Applying Regulatory Science to Neonates: Launch of the International Neonatal Consortium

The ABCs of Regulatory Science

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International Neonatal Consortium

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CRITICAL PATH INSTITUTE
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10 YEARS

Session 1
May 18, 2015

Disclaimer

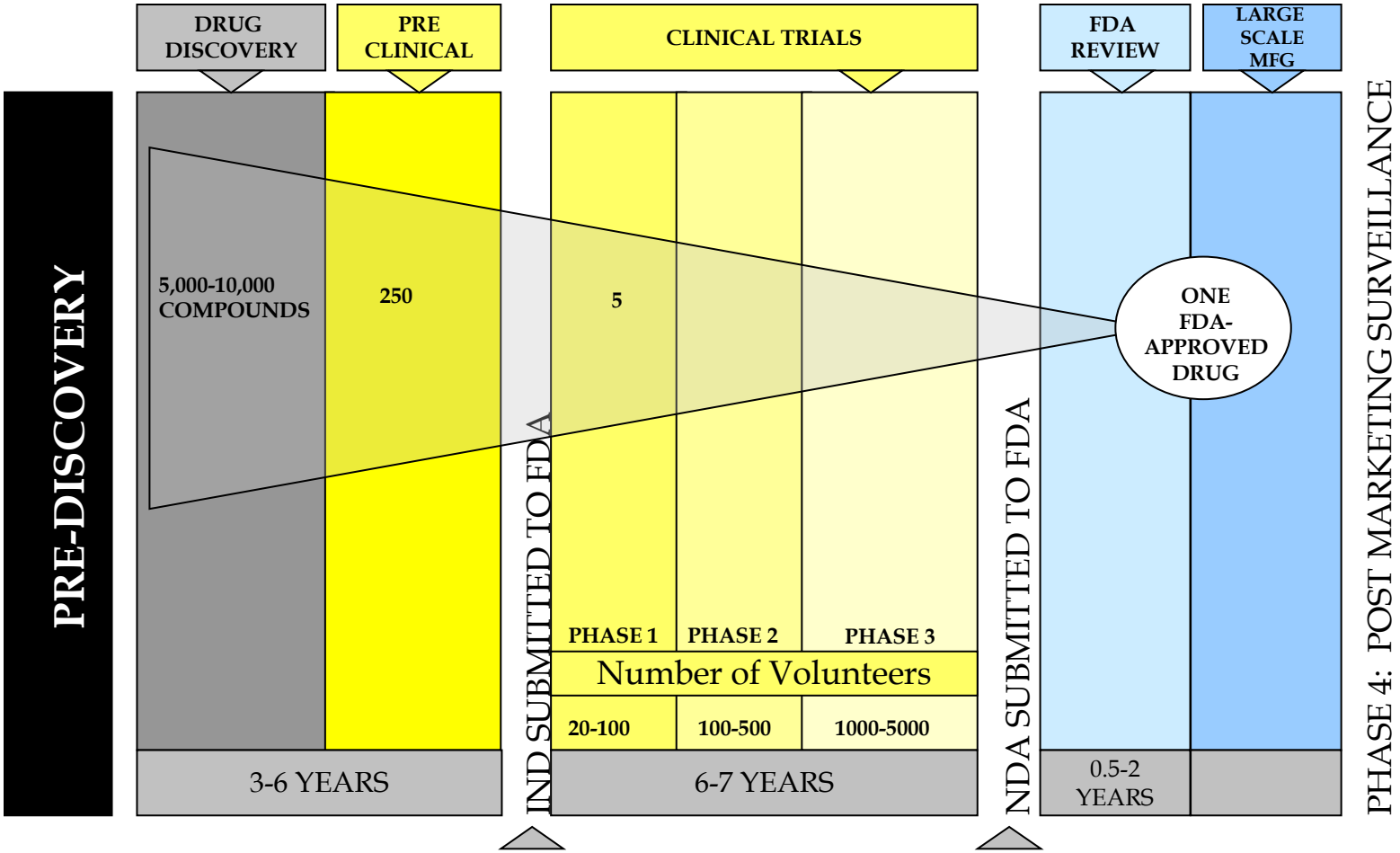
- The views presented here are personal and do not necessarily reflect the views of the Agency
- All specific drug development questions should be discussed with the relevant review division
- Off-label use of drugs will be discussed

Agenda

- US Drug Regulation and Definitions
  - General Considerations
  - Expedited Programs for Serious Conditions
  - Master Protocols
  - Drug Development Tools
    - Biomarkers
    - Clinical Outcome Assessments
  - FDA Drug Development Tool Qualification Program
  - Regulatory Science
- Neonatal Issues
  - Innovative Trials in Rare Diseases
  - Neonatal Specific Diseases
  - Data Standards
  - Consortia Approaches

US Drug Regulation and Definitions

Research and Development Process



SOURCE: PhRMA 2008, Stages of Drug Development Process and attrition rate of compounds as they travel through the drug development process over time.

Expedited Programs for Serious Conditions (Features)

Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
• Actions to expedite development and review • Rolling review	• Intensive guidance on efficient drug development • Organizational commitment • Rolling review • Other actions to expedite review	• Approval based on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	• Shorten clock for review of marketing application (6 months compared with the 10-month standard review

Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pd

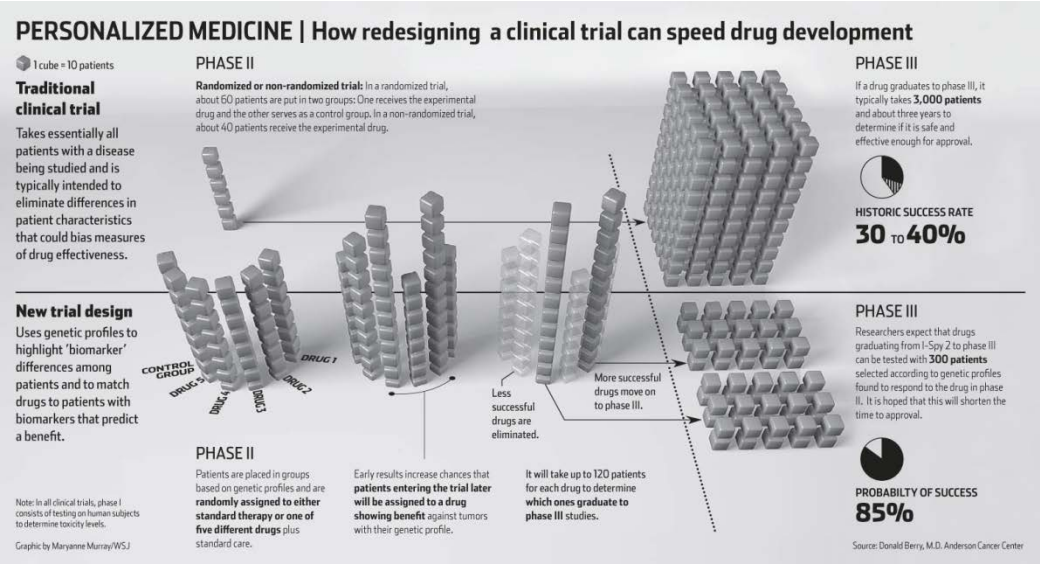
Expedited Programs for Serious Conditions (Qualifying Criteria)

Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
• A drug that is intended to treat a serious condition **AND** nonclinical or clinical data demonstrate the potential to address unmet medical need **OR** • A drug that has been designated as a qualified infectious disease product	• A drug that is intended to treat a serious condition **AND** preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies	• A drug that treats a serious condition **AND** generally provides meaningful advantage over available therapies **AND** demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity of mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	• An application (original or efficacy supplement) for a drug that treats a serious condition **AND** if approved, would provide a significant improvement in safety or effectiveness **OR** • Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A **OR** • An application for a drug that has been designated as a qualified infectious disease product **OR** • Any application or supplement for a drug submitted with a priority review voucher

Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pd

Master Protocols

Lung-MAP – the Lung Cancer Master Protocol
A groundbreaking clinical trial model that uses a multi-drug, targeted screening approach to match patients with promising new treatments based on their unique tumor profiles.
http://www.focr.org/lung-map



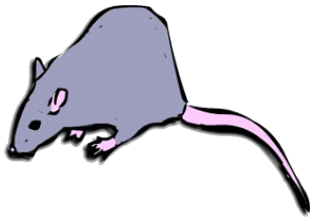
May include:

- One protocol
- Central governance structure
- Central Institutional Review Board
- Central Data Monitoring Committee
- Central independent review committee
- Central repository of data and specimens
- Leverage common control groups
- Potential to study multiple drugs or multiple markers

Biomarker Definitions

- **Prognostic biomarker**
  - Indicates future clinical course of the patient with respect to some specified clinical outcome
- **Predictive biomarker**
  - Measured prior to an intervention
  - Identifies patients who are relatively susceptible to a particular drug effect versus less susceptible patients
- **Pharmacodynamic biomarker**
  - Response-indicator biomarker
  - Post treatment measurement
  - Marker that reveals whether, or how large, a particular biological response has occurred in that particular patient
- **Efficacy-response biomarker**
  - Efficacy-surrogate biomarker, Surrogate endpoint
  - Subset of general pharmacodynamic biomarkers
  - Predicts a *specific* clinical outcome of the patient at some later time after treatment

Exploratory Biomarker



Discover a biomarker involved in the mechanism of action of a disease

Test the biomarker in animal models of the disease for use as a diagnostic, predictive, prognostic, or pharmacodynamic biomarker

Test the biomarker in humans with the disease for use as a diagnostic, predictive, prognostic, or pharmacodynamic biomarker

Regulatory Biomarker

"The best setting in which to evaluate a predictive biomarker for an experimental targeted therapy is a randomized clinical trial (RCT) of the targeted therapy vs a standard treatment, where the biomarker status is obtained on the patients but not used to direct treatment."

Polley MYC, Freidlin B, Korn EL, Conley BA, Abrams JS, and McShane LM. Statistical and practical considerations for clinical evaluation of predictive biomarkers. J. Natl. Cancer Inst. 105:1677-1683, 2013

"These roles will often involve a quantitative imaging biomarker (QIB), a quantifiable feature extracted from a medical image that is relevant to the underlying anatomical or biochemical aspects of interest. The ultimate test of the readiness of a QIB for use in the clinic is not only its biological or clinical validity, namely its association with a biological or clinical endpoint of interest, but also its clinical utility, in other words, that the QIB informs patient care in a way that benefits patients. But first, the imaging procedure to acquire the QIB must be shown to have acceptable technical performance; specifically, the QIB it produces must be shown to be accurate and reliable measurements of the underlying quantity of interest."

Huang EP, Wang XF, Choudhury KR, McShane LM, Gonen M, Ye J, Buckler AJ, Kinahan PE, Reeves AP, Jackson EF, Guimaraes AR, Zahlmann G, for the Meta-Analysis Working Group. Meta-analysis of the technical performance of an imaging procedure: guidelines and statistical methodology. Statistical Methods in Medical Research. 24:141-174, 2015

Table 1 | Criteria for the use of omics-based predictors in NCI-supported clinical trials

