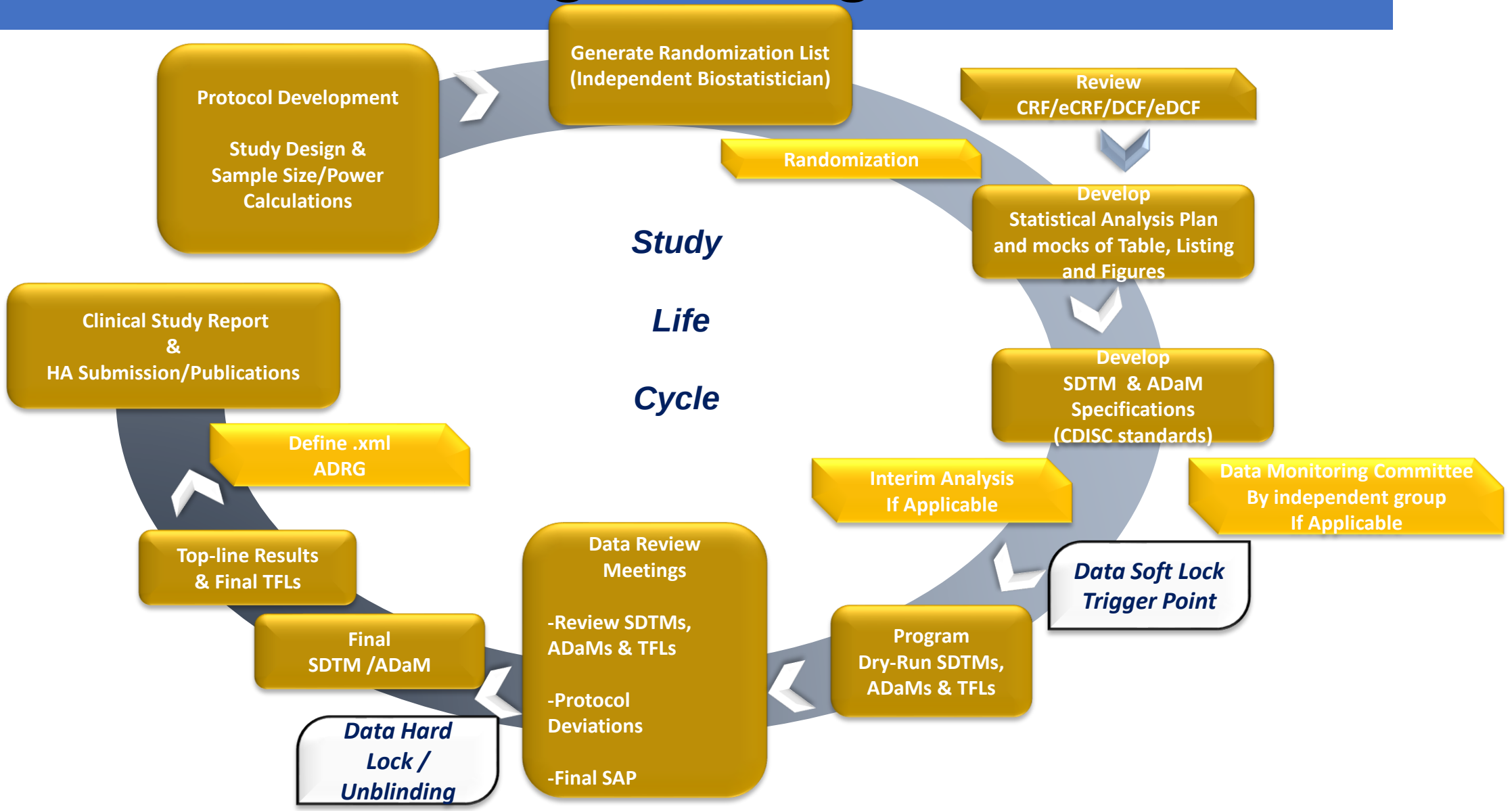
Source: Introduction to Clinical Research by Benhur Pradeep

Clinical Trial Collaborators



Clinical Trial Cross-functional Team

Biostatistics and Programming Tasks



Highlights of Biostatistician Roles

- Play a role in all areas of drug R&D
- Start from early on – input to protocol development
- Teamwork – work with people from different disciplines
- Core competencies include
  - statistical knowledge
    - understanding of drug development, and its goal
    - study design, sample size/power, statistical procedures
  - personal
    - Finding your grit, passion, integrity
  - Communication
    - active listener, across function communication, speak in client language
  - Adapt to change & agility

Trends Changing and Statistical Considerations

New Drug Development Challenges

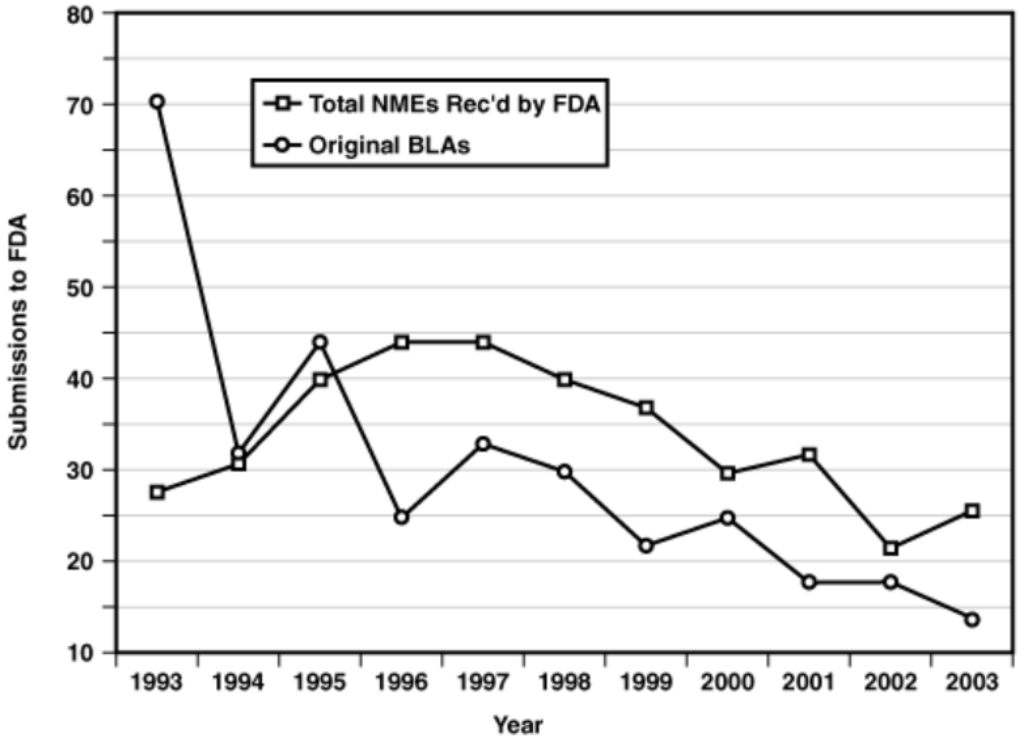
New drug development ~ costly and time-consuming

