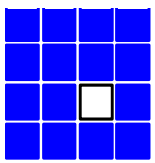
International SAE Consortium, Ltd

An International Industrial Biomedical Consortium Researching the Genetic Basis of Drug Related Serious Adverse Events

Brookings / FDA event on Sentinel Initiative

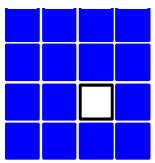
January 11, 2009



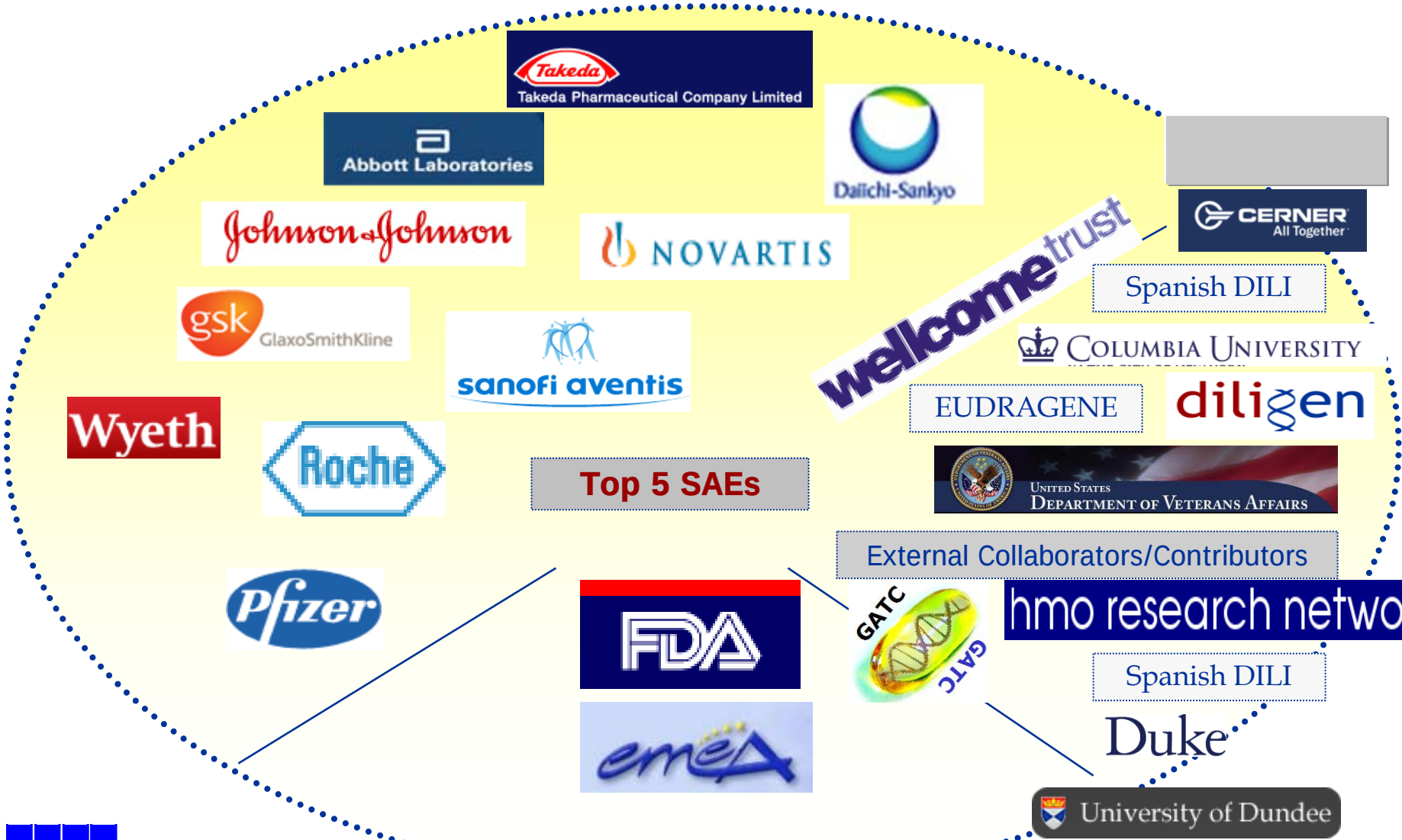
SAE Consortium

SAEC's Mission

"The SAEC will identify and validate DNA-variants useful in predicting the risk of drug induced serious adverse events."



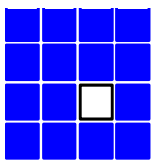
Current SAEC's Membership *[11]*



SAE Consortium

Key iSAEC Phase 1 Objectives

- Coordinate international network[s] for obtaining well phenotyped cases and controls for SAE PGx research *[SSR and DILI]*
- Using GWAS, explore cross drug/within drug DNA-variants useful in predicting the risk of SSR and DILI
- Create a publicly available "knowledge base" of cross drug safety PGx markers for predicting key SAEs
- Manage IP relating to PGx markers useful in predicting SAEs to ensure broad and open access
- Develop a cross-disciplinary forums to address clinical and scientific issues related to PGx of SAEs *[e.g. Phenotype Standardization Program]*
- Support the execution of the FDA Critical Path and related international safety PGx regulatory efforts

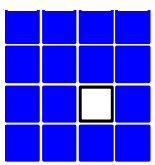


iSAEC Phase 1 Operational "Dividends"

Phase 1 Execution

- DACC development
- SJS characterization & analysis
- DILI network expansion
- DILI characterization & analysis
- Data release[s]
- Phase 2 planning

09/07-6/10



SAE Consortium

Core Investments

SSR GWAS, Paper & DR1

DILI GWAS, Papers (3) & DRs 2 & 3

Dividends!

