Implementing GeNomics In pracTicE II (IGNITE II): Pragmatic Clinical Trials in Genomic Medicine

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NHGRI Networks on Use of Genomic Information in Clinical Care

emerge network
ELECTRONIC MEDICAL RECORDS AND GENOMICS

NSIGHT
Newborn Sequencing

IGNITE Implementing GeNomics In pracTicE

cser
Clinical Sequencing Exploratory Research

Undiagnosed Diseases Network

ClinGen
Clinical Genome Resource

Gm10
Genomic Medicine Meetings

- EHR-driven phenotyping and follow-up
- Return of genomic results
- Newborn and clinical genome sequencing
- Variant curation
- Diverse clinical settings and populations
- Pharmacogenomics
- Complex disease risk assessment

Need for Evidence in Genomic Medicine

"The gold standard of clinical utility is the evaluation of results from prospective trials that have randomized subjects to genetic testing or no genetic testing in an effort to compare different genetically informed treatments with usual care…."

-- NAM, Evidence Framework for Genetic Testing, 2017

"Our enthusiasm for advancing molecular technology and defining the human genome has not yet been matched by a willingness to incorporate this technology and knowledge into well-controlled and monitored clinical trials…."

-- Evans and Relling, *Nature* , 2004

Sources of Evidence on Clinical Utility

Confidence

- Well-designed and independently replicated RCTs
- Single well-designed RCT
- Controlled trial(s) without randomization
- Observational studies
- Case-control studies
- Case series

Adapted from Committee on the Evidence Base for Testing, *An Evidence Framework for Genetic Testing*, National Academies Press

Need for Randomized Clinical Trials

- Impact on patient outcomes widely viewed as most solid form of evidence supporting clinical adoption
- Minimize or eliminate critical biases
  - Selection bias
  - Adherence bias
- May at times contradict observational evidence
  - Hormone replacement therapy

But RCTs are expensive, lengthy, cannot be conducted for every intervention or every gene

Pragmatic Clinical Trials (PCTs)

THE NEW ENGLAND JOURNAL of MEDICINE

conditions– "efficacy"

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

PRAGMATISM IN CLINICAL TRIALS AROSE FROM CONCERNS THAT MANY trials did not adequately inform practice because they were optimized to determine efficacy.[1] Because such trials were performed with relatively small

practice settings outside tertiary care

Patsopoulos, N. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci. 2011 Jun; 13(2): 217–224; Ford, I. and Norrie, J. Pragmatic trials. N Engl J Med 2016; 375:454-463

Standard versus Pragmatic Clinical Trials

Standard Clinical Trials	Pragmatic Clinical Trials
High internal validity	High external validity
Smaller sample size	Large sample size
Sophisticated design	Simpler design
Controlled environment	Diverse settings
Rigid protocols	Local customization
Strict eligibility criteria	Greater generalizability
High-cost	Usually lower-cost

Patsopoulos, N. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci. 2011 Jun; 13(2): 217–224; Ford, I. and Norrie, J. Pragmatic trials. N Engl J Med 2016; 375:454-463

All About Pragmatism

Back in 2012…

- Major questions about feasibility of genomic medicine implementation outside highly specialized centers
- Initiated to assess and disseminate methods for effective implementation in diverse care settings
- Series of networked groups with lead site and "partner" sites in diverse populations and settings
- Translated well to Harlem, the Bronx, rural Iowa

IGNITE II Goals: Conducting Pragmatic Clinical Trials in Genomic Medicine

- Measure clinical utility and cost-effectiveness of genomic medicine interventions through large, network-wide pragmatic clinical trials (PCTs)
- Assess approaches for real-world application of genomic medicine in diverse clinical settings outside of specialized centers
- Produce generalizable knowledge on types of genomic medicine interventions requiring clinical trials and effective methods for conducting these trials