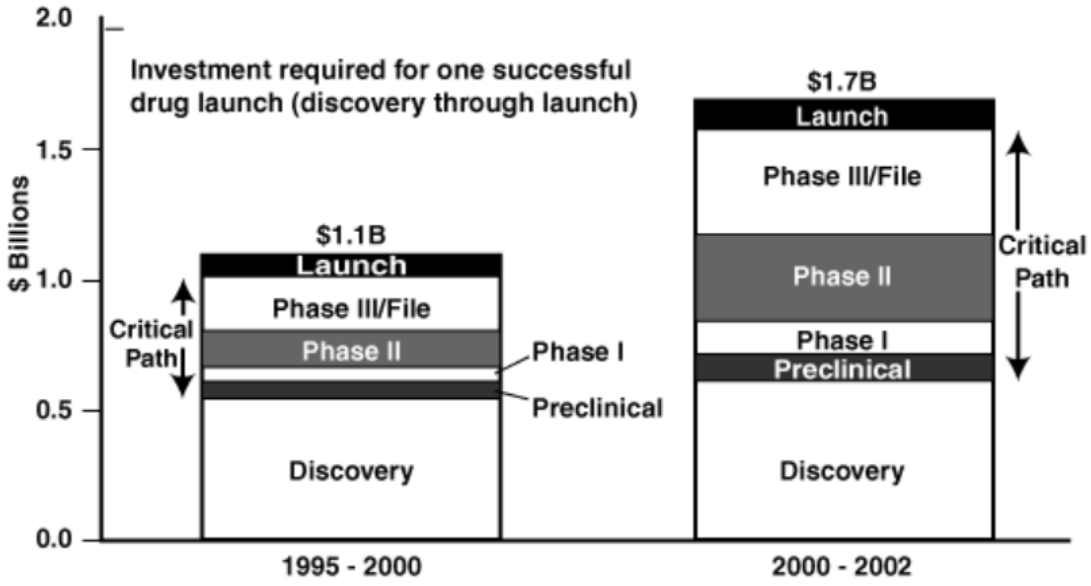
Low success rate of drug development

- Rapidly escalating costs
- Lack of safety and/or efficacy
- Ineffective dose/regime
- Ineffective patient population
- In adequate planned study design to demonstrate the desired treatment effect
- Due to complexity, unattracted to patients, couldn't retain patients and hence, attrition rate on rise
  - Round (2018), "Of 2579 clinical trials in a recent study, 19% had been terminated due to failing to recruit patients or for recruiting less than 85% of planned enrollments."
  - Compromising statistical validity

Stagnation in the development of innovative products

FDA Critical Initiative Path Report (2004)





1993-2003 Major Drug and Biological Product Submission to FDA

Responding to the Challenges

FDA initiatives	•critical path (2004) and critical path opportunity list (2006) •FDA called attention to an alarming decline in # of innovative products submitted •Highlights the need of advancing improved and innovative trial designs •Bridge the gap between basic scientificc research and drug development •Define purposes of adaptation in clinical trials
EMEA draft paper (2006)	•Flexible/adaptive design clinical trials in new drug development
FDA initiative recommendations	•Adaptive design – offer flexibility •Bayesian
FDA Update	•November 2019 – finalized FDA guidance document of 'Adaptive Design Clinical Trials for Drugs and Biologic Guidance for Industry'

Adaptive Design Clinical Trials

Adaptive Design Clinical Trials - Background

- Improper dose selection at early phase may lead to late phase (e.g. Phase III) study failure and consequently, the whole development program:
  - Hwang et. al. (2016), “Using public sources and commercial databases covering drugs and biologics that started trials between 1998 and 2008, 54% of agents carried into pivotal trials failed, primarily owing to inadequate efficacy or safety concerns.“
  - 20% of drugs approved by FDA between 1980-89 had the initial dose changed
- The need of significant rework by biopharma company “double” the cost and efforts
- Increase of time to market and hence, time for patients to get necessary treatment

Adaptive Design Clinical Trials

- The need of obtaining and accumulating information during a trial in real time
- The need to reduce the costs
- The need to streamline the time frames for clinical trials in drug development, particularly in the earlier phases during proof of concept and dose selection

Adaptive Design Clinical Trials

- AD - allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial (FDA guidance, Nov 2019)
- AD – allow adaptations/modifications to the trial and/or statistical procedures of the trial AFTER the trial without compromising its validity and integrity
- AD – prospectively planned PRIOR TO examining data in unblinded mode

Adaptive Design Clinical Trials

Historically,

- 1970 – adaptive randomization, group sequential design, sample size re-estimation at interim
- 1990 – Continual re-assessment method

Adaptive Design Clinical Trials

Based on adaptation employed,

- Adaptive randomization
- Group sequential
- Sample size re-estimation
- Drop the loser/pick the winner
- Adaptive dose finding
- Adaptive seamless Phase II/III
- Multiple adaptive