Domain	Criteria
Specimen issues	1. Establish methods for specimen collection and processing and appropriate storage conditions to ensure the suitability of specimens for use with the omics test.
	2. Establish criteria for screening out inadequate or poor-quality specimens or analytes isolated from those specimens before performing assays.
	3. Specify the minimum amount of specimen required.
	4. Determine the feasibility of obtaining specimens that will yield the quantity and quality of isolated cells or analytes needed for successful assay performance in clinical settings.
Assay issues	5. Review all available information about the standard operating procedures (SOPs) used by the laboratories that performed the omics assays in the developmental studies, including information on technical protocol, reagents, analytical platform, assay scoring, and reporting method, to evaluate the comparability of the current assay to earlier versions and to establish the point at which all aspects of the omics test were definitively locked down for final validation.
	6. Establish a detailed SOP to conduct the assay, including technical protocol, instrumentation, reagents, scoring and reporting methods, calibrators and analytical standards, and controls.
	7. Establish acceptability criteria for the quality of assay batches and for results from individual specimens.
	8. Validate assay performance by using established analytical metrics such as accuracy, precision, coefficient of variation, sensitivity, specificity, linear range, limit of detection, and limit of quantification, as applicable.
	9. Establish acceptable reproducibility among technicians and participating laboratories and develop a quality assurance plan to ensure adherence to a detailed SOP and maintain reproducibility of test results during the clinical trial.
	10. Establish a turnaround time for test results that is within acceptable limits for use in real-time clinical settings
Model development, specification, and preliminary performance evaluation	11. Evaluate data used in developing and validating the predictor model to check for accuracy, completeness and outliers. Perform retrospective verification of the data quality if necessary.
	12. Assess the developmental data sets for technical artefacts (for example, effects of assay batch, specimen handling, assay instrument or platform, reagent, or operator), focusing particular attention on whether any artefacts could potentially influence the observed association between the omics profiles and clinical outcomes.
	13. Evaluate the appropriateness of the statistical methods used to build the predictor model and to assess its performance.
	14. Establish that the predictor algorithm, including all data pre-processing steps, cutpoints applied to continuous variables (if any), and methods for assigning confidence measures for predictions, are completely locked down (that is, fully specified) and identical to prior versions for which performance claims were made.
	15. Document sources of variation that affect the reproducibility of the final predictions, and provide an estimate of the overall variability along with verification that the prediction algorithm can be applied to one case at a time.
	16. Summarize the expected distribution of predictions in the patient population to which the predictor will be applied, including the distribution of any confidence metrics associated with the predictions.
	17. Review any studies reporting evaluations of the predictor's performance to determine their relevance for the setting in which the predictor is being proposed for clinical use.
	18. Evaluate whether clinical validations of the predictor were analytically and statistically rigorous and unequivocally blinded.
	19. Search public sources, including literature and citation databases, journal correspondence, and retraction notices, to determine whether any questions have been raised about the data or methods used to develop the predictor or assess its performance, and ensure that all questions have been adequately addressed.
Clinical trial design	20. Provide a clear statement of the target patient population and intended clinical use of the predictor and ensure that the expected clinical benefit is sufficiently large to support its clinical utility.
	21. Determine whether the clinical utility of the omics test can be evaluated by using stored specimens from a completed clinical trial (that is, a prospective–retrospective study).
	22. If a new prospective clinical trial will be required, evaluate which aspects of the proposed predictor have undergone sufficiently rigorous validation to allow treatment decisions to be influenced by predictor results; where treatment assignments are randomized, provide justification for equipoise.
	23. Develop a clinical trial protocol that contains clearly stated objectives and methods and an analysis plan that includes justification of sample size; lock down and fully document all aspects of the omics test and establish analytical validation of the predictor.
	24. Establish a secure clinical database so that links among clinical data, omics data, and predictor results remain appropriately blinded, under the control of the study statistician.
	25. Include in the protocol the names of the primary individuals who are responsible for each aspect of the study.
Ethical, legal and regulatory issues	26. Establish communication with the individuals, offices, and agencies that will oversee the ethical, legal, and regulatory issues that are relevant to the conduct of the trial.
	27. Ensure that the informed consent documents to be signed by study participants accurately describe the risks and potential benefits associated with use of the omics test and include provisions for banking of specimens, particularly to allow for 'bridging studies' to validate new or improved assays.
	28. Address any intellectual property issues regarding the use of the specimens, biomarkers, assays, and computer software used for calculation of the predictor.
	29. Ensure that the omics test is performed in a Clinical Laboratory Improvement Amendments-certified laboratory if the results will be used to determine treatment or will be reported to the patient or the patient's physician at any time, even after the trial has ended or the patient is no longer participating in the study.
	30. Ensure that appropriate regulatory approvals have been obtained for investigational use of the omics test. If a prospective trial is planned in which the test will guide treatment, consider a pre-submission consultation with the US Food and Drug Administration.

PERSPECTIVE

OPEN

doi:10.1038/nature12564

Criteria for the use of omics-based predictors in clinical trials

Lisa M. McShane[1], Margaret M. Cavenagh[1], Tracy G. Lively[1], David A. Eberhard[2], William L. Bigbee[3], P. Mickey Williams[4], Jill P. Mesirov[5], Mei-Yin C. Polley[1], Kelly Y. Kim[1], James V. Tricoli[1], Jeremy M. G. Taylor[6], Deborah J. Shuman[1], Richard M. Simon[1], James H. Doroshow[1] & Barbara A. Conley[1]

Examples of the Criteria for the Use of Omics-Based Predictors in NCI Supported Trials

- Specimen issues
  - Determine the feasibility of obtaining specimens that will yield the quantity and quality of isolated cells or analytes needed for successful assay performance in clinical settings
- Assay issues
  - Validate assay performance by using established analytical metrics such as accuracy, precision, coefficient of variation, sensitivity, specificity, linear range, limit of detection, and limit of quantification, as applicable

McShane LM, Cavenagh MM, Lively TG, Eberhard DA, Bigbee WL, Williams PM, Mesirov JP, Polley M-YC, Kim KY, Tricoli JV, Taylor JMG, Shuman DJ, Simon RM, Doroshow JH, and Conley BA. 2013. Criteria for the use of omics-based predictors in clinical trials. 502:317-320.

Examples of the Criteria for the Use of Omics-Based Predictors in NCI Supported Trials

- Model development, specification, and preliminary performance evaluation
  - Evaluate data used in developing and validating the predictor model to check for accuracy, completeness, and outliers. Perform retrospective verification of the data quality if necessary
- Clinical trial design
  - Provide a clear statement of the target population and intended clinical use of the predictor and ensure that the expected clinical benefit is sufficiently large to support its clinical utility
- Ethical, legal and regulatory issues
  - Establish communication with the individuals, offices, and agencies that will oversee the ethical, legal, and regulatory issues that are relevant to the conduct of the trial

McShane LM, Cavenagh MM, Lively TG, Eberhard DA, Bigbee WL, Williams PM, Mesirov JP, Polley M-YC, Kim KY, Tricoli JV, Taylor JMG, Shuman DJ, Simon RM, Doroshow JH, and Conley BA. 2013. Criteria for the use of omics-based predictors in clinical trials. 502:317-320.