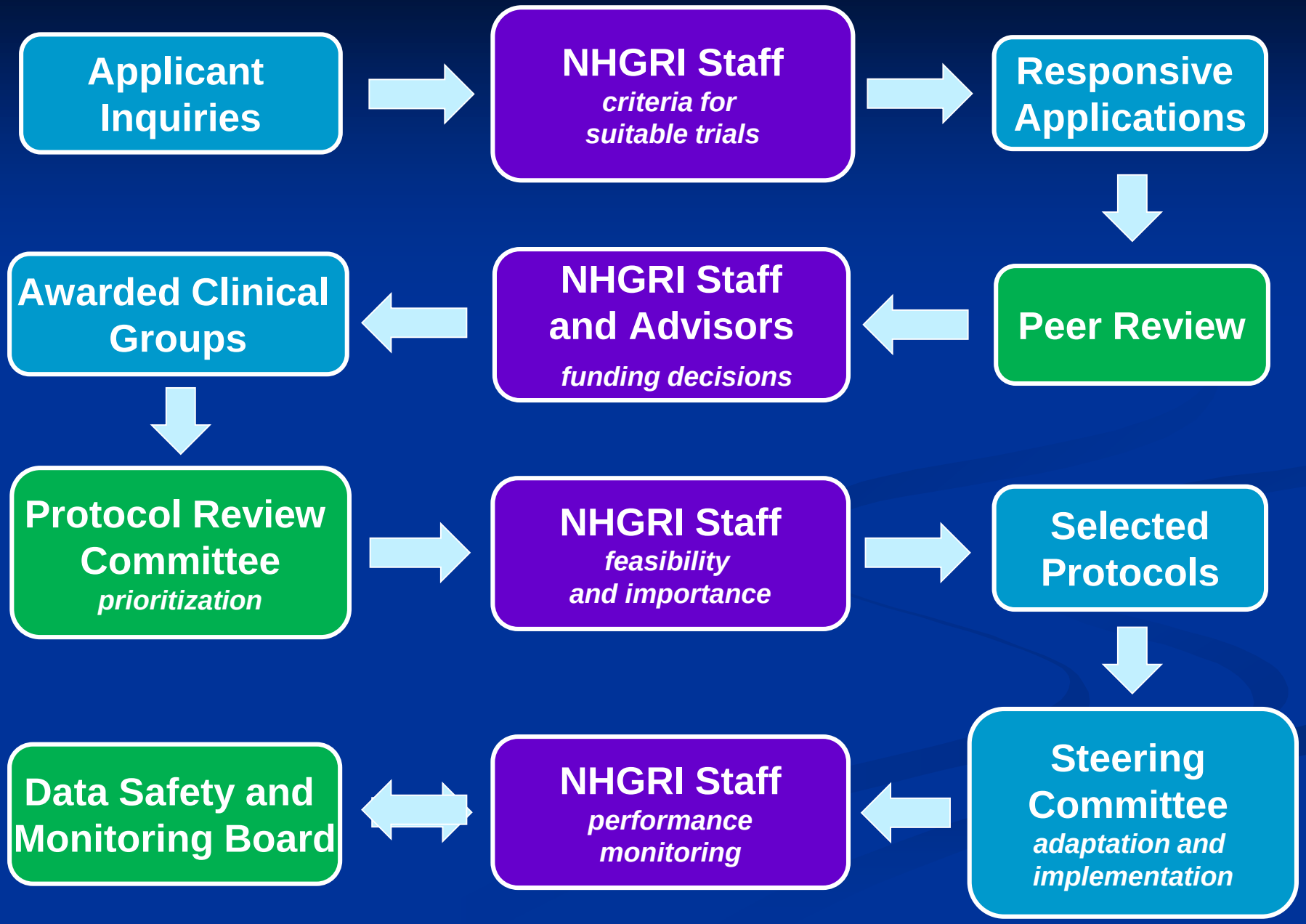
IGNITE II Design

- Support 4-6 multi-site Clinical Groups (CGs) involving diverse settings and populations
- Conduct 2-4 pragmatic clinical trials of "established" genomic medicine interventions
- Each CG application will propose one trial to test an intervention that:
  - Has evidence of feasibility in prior studies
  - Addresses clinically important outcomes achievable within 1 year of randomization
  - Is adaptable to a wide range of clinical settings
- One embedded ELSI study of impact of genomic medicine implementation in diverse settings and populations

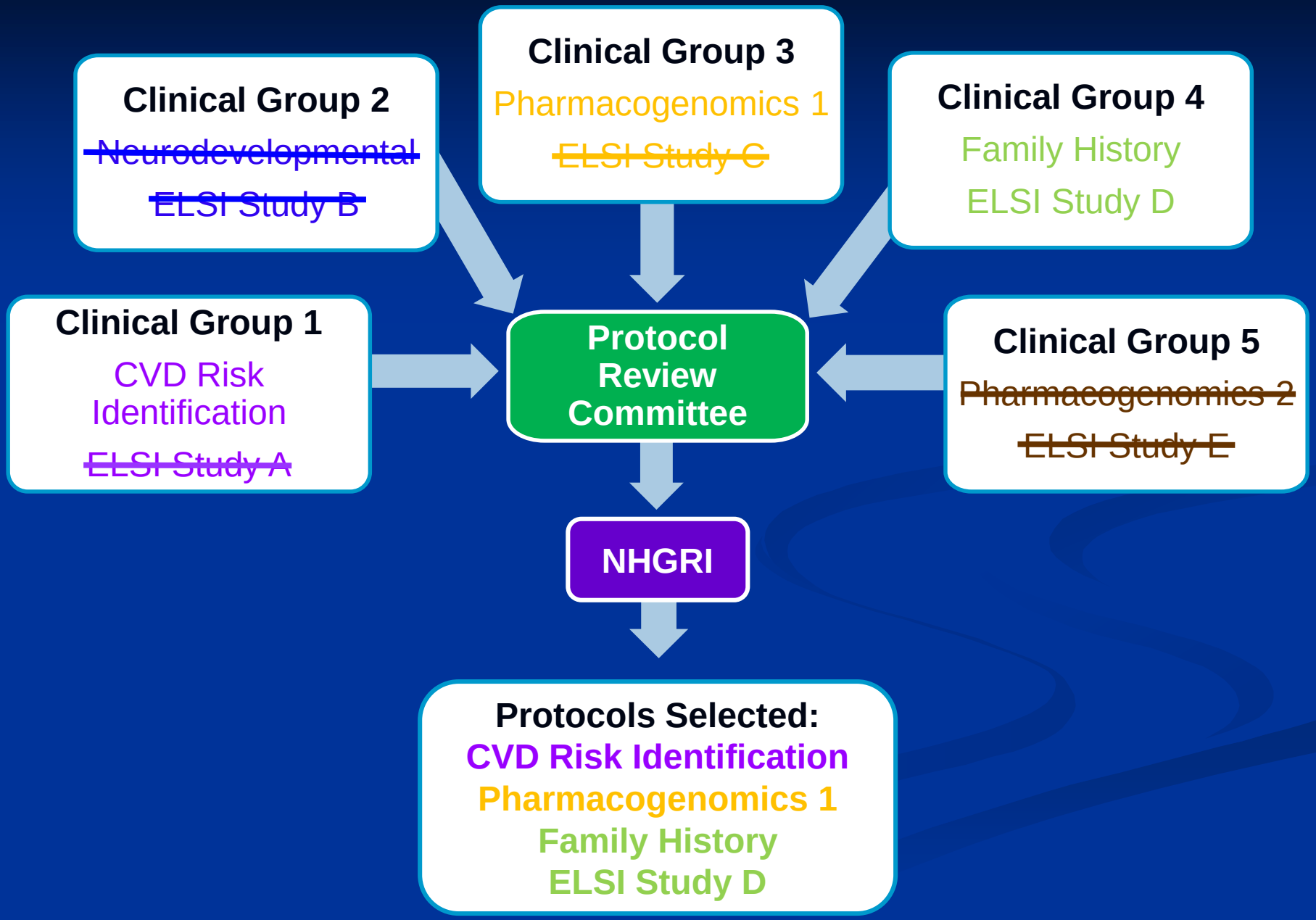
Scope and Objectives

- Expand and test interventions proven feasible and successful on smaller scale
- Include stakeholders in study design and protocol prioritization
- Ensure at least 50% of patients recruited from diverse clinical settings
- Ensure at least 35% racial and ethnic minority populations
- Release separate RFA for enhanced diversity – at least 75% racial/ethnic minority populations