Adaptive Design Clinical Trials

Based on rules,

- Allocation
- Sampling
- Decision
- Multiple adaptation

Phase 1 Dose Finding

- Traditionally, Phase 1 is to determine the dose and schedule of an investigational agent and/or drug
  - Dose finding ~ dose escalation
  - Classic assumption of monotonic relationship between dose and toxicity
  - To identify maximum tolerated dose (MTD)
    - the highest dose that can be administered to patients safely
  - Dose Limiting Toxicity (DLT)
    - unacceptable or unmanageable safety profile which is pre-defined by some criteria such as Grade 3 or greater hematological toxicity according to the US National Cancer Institute's Common Toxicity Criteria (CTC)

Classic Phase I Assumption:
Efficacy and toxicity both increase with dose

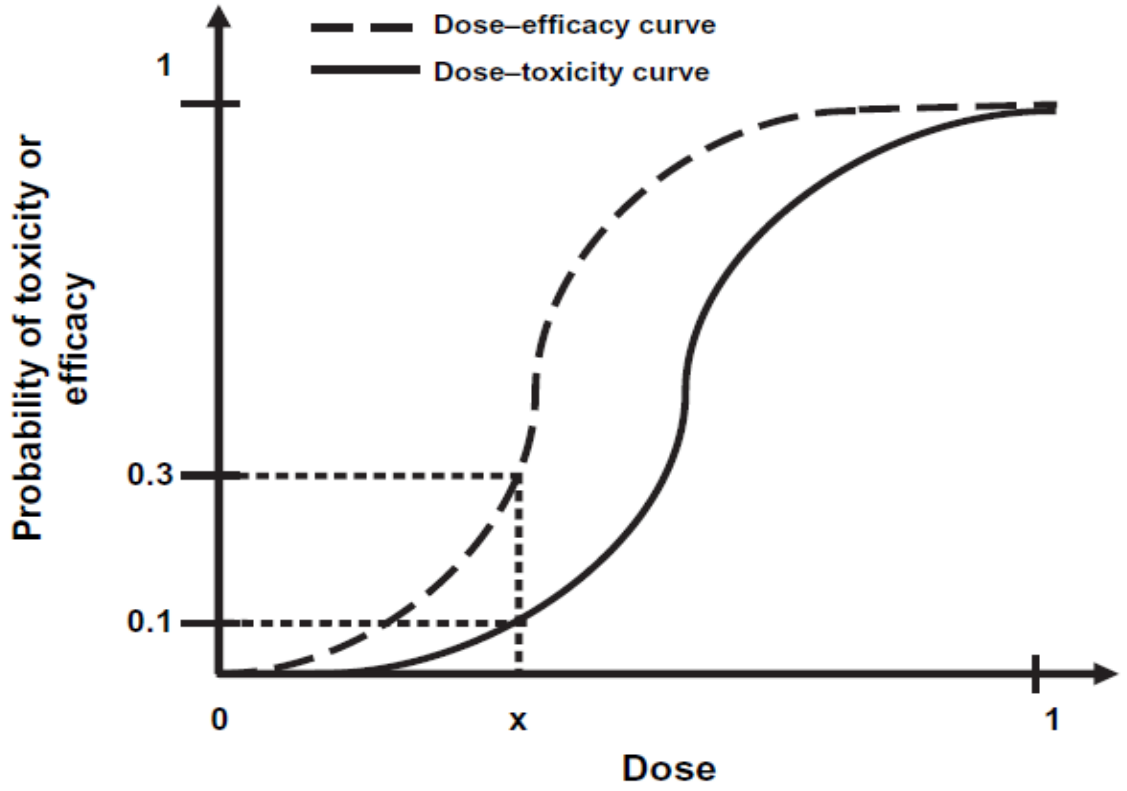
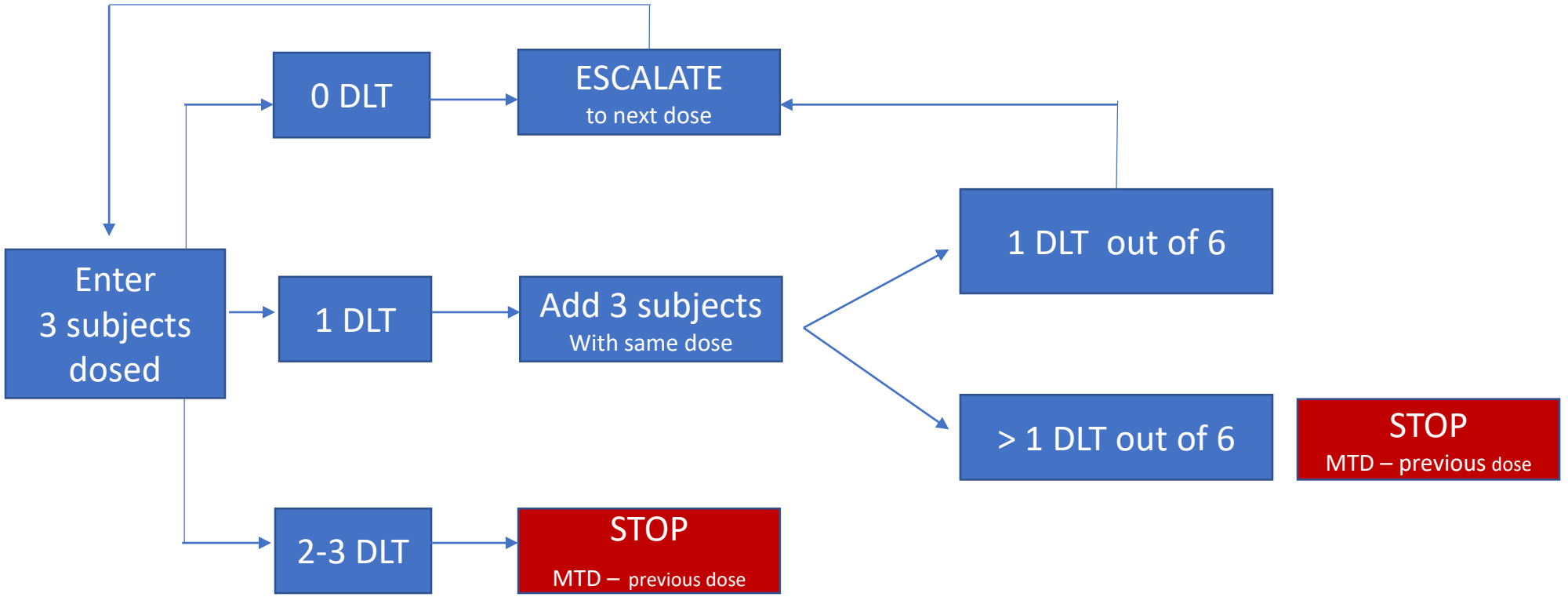


Figure 1. Typical dose–toxicity and dose–efficacy curves for cytotoxic agents. This example illustrates that at dose *x*, the probability of efficacy is 30% and the probability of toxicity is 10%; hence, the therapeutic index of the drug at dose *x* is 10% divided by 30% = 1/3.