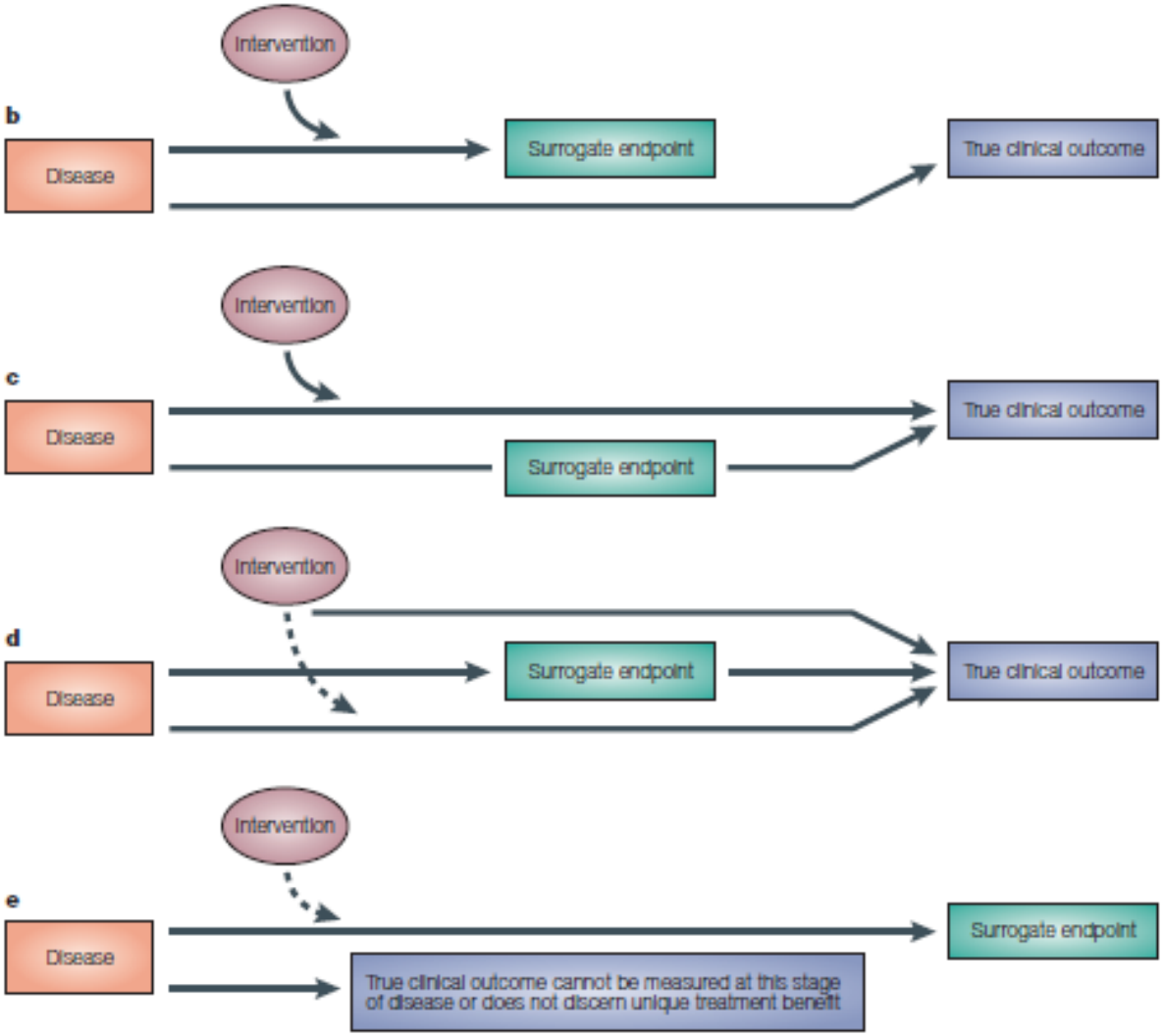
Support for Use of Surrogate Biomarkers

Table 1. Support for Surrogates

Factor	Favors Surrogate	Does Not Favor Surrogate
Biological plausibility	Epidemiologic evidence extensive and consistent	Inconsistent epidemiology
	Quantitative epidemiologic relationship	No quantitative epidemiologic relationship
	Credible animal model shows drug response	No animal model
	Well-understood disease pathogenesis	Pathogenesis not clear
	Drug mechanism of action well understood	Novel actions not previously studied
	Surrogate relatively late on biological path	Surrogate remote from clinical outcome
Success in clinical trials	Effect on surrogate has predicted outcome with other drugs of same pharmacologic class (supports surrogate in class)	A negative outcome without clear explanation
	Effect on surrogate has predicted outcome in several classes (supports more general use)	Inconsistent results across classes
Risk-benefit, public health considerations	Serious or life-threatening illness and no alternative therapy	Nonserious disease and alternative therapy with different pharmacologic action known to affect outcome
	Large safety database	Little safety data
	Short-term use	Long-term use
	Difficulty of studying clinical end point (rare, delayed)	Easy to study clinical end point (short-term study)
		Long-delayed, small effect in healthy people

Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA 282:790-795, 1999.

Surrogate Endpoint Challenges



Frank R and Hargreaves R. 2003. Clinical biomarkers in drug discovery and development. *Nature Reviews Drug Discovery*. 2:566-580.

Clinical Outcome Assessments

- Clinical outcome assessments (COAs) measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. COAs can be used to determine whether or not a drug has been demonstrated to provide treatment benefit. Treatment benefit can also be defined in terms of a safety benefit compared to other treatments. A conclusion of treatment benefit is described in labeling in terms of the concept of interest, the *thing* measured by the COA
- Four types of COAs
  - Patient reported outcome (PRO) measures
  - Clinician reported outcome (ClinRO) measures
  - Observer reported outcome (ObsRO) measures
  - Performance outcome (PerfO) measures

Drug Development Tools Qualification

DDT Qualification

Clinical Outcome Assessments

Biomarkers

Animal Models (Animal Rule)

Drug Development Tools Qualification

- Concept: Qualification is a conclusion that within the stated context of use, the results of biomarker measurements can be relied upon to have a stated interpretation and utility
  - Context of use to be clearly specified

- Regulatory implication: Can rely upon using the biomarker in the qualified manner in the IND period, and in NDA and BLA submissions, without needing to resubmit extensive data and request that the relevant CDER review group consider and reconfirm the biomarker

- Importance of predictive and prognostic biomarkers, not just biomarkers as surrogate endpoints

Biomarkers in Drug Development

***Objective**: Use the biomarker in a single drug development program*

Acceptance through IND, NDA and BLA submissions (Drug approval process)

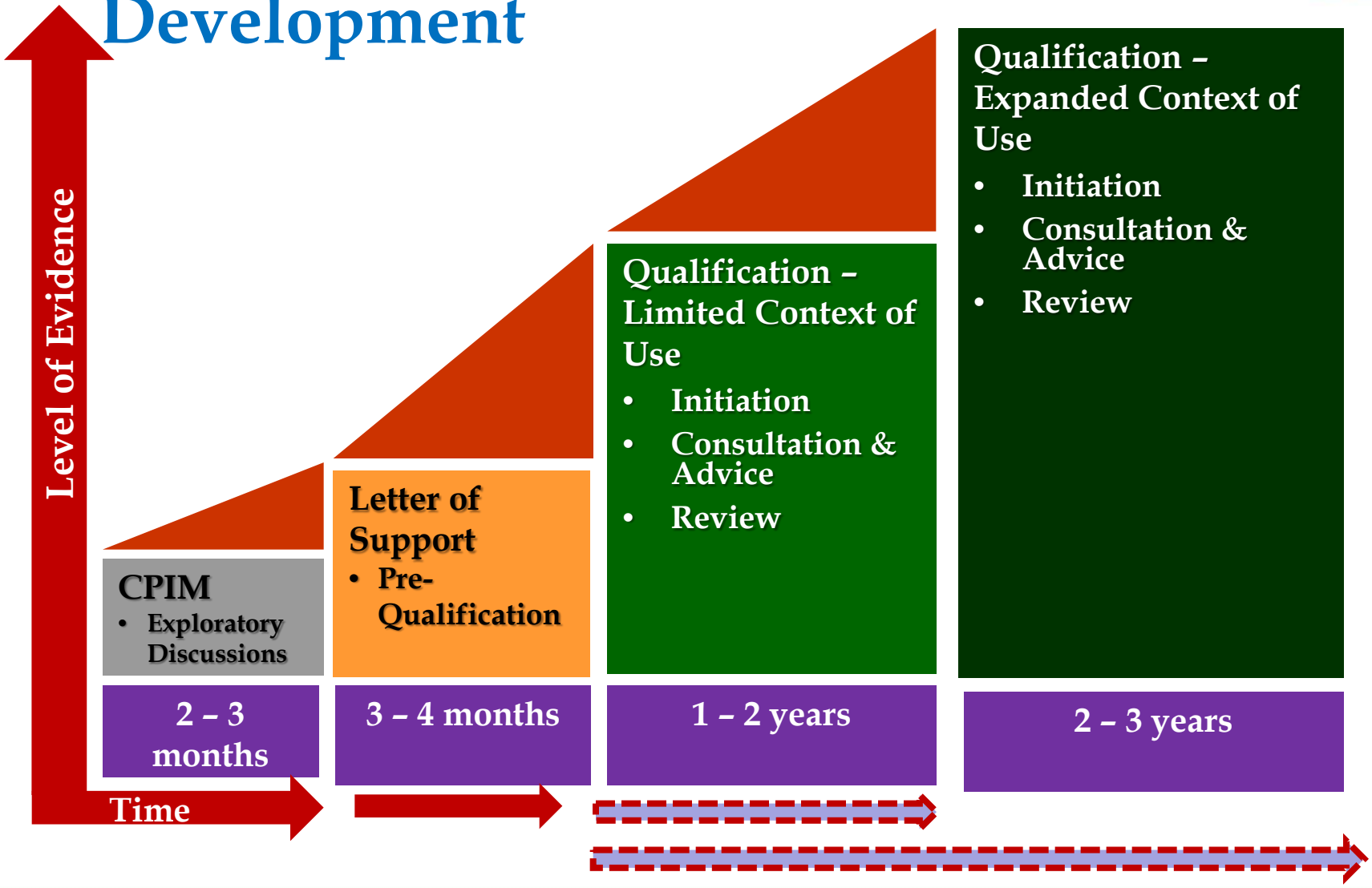
- **Responsible Parties**: One sponsor contacts the review division
- **Process:** Discuss, provide rationale and data to the review division
- **Risk and resource:** burden on one sponsor
- **Biomarker Information**: Embedded in drug labels