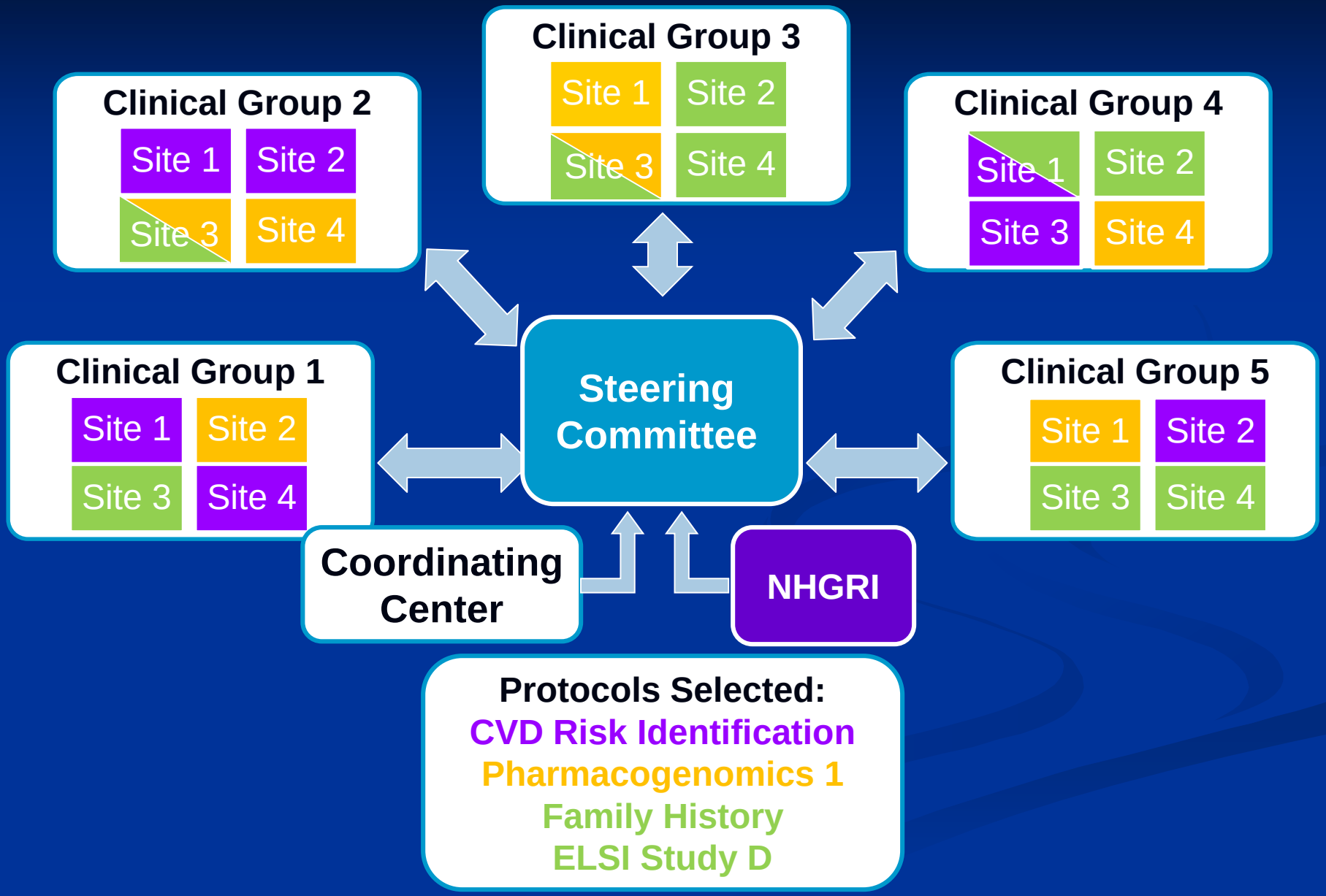
Protocol Selection and Monitoring



Protocol Prioritization



Protocol Adaptation



Proposed PCT Protocols

- Should:
  - Be adaptable to wide range of settings, including resource-limited sites
  - Propose an intervention with preliminary evidence of improved health outcomes and cost effectiveness
  - Be able to be expanded network-wide
  - Be relevant to racial/ethnic minority participants and resource-limited sites
  - Address conditions of high public health significance

Expectations of IGNITE Clinical Groups

- Demonstrated ability to implement agreed upon genomic medicine and ELSI research protocols
- Evidence of institutional support and success in participant recruitment and retention
- Genomic testing in a CLIA-certified environment
- Plan for integrating genomic results and harmonizing CDS into patients' EHRs
- Ability to recruit at least 3,000 patients per CG
- High proportion of diverse clinical settings and racial and ethnic minority populations

Possible PCT Research Topics

- Pharmacogenomics-based drug selection and dosing
- Risk reduction in genetically-defined high-risk individuals
- Early diagnosis in critically-ill newborns

Applicants strongly encouraged to discuss proposed trials with NHGRI staff before submission

Embedded ELSI Study

- One Network-wide ELSI research study of genomic medicine implementation in diverse populations and clinical settings
- Possible projects:
  - Assessment of near, mid and/or long-term outcomes of importance to patients, clinicians or communities;
  - Comparison of implementation strategies across the Network to identify potential barriers and solutions in different communities and settings

Coordinating Center

- Participate in the planning and development of the network infrastructure and committee structure
- Participate in adaptation of protocols
- Develop manual of operations and reporting forms
- Receive and disseminate recruitment and other monitoring reports
- Receive data from CG sites for data analysis
- Help in preparation and writing of reports and manuscripts for publication

Network Timeline and Design

		Yr 1				Yr 2				Yr 3				Yr 4				Yr 5			
		Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4
Stage I	**Protocol prioritization and adaptation**																				
	IRB submission and approval																				

- Protocols should have power to detect clinically meaningful differences within 2-3 year recruitment and intervention period.

Why this complex, network-wide design?