Le Tourneau , Lee and Siu (2009)

Conventional Phase 1 Design – 3+3 design



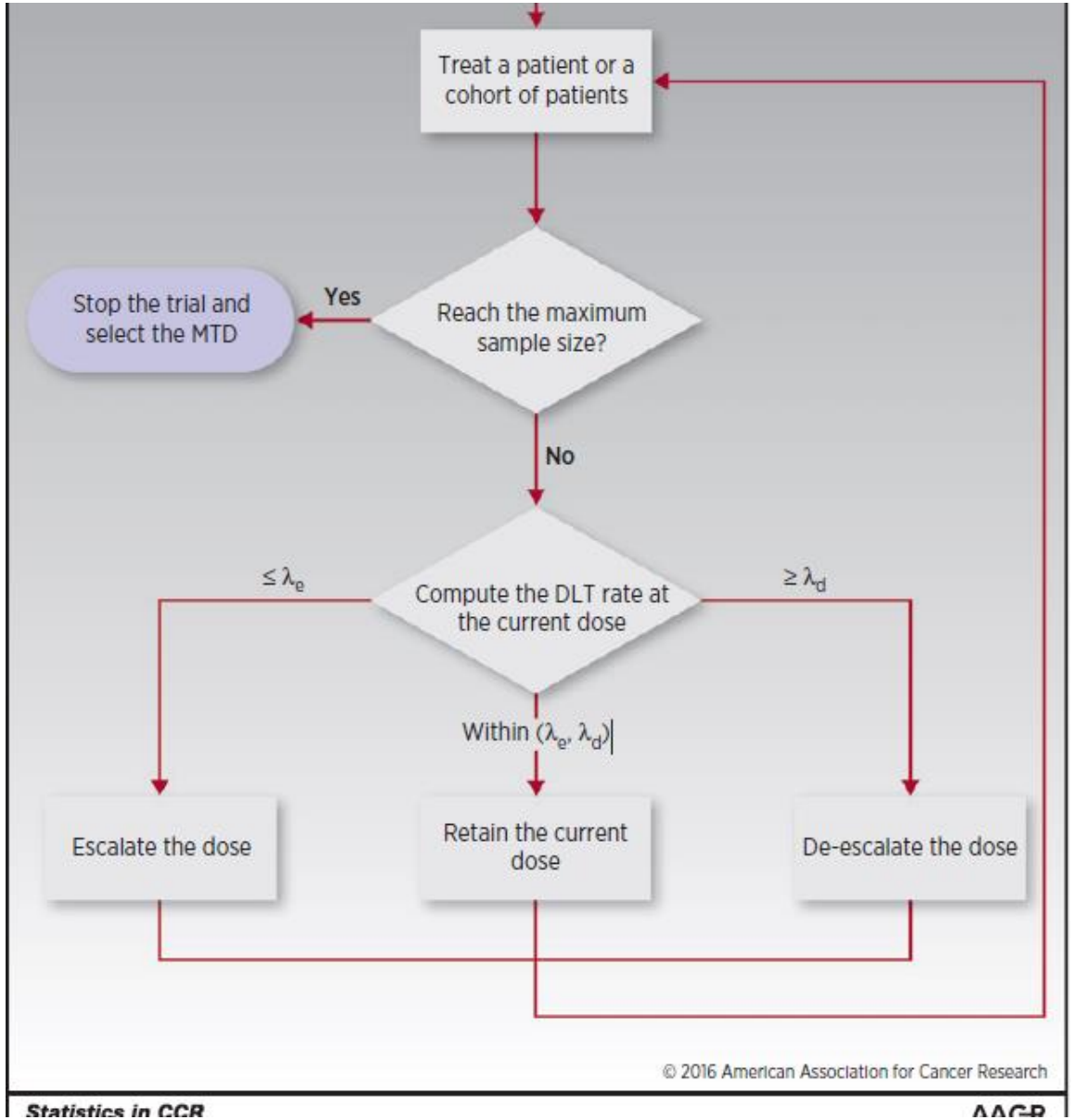
Phase 1 Design Comparison

Dose-escalation Method	Advantage	Drawback
Traditional (Algorithm-based)		
3+3 design	Easy to implement and safe; simple escalation/de-escalation rule; Provide some data on PK interpatient variability	Slow dose escalation; Only result from current dose used for determining the dose of next cohort ; Inaccurate MTD
Model based design:		
Continual reassessment method (CRM)	More accurate MTD (than Rule based designs)	Random dose escalation/de-escalation rule; Lack of standard in practice; challenges in interpreting method to clinician
Model assisted design:		
Bayesian Optimal Interval (BOIN) (improved CCD)	Simple dose escalation/de-escalation rule (pre-determined); Substantially lower risk of overdosing patients, more intuitive and transparent (than MTPI designs); Accurate MTD; Simpler to implement and free of the issue of irrational dose assignment caused by model misspecification (than CRM)	