***Objective**: Establish the biomarker for use in multiple development programs*

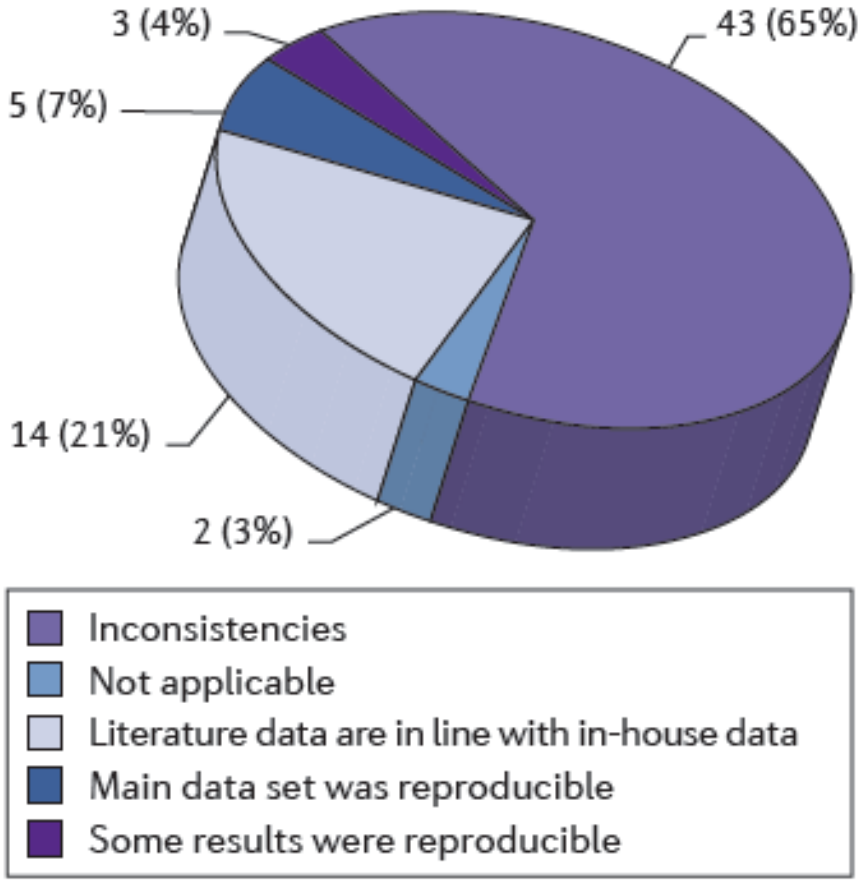
Biomarker Qualification

- **Responsible Parties**: Generally, consortia contact the BQ Program
- **Process:** Submit letter of intent. Follow the BQ process
- **Risk and resources:** shared among consortia members
- **Biomarker Information**: qualified biomarkers announced as draft guidance

Opportunities for Biomarker Development



Reproducibility of Published Data



Relationship of published data to in-house data (Bayer HealthCare) for drug targets

Prinz F, Schlange T, and Asadullah K. 2011. Believe it or not: how much can we rely on published data on potential drug targets? Nature Reviews Drug Discovery. 10:712-713.