- Permits multiple investigator-initiated trials rather than single NHGRI-selected trial
- Adaptation for network-wide implementation after review ensures currency and timeliness
- Permits trials of up to 15,000 patients across broadest spectrum of clinical settings
- Utilizes mechanism proven effective, nimble, adaptable in numerous other studies

Recent NIH Pragmatic Clinical Trials

Program	Length of Program	Costs/year ($000)
Adult Respiratory Distress Syndrome Network (ARDSnet)	1994-2014	5,000
Pediatric Cardiac Genomics Consortium (PCGC)	2009-	9,000
Prevention and Early Treatment of Acute Lung Injury (PETAL)	2014-	12,000
NIH Collaboratory Demonstration Projects	2017-	4,000

Funding Model

- Base level funding $250K/yr direct costs
- CGs will agree to milestones and timelines for each protocol implemented
- Each CG will receive a multiyear supplement to carry out selected trials in addition to base level of funding
- Supplements for each selected trial will be reviewed for approval by NACHGR

Budget Estimate: Total Costs (dollars in thousands)

	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Total
CC	1,000	1,000	1,000	1,000	1,000	5,000
CGs*	2,375	6,375	6,375	6,375	5,875	27,375
Total*	3,375	7,375	7,375	7,375	6,875	32,375

*Includes $375K/yr from ELSI Research Group
Estimated ~3,000 patients/clinical group

IGNITE II Unique Aspects

- Conducting network-wide, genomic medicine implementation trials in multiple disease areas
- Providing generalizable knowledge about use of PCTs in genomic medicine– who, when, how
- Comparing trial results to non-interventional studies to identify potential biases in observational data
- Providing clinical as well as cost-effectiveness outcomes
- Assessing genomic medicine implementation across diverse settings and populations