Flowchart of the BOIN Design –

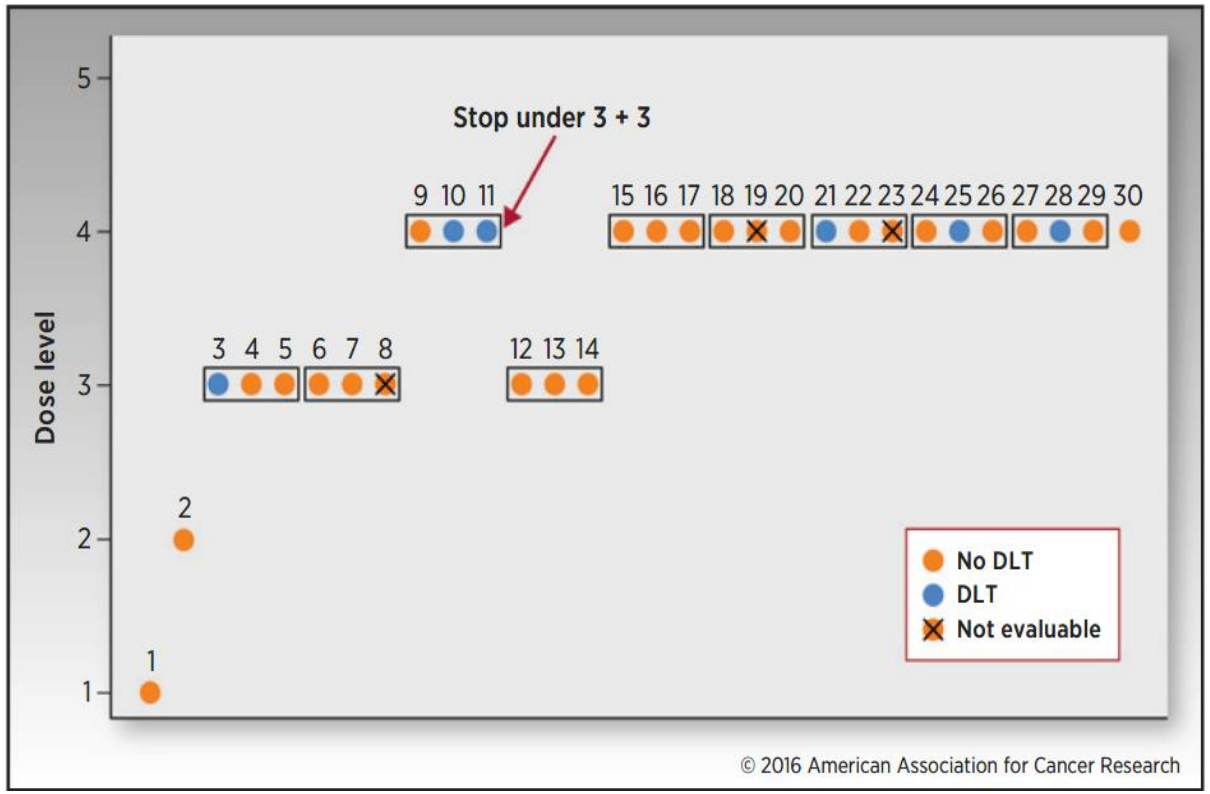
adaptive & bayesian combined

Reference: Yuan Y, Hess KR, Hilsenbeck SG, and Gilbert M (2016)



Reference: Yuan Y, Hess KR, Hilsenbeck SG, and Gilbert M (2016)

Hypothetical Phase I Clinical Trial using BOIN



BOIN Design

- Flexibility of target toxicity rate
- Flexibility of number of patients for each cohort
- Total number of patients pre-determined
- Minimizes number of patients treated at sub-therapeutic or overly-toxic doses
- Provides greater confidence that the MTD has been correctly chosen
- Does not require post-hoc expansion cohort: patients continue at a dose near evolving MTD in a seamless design

Phase 1-2 seamless design

Combine objectives and goals of what would normally be considered separate trials into one study

E.g. Phase 1 MTD with Phase 2a for assessing the efficacy of drug at the dose

Compared to 2 separate studies, reduced sample size and lower cost

Important to plan ahead

Statistical method should consider:

- potential biases
- multiple looks at the data, and
- how to combine the data from the different stages to make sure that the overall validity of the study can be maintained.

Types of Adaptive Design – Bhatt and Mehta (2016)

Table 1. Types of Adaptive Designs.*

Stage of Development and Design Type	Strength	Weakness
First-in-human, phase 1 design with goal of establishing the MTD		
Single ascending dose or multiple ascending doses	Establishes MTD and biologic activity	Uses larger cohort sizes at potentially safe doses
Dose-escalation, 3+3, continual reassessment method, Bayesian logistic-regression method, or modified toxicity probability interval design	Provides more accurate estimate of MTD with smaller cohort size	May yield more cases of toxic events than design with single ascending dose or multiple ascending doses
Phase 2 design, with the goal of establishing efficacy and choosing doses for phase 3 trial		
Fixed-sample design, traditional proof-of-concept design (MTD vs. placebo), or dose-ranging design (MTD, placebo, and intermediate doses)	Is simple to implement and easy to design	Has less precision than adaptive design
Adaptive design with proof of concept, early stopping and sample-size reestimation, dose ranging with selection at interim analysis, or dose ranging with frequent Bayesian adaptation of randomization ratios	Yields more precise estimates for same sample size	Is more complex to implement; requires more lead time to set up; operating characteristics determined only by simulation
Seamless phase 2–3 design		
Operationally seamless	Eliminates time between phase 2 and phase 3; permits sponsor involvement for dose selection at the end of phase 2; uses conventional final analysis, parameter estimates, and confidence intervals	Has a final analysis based only on data from phase 3
Inferentially seamless	Combines data from both phases for final analysis	Has no sponsor involvement in dose selection at end of phase 2; has risk of inadequate dose–response modeling; has a complex final analysis involving closed testing; uses nonconventional parameter estimates and confidence intervals; data from the two phases may not be homogeneous
Sample-size reestimation		
With blinded data	Uses conventional final analysis; has fewer regulatory hurdles	Allows sample-size adjustments due to unknown variance only
With unblinded data	Allows sample-size adjustments due to unknown treatment effect or unknown variance; can determine sample size after review of actual data from the trial instead of from pilot studies	Interim estimate of treatment effect can be misleading; requires strict firewalls to prevent leakage of information about adaptive rules or decisions; potential for operational bias if investigator behavior changes; requires meticulous up-front planning; uses nonconventional final analysis with prespecified weighting of the cohorts before and after sample-size reestimation; may face regulatory hurdle
Group sequential design		
Classic	Enables early stopping for efficacy, futility, or harm; has flexible alpha spending functions; can alter maximum sample size in a blinded manner	Cannot alter maximum sample size or events in an unblinded manner; uses nonconventional parameter estimates and confidence intervals; if trial terminates early for efficacy, overruns pose risk of downturn from significance to nonsignificance; greater burden on data and safety monitoring committee to review totality of evidence before premature termination†
Adaptive	Includes all advantages of classic group sequential designs; can alter maximum sample size in an unblinded manner; can switch end point from noninferiority to superiority; can alter number and spacing of interim analyses, and alpha spending function, on the basis of unblinded interim analysis; overruns are not a problem since trial proceeds to completion with increased enrollment and resolution of responses in all patients instead of being terminated early with risk of downturn from unknown or unadjudicated responses	Includes all the disadvantages of sample-size reestimation with unblinded data; uses nonconventional parameter estimates and confidence intervals
Population-enrichment design	Can eliminate nonperforming subgroups at interim analysis if treatment is effective in selected subgroups only	Must prospectively identify which subgroups to target; may eliminate subgroups in which treatment is effective; loses power as number of targeted subgroups increases; loses power if there is low prevalence of effective subgroups; biomarker cutoff points for subgroup partitioning not known