Regulatory Science

Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

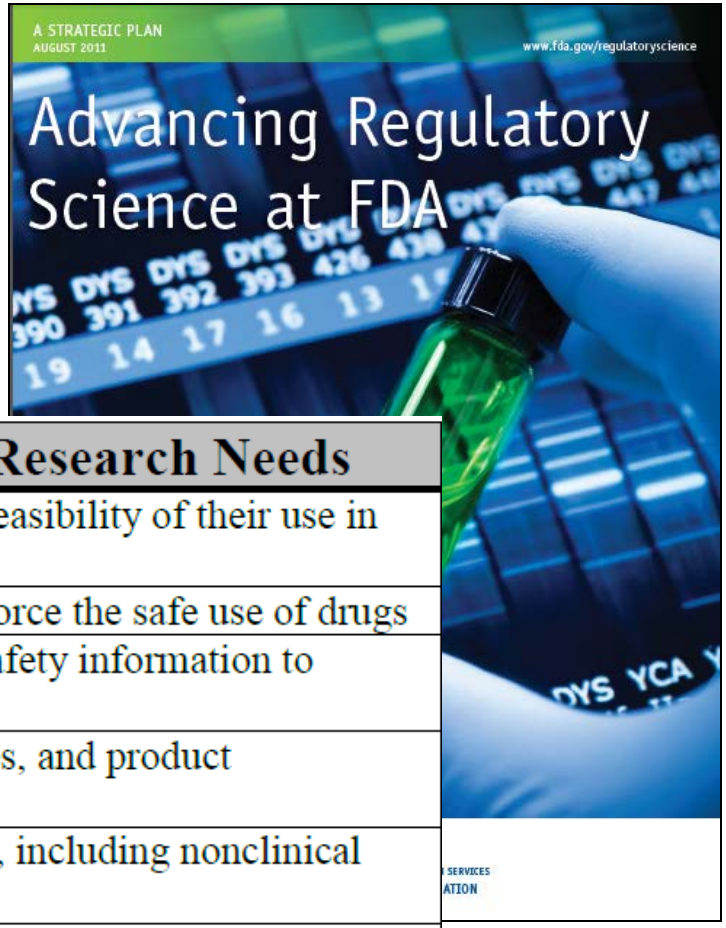


Table 1: Seven CDER Drug Safety-Related Research Needs
1. Improve access to postmarket data sources and explore the feasibility of their use in safety signal analyses
2. Improve risk assessment and management strategies to reinforce the safe use of drugs
3. Evaluate the effectiveness of risk communications of drug safety information to health care providers and the public
4. Improve product quality and design, manufacturing processes, and product performance relating to safety
5. Develop and improve predictive models of safety in humans, including nonclinical biomarkers
6. Improve clinical trial statistical analyses for safety, including benefit-risk assessment
7. Investigate clinical biomarkers of safety, including standards for qualification

http://www.fda.gov/downloads/Drugs/ScienceResearch/UCM438138.pdf

Neonatal Issues

Right Drug

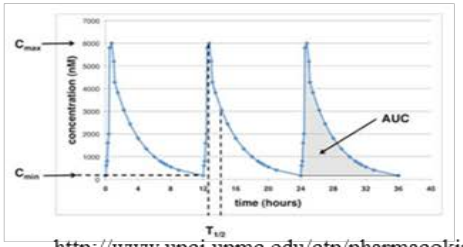




Right Population

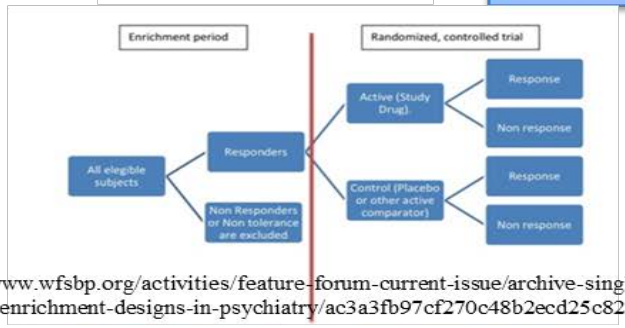


Right Dose

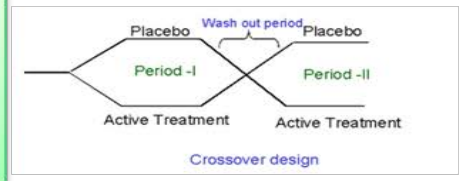



http://www.upci.upmc.edu/ctp/pharmacokinetics.cfm

Right Trial Design



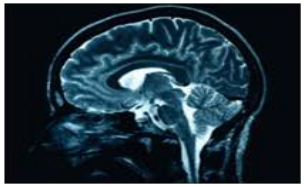
http://www.wfsbp.org/activities/feature-forum-current-issue/archive-single/should-we-accept-enrichment-designs-in-psychiatry/ac3a3fb97cf270c48b2ecd25c825ee9b.html



http://accp1.org/pharmacometrics/theory.htm

Right Endpoints

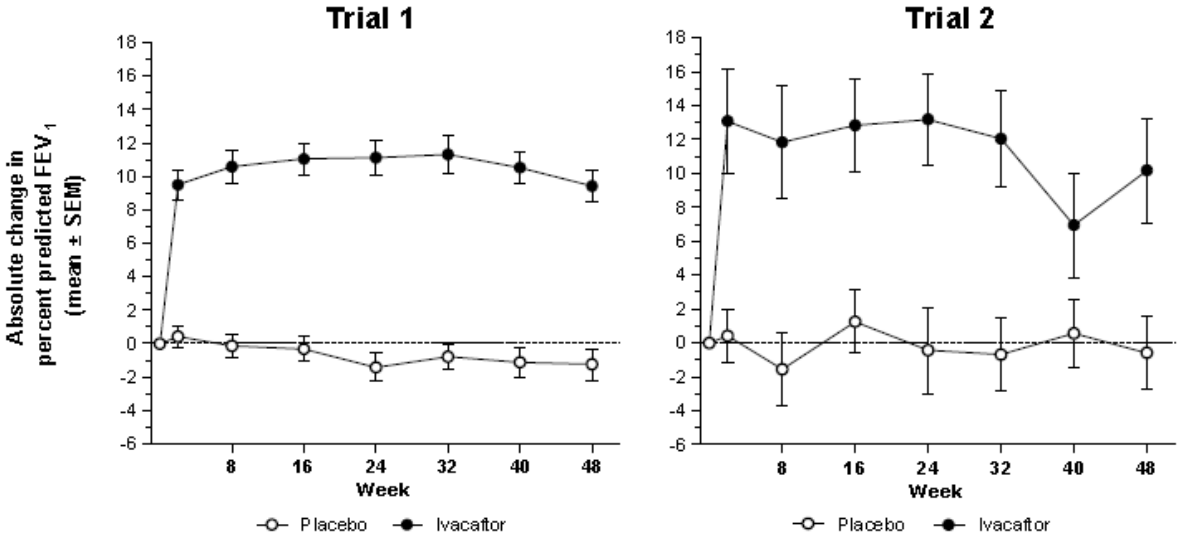


Ivacaftor

- Two randomized double-blind placebo controlled clinical trials (n=213) in cystic fibrosis (CF) patients with *G551D* mutation in the *CFTR* gene
- Third most common CF mutation (worldwide ~3%)
- Primary efficacy endpoint – improvement in lung function as determined by the mean absolute change from baseline in percent predicted pre-dose FEV_1 through 24 weeks of treatment
- No direct correlation between decrease in sweat chloride levels and improvement in FEV_1

Figure 3: Mean Absolute Change from Baseline in Percent Predicted FEV_1 *



*Primary endpoint was assessed at the 24-week time point.