Thank You

IGNITE Study Participants and Investigators

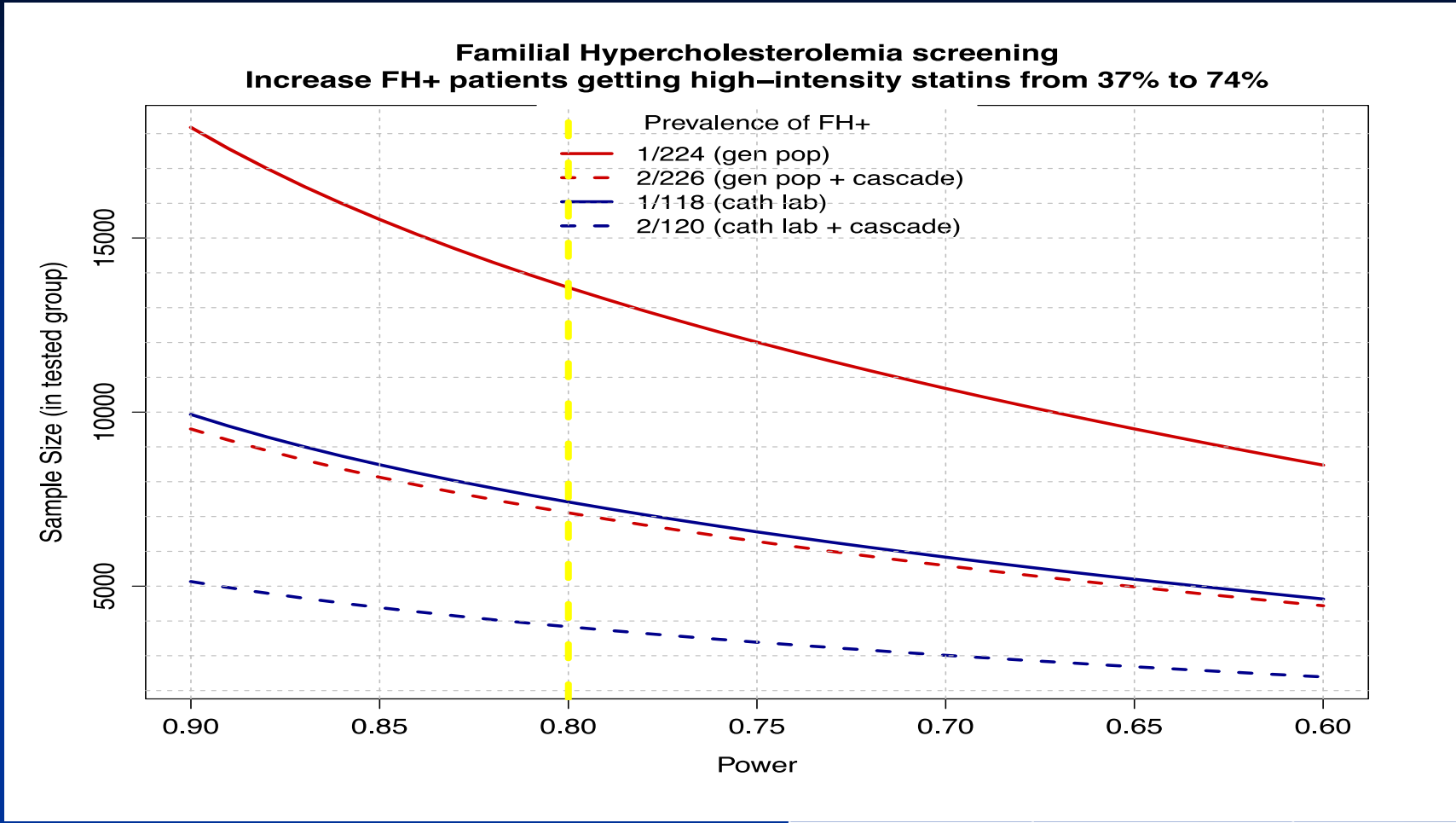
IGNITE and Beyond Meeting Participants

NHGRI Extramural Research Program

Genomic Medicine Consortia

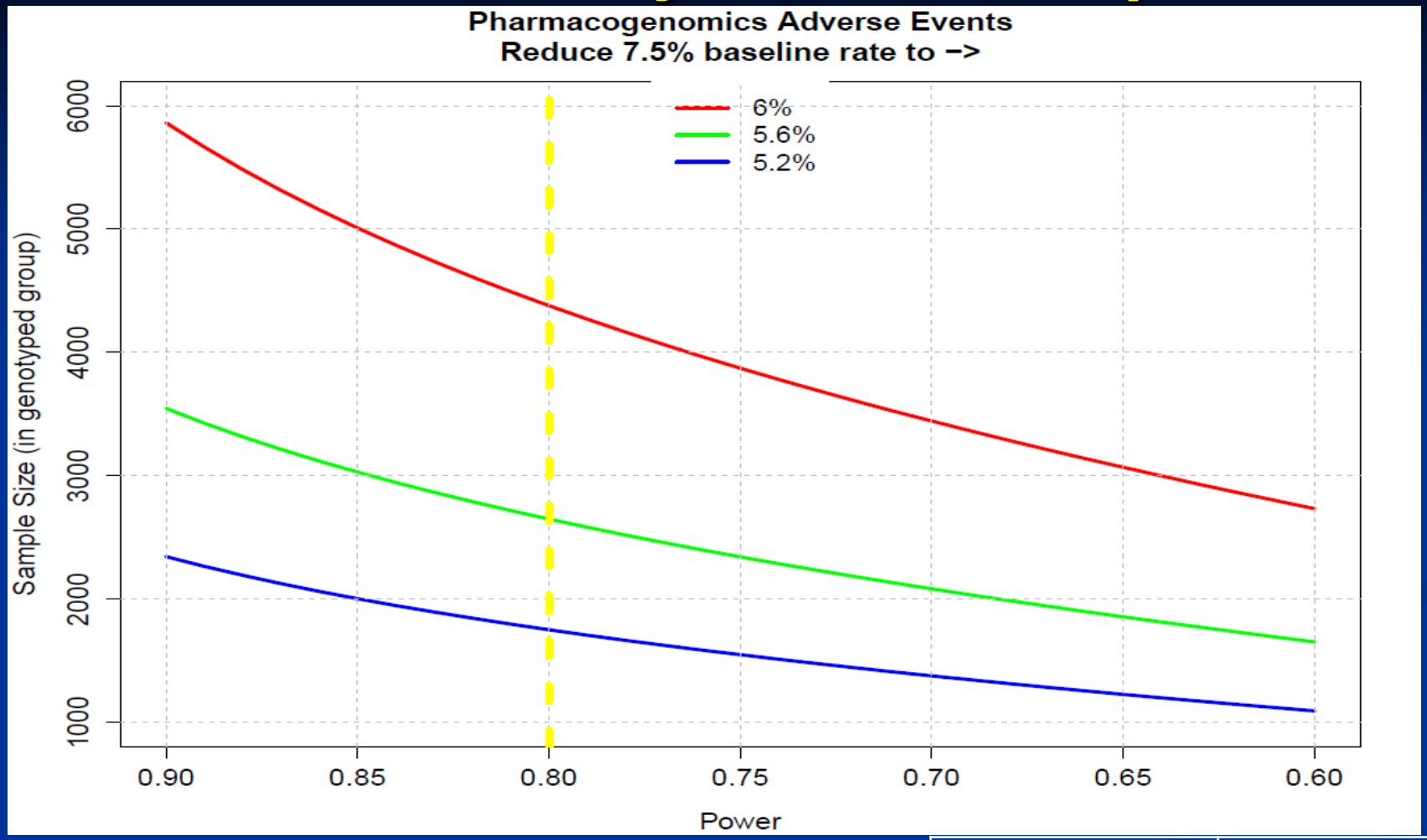
IGNITE II	Pragmatic clinical trials of multiple genomic medicine interventions
ClinGen	Variant curation and actionability
CSER2	Establishing clinical utility of clinical sequencing
eMERGE	Estimating penetrance
NSIGHT	Use of sequencing in prenatal, newborn, and pediatric care
UDN	Clinical evaluation, deep phenotyping of undiagnosed diseases

Potential Study Size – Example 1



Study Design	Sample Size	Sample Size w/ Cascade
General population	~14,000	~7,000
Cath. lab	~7,300	~3,700

Potential Study Size – Example 2



Expected AE Reduction	Sample Size
20%	~4300
25%	~2700
30%	~1800

Allele Frequency – 30%
LOF carrier adverse event rate – 25%

Stream C Budget March 2017

		FY2017	FY 2018	FY 2019	FY 2020	FY 2021	
Budget (base plus alloc adj)		48,380,696	46,814,461	49,014,461	49,014,461	49,014,461	
Continuing programs and RFAs							
eMERGE		-12,700,000	-11,300,000				
CSER		-13,000,000	-13,000,000	-13,000,000	-13,000,000		
IGNITE		-5,559,124					
ClinGen		-8,500,000	-8,500,000	-8,500,000	-8,500,000	-8,500,000	Amount may change
OMIM		-1,935,000	-1,935,000	-1,935,000	-1,935,000	-1,935,000	
NSIGHT		-2,368,496					
CPIC & PharmGKB Legacy co-fund			-400,000	-400,000			Amount may change
Misc		-611,143					
Unsolicited awards							
Existing obligations		-1,610,420	-1,221,400	-847,854	-166,235	-166,235	
Training & educ			-200,000	-400,000	-600,000	-800,000	One new K08 each year
FY 2017 iCSER PA		-2,096,513	-3,200,000	-3,200,000	-3,200,000	-1,200,000	Amounts may change
FY 2018 - FY2021 cohorts			-1,200,000	-2,400,000	-3,300,000	-4,200,000	Estimates only
Total available or deficit		0	5,858,061	18,331,607	18,313,226	32,213,226	

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Total available or deficit		0	5,858,061	18,331,607	18,313,226	32,213,226	
IGNITE-2			-6,100,000	-6,100,000	-6,100,000	-6,100,000	Renewal (Stream C only)
Subtotal			(241,939)	12,231,607	12,213,226	26,113,226	