* MTD denotes maximum tolerated dose.
† In an overrun situation, patients for whom the primary end points are unknown (because of unadjudicated data or delayed response) at the time of an early-termination decision will be included in the final analysis.

The implementation of AD (Bothwell et. al. 2018)

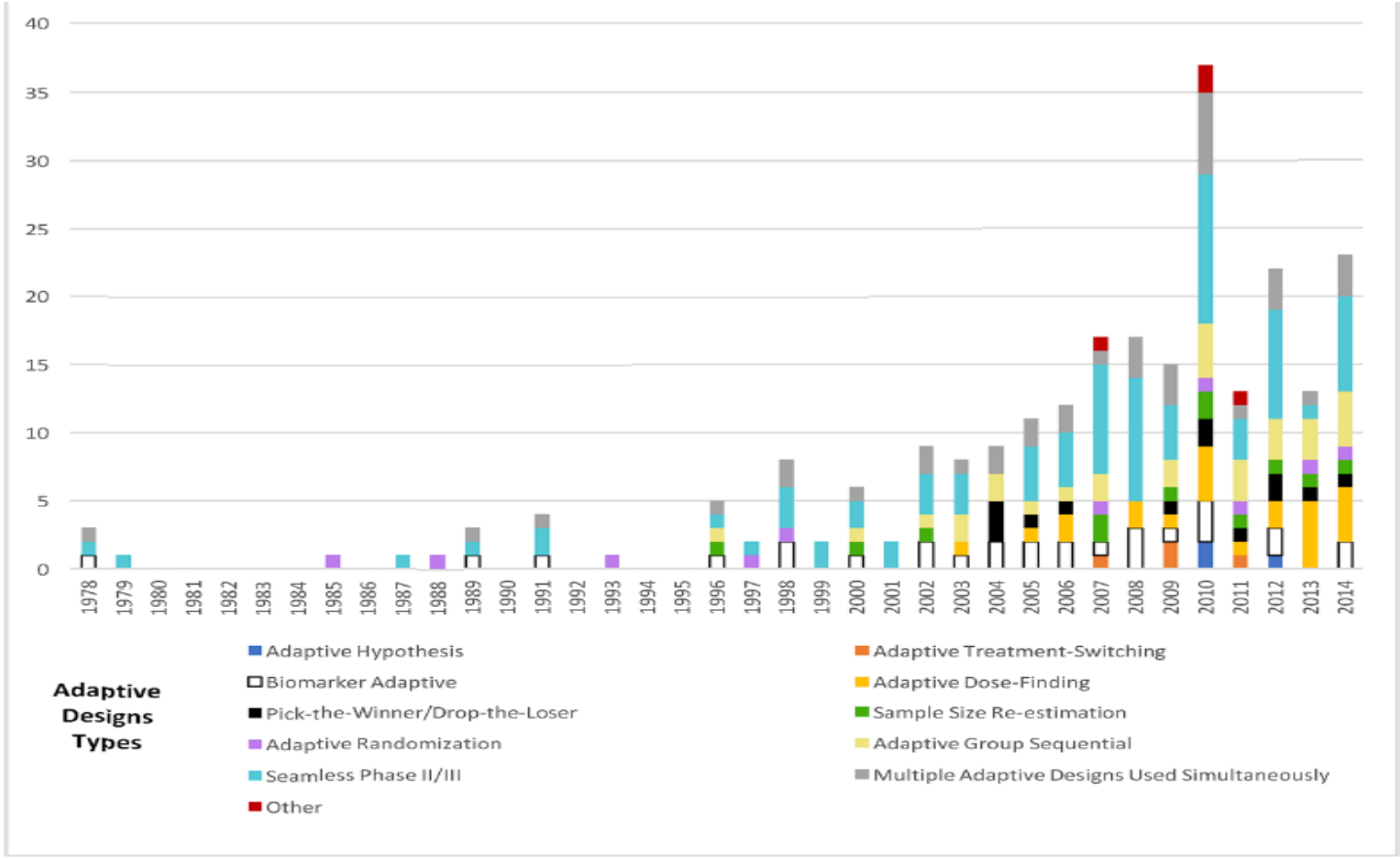
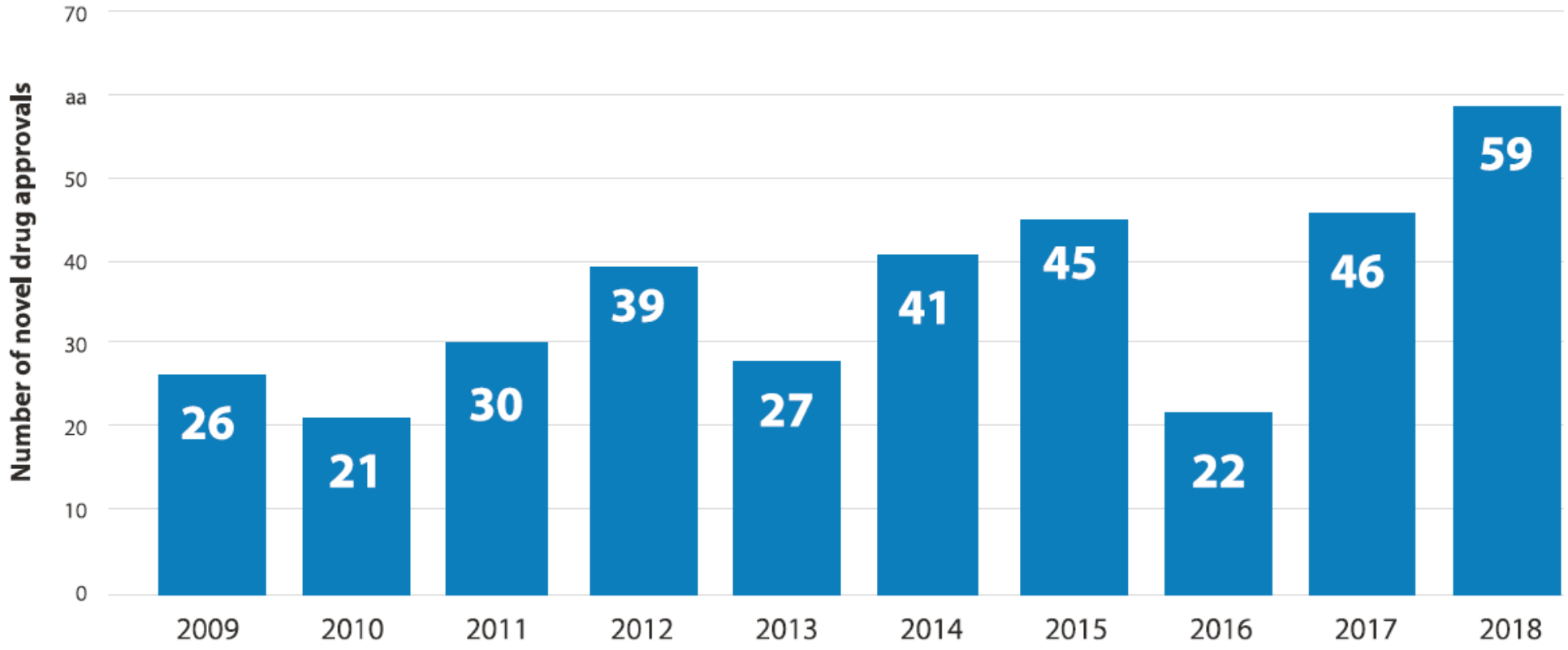