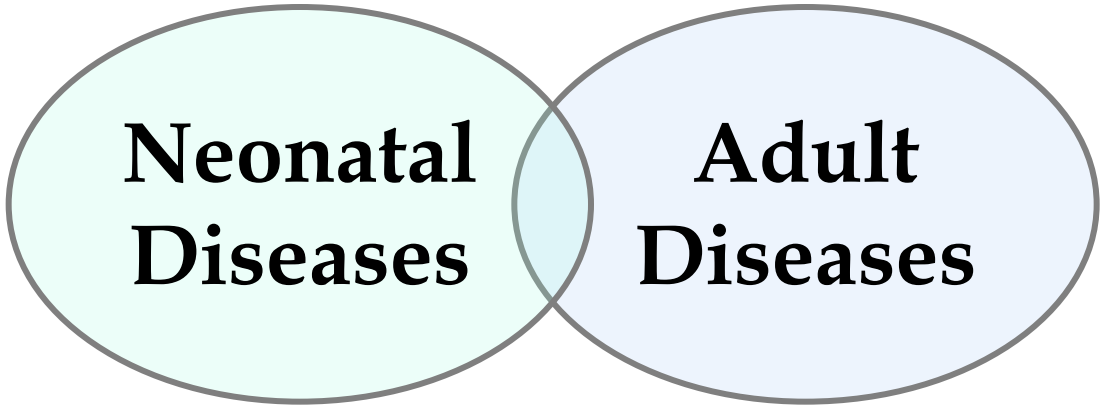
Innovative Trials in Rare Diseases

- Carglumic acid for N-acetylglutamate synthase (NAGS) deficiency
  - Rare urea cycle disorder (~ 10 patients in U.S.)
  - Retrospective review of a 23 patient case series in Europe
  - Short-term (ammonia) and long-term (neurocognitive) outcomes
  - Compared to historical control (not formally conducted)
- Deferiprone for transfusional iron overload in patients with thalassemia syndromes not responding to other therapies
  - Planned pooled analysis of patients from several studies (n=236)
  - Endpoint was change in serum ferritin, not a clinical outcome
- Cysteamine bitartrate for nephropathic cystinosis
  - 2 open-label studies (n=94) children treated with product or innovator cysteamine HCl
  - Largely a pharmacodynamic comparison based on WBC cystine levels vs. historical control pharmacokinetic/pharmacodynamic levels

Drug Development Disconnect

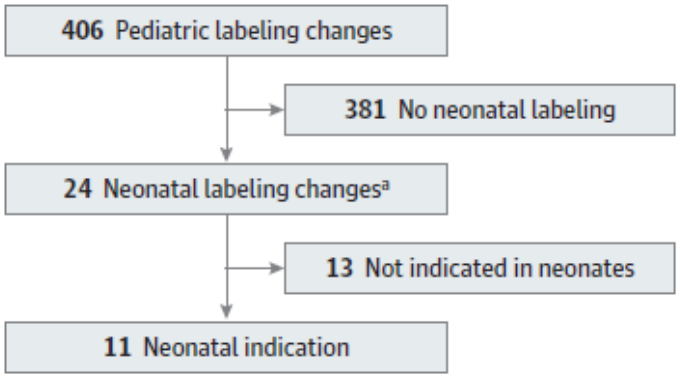
Majority of drugs used are off-label

Very few new therapies are being developed specifically for neonates



Pediatric Plans to include neonates

Figure. Neonatal Labeling Changes Under Legislation From 1997 to 2010 and Exposure of Neonates to Drugs With a Neonatal Indication



[a]There are 24 neonatal labeling changes involving 23 drugs. Linezolid has 2 labeling changes.

28 drugs studied in neonates

- 46% not used in NICUs
- 29% used in fewer than 60 neonates

Laughon MM, Avant D, Tripathi N et al. 2014. Drug labeling and exposure in neoates. *JAMA Pediatr.*168:130-136.

Neonatal Issues

Patients → Conditions → Treatments → Endpoints

- Neonatal populations
  - Extreme prematurity
  - SGA
- Biomarkers
- Confounding conditions
- Risk of unique adverse events (IVH, NEC, PPHN)
- Ethics
- Role of parents/staff

- Unique conditions
  - PPHN
  - HIE
  - IVH
  - RDS
  - CLD
  - NEC
- Diseases not able to be extrapolated from adult disease

- Absorption
- Distribution
- Metabolism
- Excretion
- Equipoise
- Formulations

- Efficacy endpoints
  - Definition of normal
  - Differ from adult definitions
  - Short term and long term
  - Discharge criteria
  - Neurodevelopmental outcomes
- Safety endpoints
  - Short term and long term

Data Standards

Jane Smith
111 North South Street
Berlin, MD 21111

John James
222 East West Street
London, Georgia 11111

Jane Smith

London, Berlin, Georgia, MD

James John

11111
21111

South North Street 111

222 West East Street

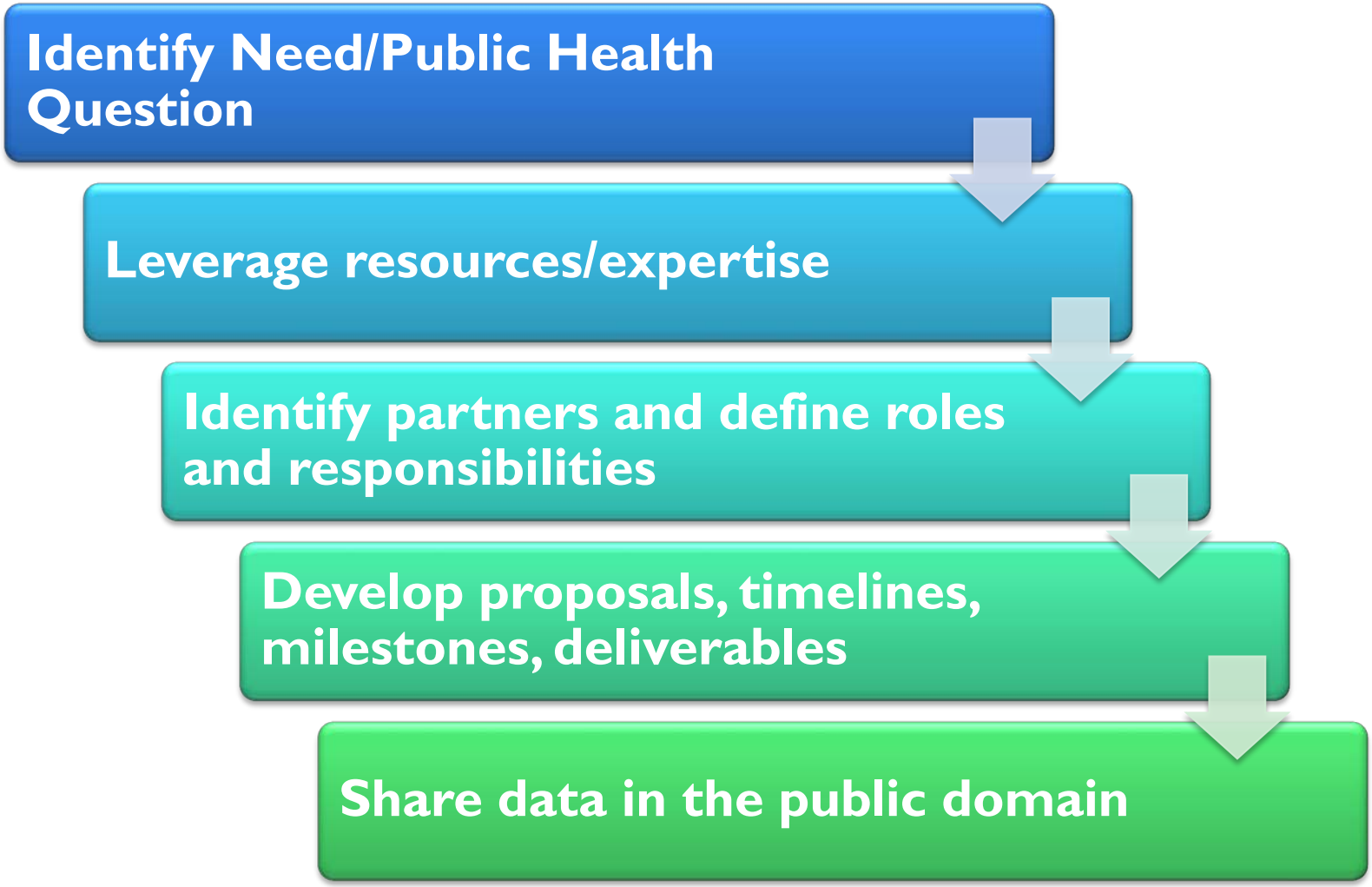
Massive amounts of clinical research data in extremely disparate formats