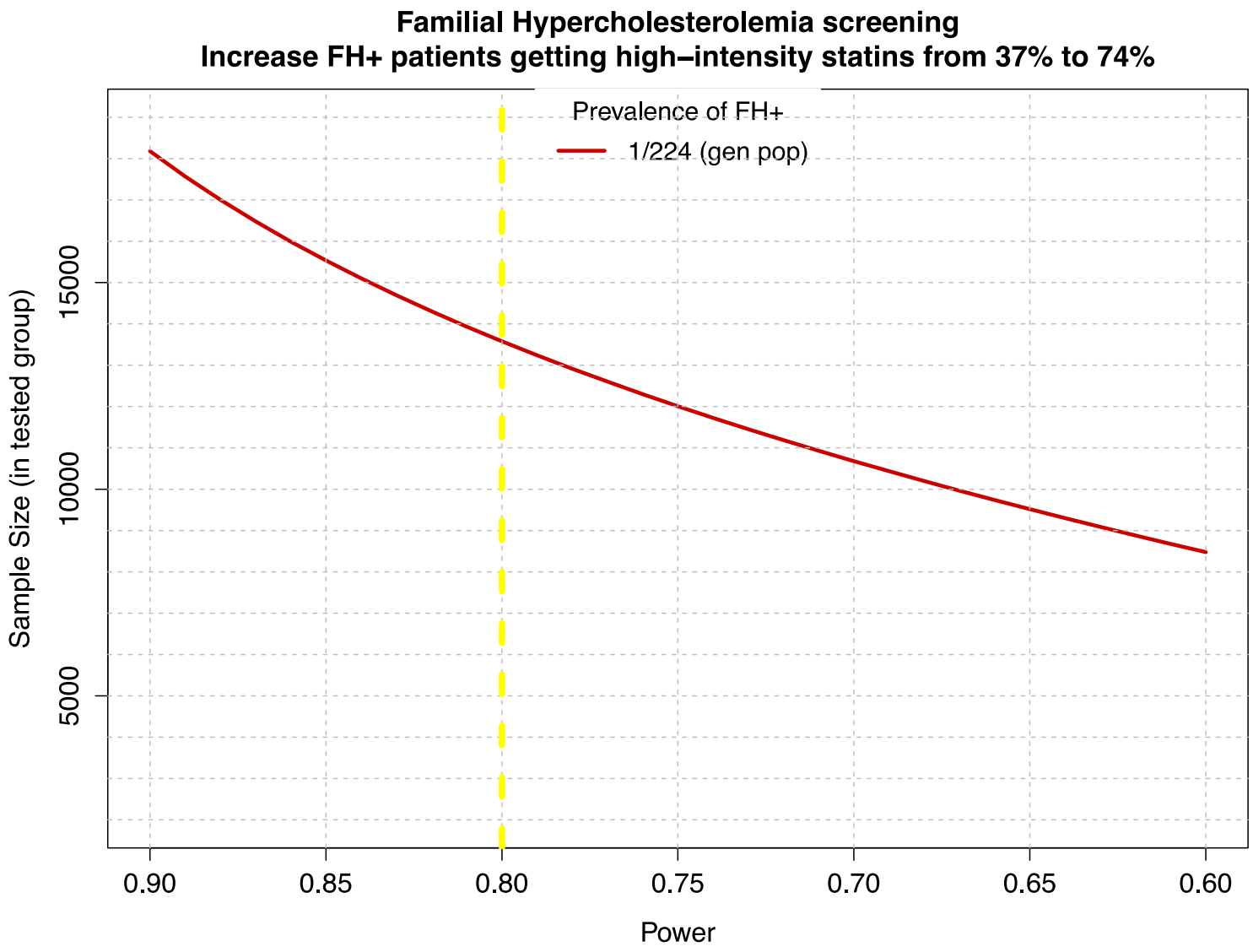
Stream C Budget March 2017

		FY2017	FY 2018	FY 2019	FY 2020	FY 2021	
Budget (base plus alloc adj)		48,380,696	46,814,461	49,014,461	49,014,461	49,014,461	
Total available or deficit		0	5,858,061	18,331,607	18,313,226	32,213,226	
IGNITE-2			-6,100,000	-6,100,000	-6,100,000	-6,100,000	mean $6.1M/year
Subtotal			(241,939)	12,231,607	12,213,226	26,113,226	
CPIC & PharmGKB				-1,000,000	-3,000,000	-3,000,000	
Smaller RFA in lieu of eMERGE-4				-10,000,000	-10,000,000	-10,000,000	
Sandbox or Variant Interpretation						-3,000,000	
NHGRI-NICHD program						-5,000,000	
Other unsolicited						-3,000,000	
Balance			(241,939)	1,231,607	(786,774)	2,113,226	

Stream C Budget March 2017

		FY2017	FY 2018	FY 2019	FY 2020	FY 2021	
Budget (base plus alloc adj)		48,380,696	46,814,461	49,014,461	49,014,461	49,014,461	
Total available or deficit		0	5,858,061	18,331,607	18,313,226	32,213,226	
IGNITE-2			-3,000,000	-7,000,000	-7,000,000	-7,000,000	mean $6.1M/year
Subtotal			2,858,061	11,331,607	11,313,226	25,213,226	
CPIC & PharmGKB				-1,000,000	-3,000,000	-3,000,000	
Smaller RFA in lieu of eMERGE-4				-10,000,000	-10,000,000	-10,000,000	
Sandbox or Variant Interpretation						-3,000,000	
NHGRI-NICHD program						-5,000,000	
Other unsolicited						-3,000,000	
Balance			2,858,061	331,607	(1,686,774)	1,213,226	