Figure 2 Prevalence of adaptive design type in surveyed trials. Adaptive trials first appeared in ClinicalTrials.gov search results in 2002; data prior to 2002 reflect only literature review results and data after 2002 reflect combined literature review and ClinicalTrials.gov results.

FDA-CDER Novel Drug Approvals up to 2018



- From 2009 through 2017, CDER has averaged about 33 novel drugs approved.
- 34 of CDER's 59 novel drugs (58%) were approved to treat rare or "orphan" diseases.

Patient Centric

Patient centricity – patient first

- Address challenges on patient recruitment and retention with complex clinical trials

Table 1: FDA and Sponsor Perspectives on Patient Centricity Interpretation

Patient Centricity Factor	FDA Perspective	Sponsor Perspective
Involving Patients	Obtain patient's perspective on Clinically Meaningful Outcomes	Establishing patient panels and engaging advocacy groups to design less burdensome studies
Better study performance	Collecting data points and PROs focused on established Clinical Outcomes that are valued by patients	Optimizing protocol inclusion/exclusion criteria (better enrollment)
Patient engagement	Involving the patient as a colleague throughout the study process from beginning to end	Creating materials, and implementing engagement initiatives (i.e., mHealth) to enhance the clinical trial experience with patients

Source: Alsumidale (2016)

Patient Centric

How to make trials to be more responsive to the needs of patients are?

- Recruitment – data driven
- Adaptive clinical trials
- Patient reported outcomes and patient focused endpoints
- Patient friendly trial
  - – reduce patient burden for clinic visit
    - Consider e-visit and telemedicine
    - Mobile platform
    - Wearable device
  - – integrate trial with day to day medical practice

Advantages

- Increase recruitment and
- Reduce lost to follow-up

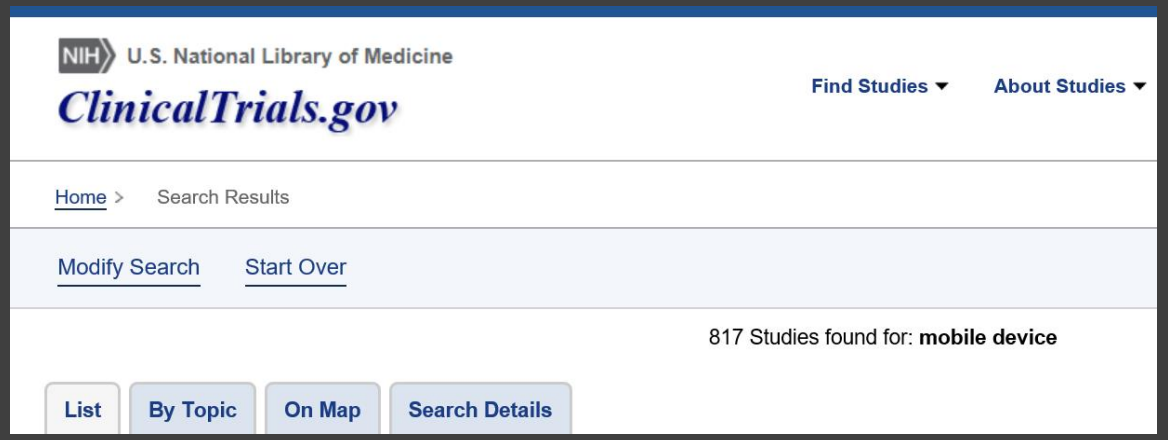
Virtual Trials

Mobile platform use

- mobile messaging to recruit patients can increase recruitment
- reminder for patients when to take drug, or when to go for an appointment
- patient tracker during trial

Wearable device

- Can get patient data better due to device with patient at all times
- Improve effectiveness by lowering the clinical site time and the personnel needed for those sites
- Improve inclusion and exclusion criteria needed to demonstrate efficacy and safety more efficiently.
- May do fully remote clinical trial – an ongoing effort