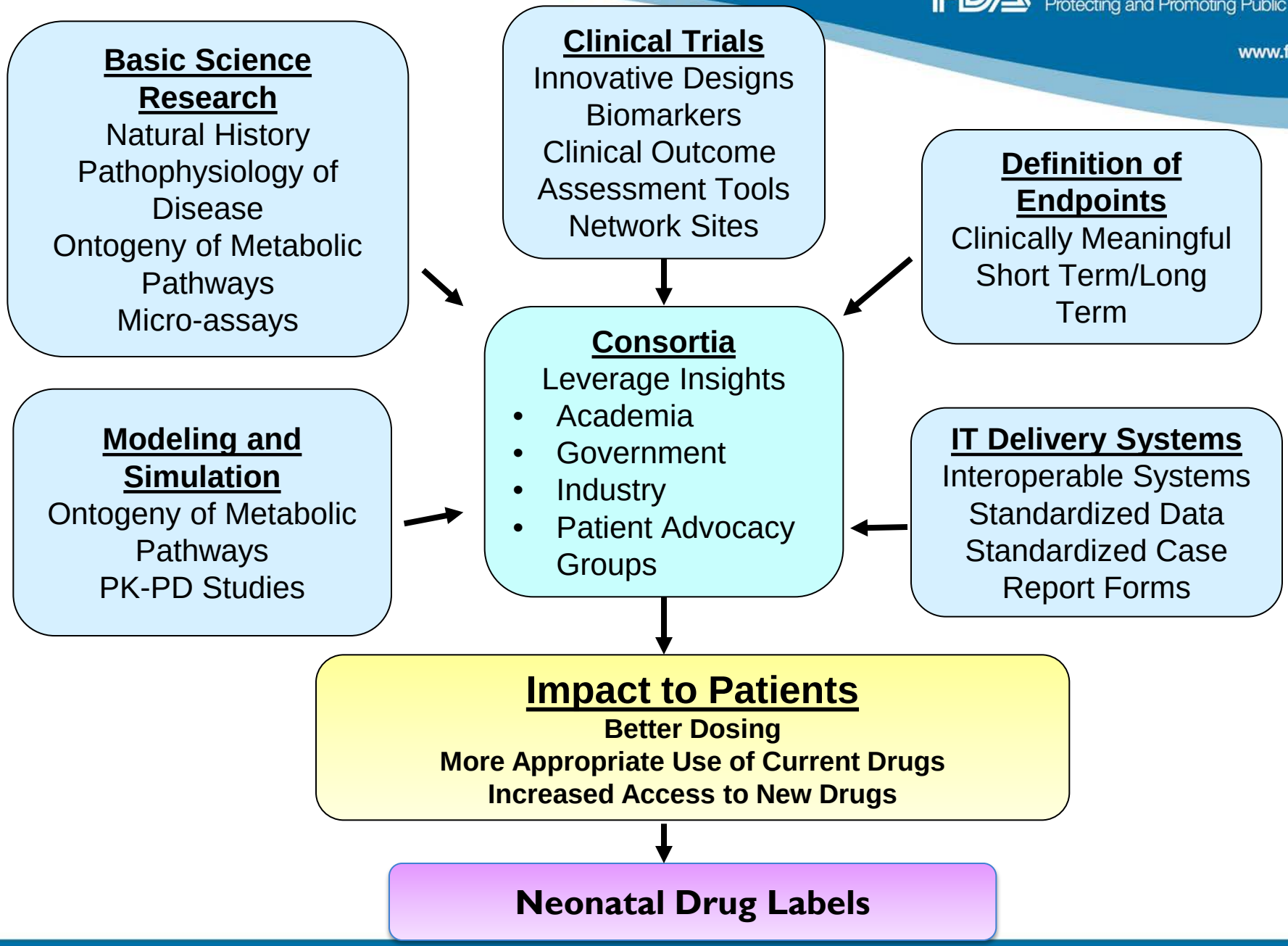
Study Number	Male/Female
1112	Male
1113	Female
1114	Female
1115	Male

S. Number	Male/Female
1112	M
1113	F
1114	F
1115	M

Study	Sex
s1112	1
s1113	2
s1114	2
s1115	1

Development of Consortia




Basic Science Research
Natural History
Pathophysiology of Disease
Ontogeny of Metabolic Pathways
Micro-assays
Clinical Trials
Innovative Designs
Biomarkers
Clinical Outcome Assessment Tools
Network Sites
Definition of Endpoints
Clinically Meaningful
Short Term/Long Term
Modeling and Simulation
Ontogeny of Metabolic Pathways
PK-PD Studies
Consortia
Leverage Insights
• Academia
• Government
• Industry
• Patient Advocacy Groups
IT Delivery Systems
Interoperable Systems
Standardized Data
Standardized Case Report Forms
Impact to Patients
Better Dosing
More Appropriate Use of Current Drugs
Increased Access to New Drugs
Neonatal Drug Labels

How Can the INC Be Impactful?

- Can we articulate clinical pharmacology needs for the neonate?
- For key therapeutic areas
  - Is there a need for animal models?
  - What are the basic science needs to support modeling and simulation?
  - What populations should be studied?
  - What would be clinically meaningful biomarkers for this population?
  - Is it possible to develop registries or databases for this population? What are the data standards and how will this data be curated?
- Are there others who can partner with INC?

Neonatal Clinical Pharmacology White Paper Considerations

- General
- Impact of developmental changes on variability in drug disposition and effects in newborns
- Use of clinical pharmacology data in neonatal drug development
- Timing of initiating clinical trials
- Methodological aspects of neonatal clinical pharmacology study design: What is relevant?
- Data analysis
- Formulations
- Glossary of terms