Potential Study Size – Example 1



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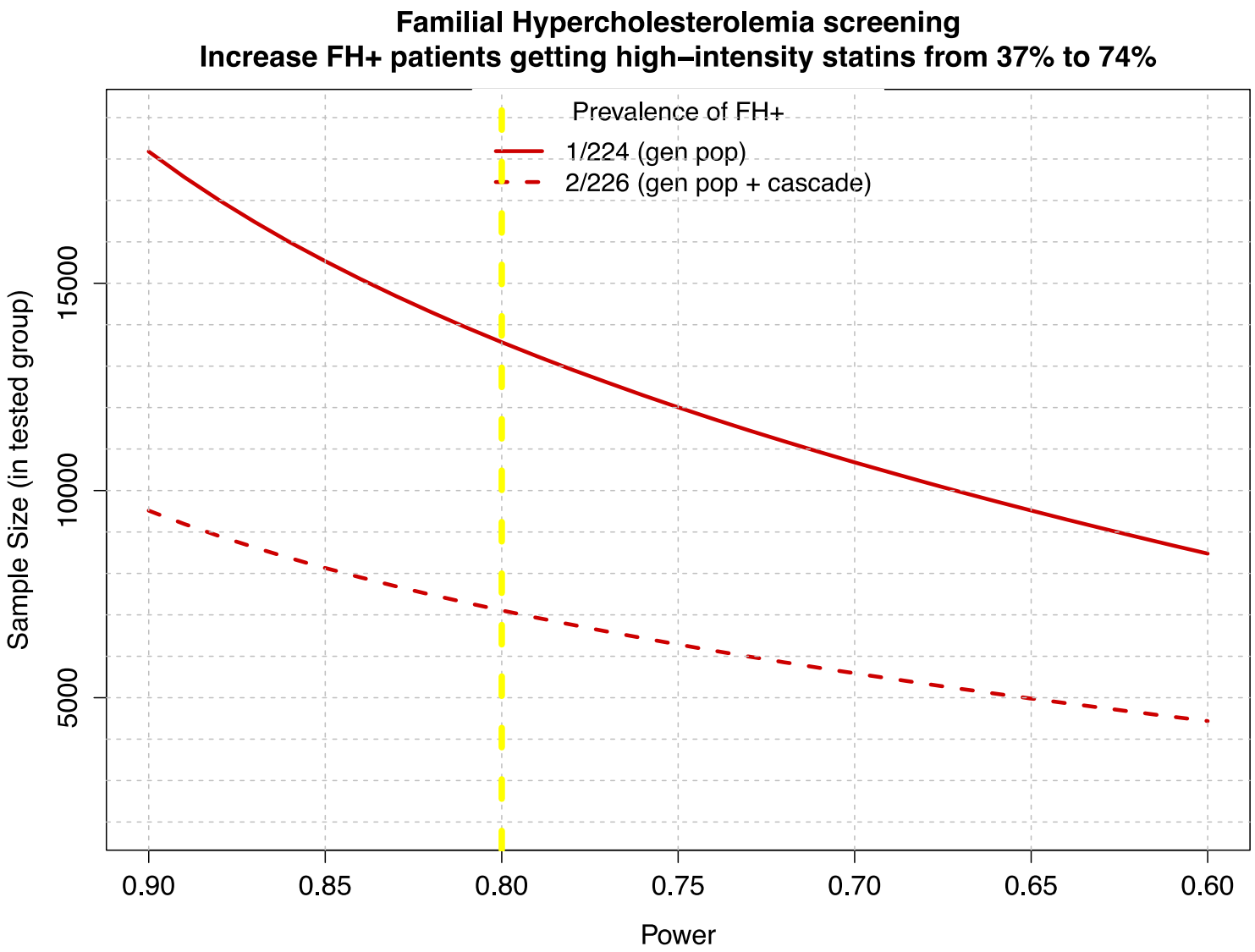
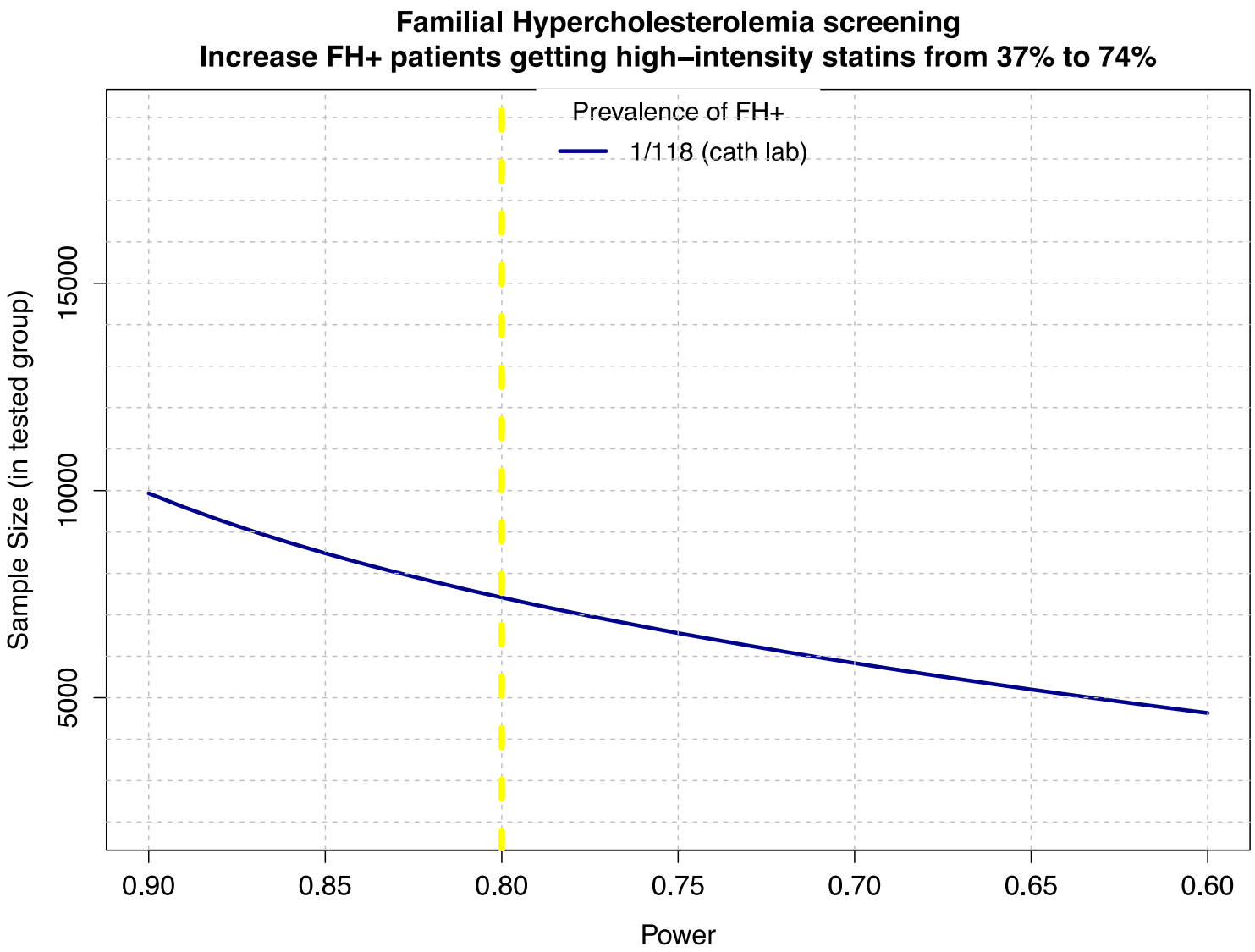