Virtual Trials: Mobile and Wearable Devices in Clinical Trials.gov

Mobile and Wearable Device Considerations

- May raise costs depending on the type of device used, what data your trying to get from that device, the infrastructure needed during collection, and the number of participants needed
- Data security and privacy
- Devices technical characteristics: size, convenience to wear, battery life, and impact on daily life activities of the user are variables involved in clinical study
- The process of regulatory agency submission and inspection

Precision Medicine

Precision Medicine

- Precision medicine ~ Personalized medicine
- Paradigm shift in oncology
  - Discovery of biomarkers and genetic mutations potentially predictive of treatment benefit
    - Organ-specific -> collection of sub-cancers
- increased efficiency in drug development when target-drug combinations exist
- an approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person
- choosing the right treatment for the right patient at the right time
- key – to discover patient-level characteristics:
  - demographic risk factors or
  - molecular or genetic biomarkers that are able to predict patients' disease condition, prognosis and response to potential treatments
- 2016 Precision Medicine Initiative - $215millions
  - near-term focus - oncology

Master Protocol

Innovative design trial

Any top-level or overarching clinical trial protocol comprised of several parallel, biomarker-based or genomically-based sub-trials or cohorts

Basket Trial: a master protocol in which each of the sub-trials (sub-studies) enrolls patients with identical or similar biomarker or genomic features but potentially vastly different disease (tumor) types .

Umbrella Trial: a master protocol where patients with a common disease (tumor) type (e.g., advanced non-squamous cell lung cancer) are enrolled to parallel cohorts or sub-trials that are similarly marker-driven.

Traditional vs. Innovative Trial Designs

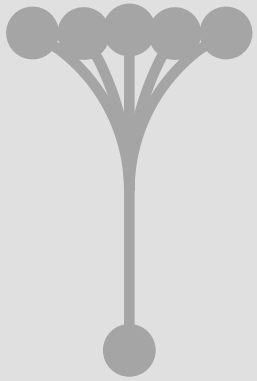
Traditional Design

Single Treatment

Single Indication

Fixed # treatment arms or add/delete treatment arms

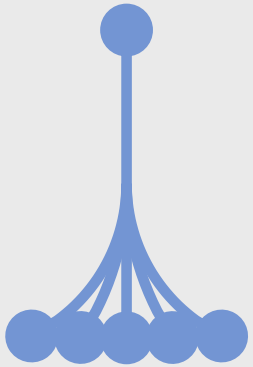
Multiple Treatments; markers driven



Single Indication; Tumor type

Genomic information; severity; lines of therapy; background characteristics

Single Treatment; identical marker



Multiple Indications; Tumor types

Basket Trial

- early stage, single-arm, phase II, proof-of-concept trials where in each basket or cohort is itself a single-arm trial studying a preliminary target-response hypothesis
- Advantages:
  - Simplicity, small size, the availability of an array of novel therapeutic agents to a broad spectrum of disease types who may benefit; have the potential to greatly increase the number of patients who are eligible to receive certain drugs relative to other trials designs.
- Challenges:
  - Prognostic heterogeneity
    - Standardized response rate used
  - Often non-randomized; historical control is used
  - Potential false positive finding due to a large number of parallel arms with no adjustment to multiplicity

- E.g. NCI-MATCH:
  - 20 or more arms
  - each testing different agents against different molecular targets and each including patients with different cancers

Umbrella Trial

- May include phase II or phase II/III trials
- The individual marker-specific sub-trials or cohorts may be either:
  - single-arm studies of paired targeted agents, or
  - randomized studies comparing targeted agents versus placebo or standard of care
- Advantage:
  - Prognostic homogeneity
- Challenges:
  - Relatively larger size, when sub-trials are randomized
  - Potentially long duration of trial
  - Difficult to enroll rare molecular subtypes of a single tumor type
  - Susceptible to modifications to the “treatment landscape” while the trial is underway
- E.g. ALCHEMIST, Lung-MAP

More….Platform Trial

- a master protocol in which sub-trials continually enter and exit, where the latter may occur due to futility or due to graduation of a marker-treatment combination to further study
- Bayesian in nature
- Advantage:
  - operational seamlessness and efficiency
- Challenges:
  - large size and scope
  - non-concurrent randomization may also arise

Master Protocol Future Opportunity

- The need of improved statistical methodology to address the ‘sophisticated’ design:
    - Patient classification based on multiple markers
    - Effect size (in contrast to sample size)
- Practical considerations:
    - Logistic to accommodate multiple trials
    - Team collaboration
    - External changes over time (long duration means years, decades, so on)

Big and Ever-more Data

Why now?

- The use of computers, mobile devices, wearables and other biosensors to gather and store huge amounts of health-related data has been rapidly accelerating
- Combined with AI algorithms, it is potential to solve many CT challenges
- Increasing role in health care decisions
    - To monitor post-market safety and adverse events and to make regulatory decisions (FDA).
    - To support coverage decisions and to develop guidelines and decision support tools for use in clinical practice (health care community).
    - To support clinical trial designs (e.g., large simple trials, pragmatic clinical trials) and observational studies to generate innovative, new treatment approaches (medical product developers).

Real World Data

- Data relating to patient health status and/or the delivery of health care routinely collected from a

  variety of sources including:

  - electronic health records (EHRs),
  - claims and billing activities, product and disease registries,
  - patient-generated data including in home-use settings and
  - data gathered from other sources
    - that can inform on health status, such as mobile devices

- The technological and methodologic challenges presented by these new data sources are the focus of active efforts by researchers:

  - FDA
  - National Institutes of Health (NIH) Collaboratory
  - Research networks and “computable phenotypes”

Real World Evidence

- The clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.
- Can be generated by different study designs or analyses

RWE program framework

- Framework for FDA's real world evidence program (2018)
- The 21st Century Cures Act, passed in 2016:
  - must evaluate the potential use of RWD
    - to generate RWE of product effectiveness
    - to help support approval of new indications for drugs approved
  - to help to support or satisfy post-approval study requirements.
  - also apply to biological products licensed

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Thank You!