Potential Study Size – Example 1



IGNITE-SPARK (Supporting Practice through Applications, Research, and Knowledge) Toolbox

Clinicians

ALL / CLINICIANS / RESEARCHERS /

BestPractice Advisory - Epicwillow,Lemongello

PROBLEM
This patients CYP2C19 genotype is associated with very impaired metabolic activation of the prodrug clopidogrel (Plavix) and elevated risk for stent thrombosis or other cardiovascular events following PCI.

REASONS
Reduced clopidogrel activation in this genotype results in significantly reduced platelet inhibition, increased residual platelet aggregation, and decreased clopidogrel efficacy.

RECOMMENDATIONS - MODIFY TREATMENT BY CHOOSING ONE OF THE FOLLOWING:

(A) Prescribe prasugrel (EFFIENT) 10mg daily
***Contraindications: History of stroke or transient ischemic attack, active bleeding**
***Caution: Increased bleeding risk: Age > 75 years; Body weight < 60 kg**

OR

(B) Prescribe ticagrelor (BRILINTA) 90mg twice daily
***Contraindications: History of intracranial hemorrhage, active bleeding, severe hepatic impairment**
***Caution: Aspirin doses >100 mg/day reduce ticagrelor effectiveness and should be avoided.**

More information on clopidogrel and CYP2C19

Last CYP2C19=*2/*8 on 4/12/2012

Acknowledge Reason:

Open order: Place order for prasugrel (EFFIENT) 10 mg daily. Note: remove order for clopidogrel on next screen.
(Last done by Ellen Kershner at 2:50 PM on 4/16/2012)

Open order: Place order for ticagrelor (BRILINTA) 90 mg twice daily. Note: remove the clopidogrel order on next screen.
(Last done by Inpatient Physician, MD at 12:12 PM on 5/16/2012)

Open order: Proceed with clopidogrel (PLAVIX) 75 mg daily. Note: please remove the bottom or second clopidogrel order as it will duplicate.
(Last done by Inpatient Physician, MD at 12:17 PM on 4/26/2012)

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are adaptable to a wide range of settings including resource-limited sites. Make sure this point is included in the slides.

Adult Respiratory Distress Syndrome Network (ARDSnet)

- 10 sites originally
- Set enrollment goal each year per CCTG (Critical care treatment group)
- 3 Phases
  - Phase I – Develop of protocols and manual of operations
  - Phase II – Enrollment
  - Phase III – Follow-up and analyses
- SC, Protocol Review Committee (ESP?), and DSMB
- Protocols reviewed for scientific merit, validity, and feasibility by PRC.
- DSMB conducts interim reviews of trial data for patient safety and overall progress.
- SC develops and prioritizes protocols
- Also has observational studies

Pediatric Cardiac Genomics Consortium (PCGC)

- Research Center can be a single institution or group of institutions with the capability of recruiting sufficient numbers of individuals with congenital heart disease to ensure robust genetic or genomic studies. RCs will comprise multidisciplinary teams.
- Each RC will perform unique genetic or genomic studies, but will participate in a cooperative and interactive manner with all other RCs and the Steering Committee.
- Each RC will be expected to recruit participants for genetic or genomic studies performed by Consortium members, and to collaborate through the Steering Committee to develop common recruitment and phenotyping procedures.
- The Steering Committee will have responsibility for overall scientific direction of the Consortium, for evaluating new research directions and opportunities.

Prevention and Early Treatment of Acute Lung Injury (PETAL)

- Focus on early treatment and/or prevention, high-priority studies of novel treatments for established ALI and ARDS in ICU patients
- Latitude to propose and conduct clinical protocols that answer other significant questions that affect ALI/ARDS patients
- Study endpoints are expected to be mortality, but other longer-term endpoints may be considered, as long as they are shown to have relevance to heart, lung, and blood disorders.
- Protocols will be selected and written by the Steering Committee (SC)

Power Calculations

- Example 1
  - Outcome - proportion of FH+ patients on high-intensity statins
  - Intervention - screen patients with targeted sequencing for variants in 3 FH genes
  - Effect size to detect - double the proportion of FH+ patients on AHA-recommended high-intensity statin therapy within 6 months of testing
  - 00847= freq of FH gene mutations (1 in 118) in cardiac catheterization patients
  - 00446 = freq of FH variant (1 in 224) in general patient population (among unrelated)
  - 0.37 = baseline freq of high-intensity statin use (i.e., without systematic FH screening program) in FH+ patients
  - 0.74 = freq of high-intensity statin use in FH+ individuals after genetic screening

Power Calculations

- Example 2
  - Outcome – serious adverse drug reactions
  - Effect size to detect – reduce outcome by 20%
  - Intervention – pre-emptive ADME screening
  - 0.3 = prevalence of LOF alleles in general population
  - 0.25 = freq of adverse event in LOF carriers
  - 0.075 = overall freq of outcome in untreated group (0.3 * 0.25)
  - 0.06 = overall freq of outcome in treated group (20% reduction)
  - Power 80%, alpha 5%
  - 20% reduction - N=4,378 patients in genotyped arm
  - 25% reduction (to 5.6%) N = 2,650
  - 30% reduction (to 5.2%) N = 1,750
  - 45% reduction (to 4.5%) N = 969

Genomic Medicine Consortia

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CSER2	Clinical utility of genome sequencing
eMERGE	Clinical decision support and dissemination
ClinGen	Variant curation
NSIGHT	Focus on newborns
UDN	Clinical evaluation and deep phenotyping