TdP GWAS, Paper (1) & DRs 4

A-E GWAS, Paper (1) & DRs 6

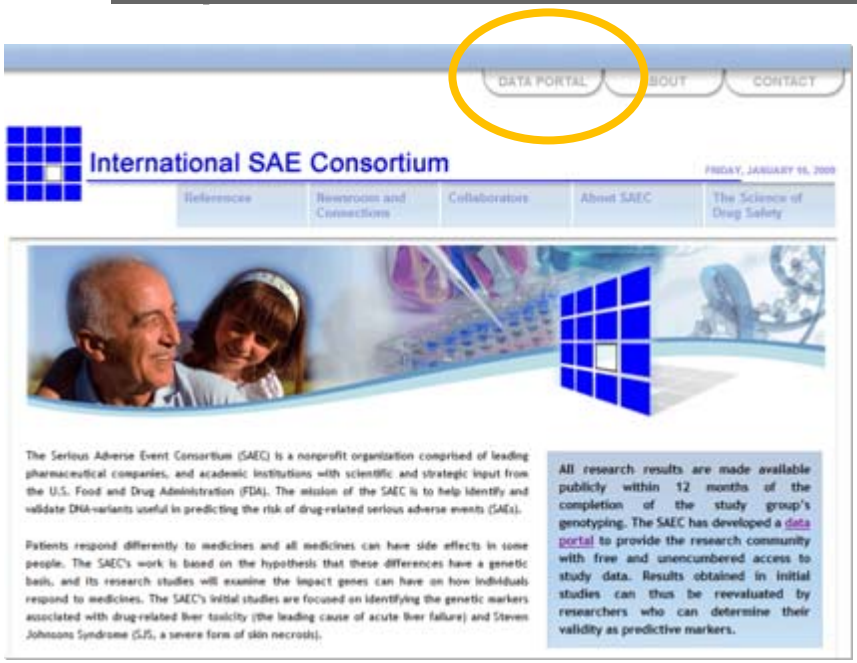
SAE Cohorts Members Pilots (3)

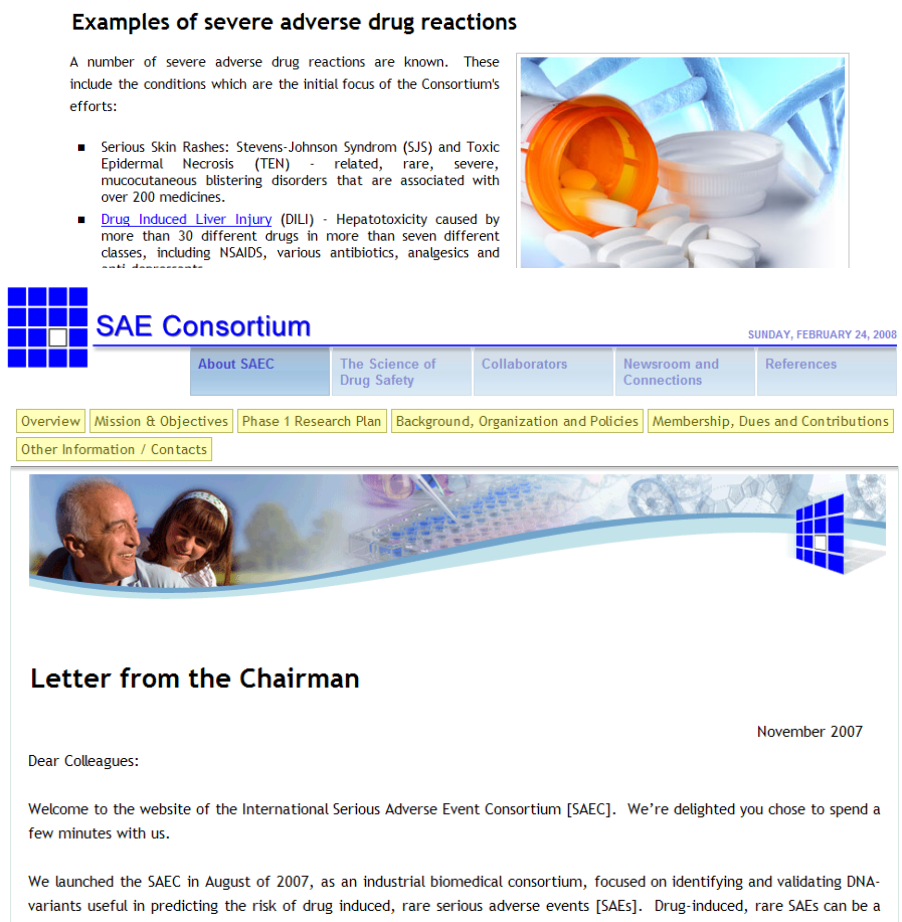
DILI & Agranulocytosis Sequencing Pilots

EMR SAE Case Sourcing Pilots (3)

SAEC Web Site

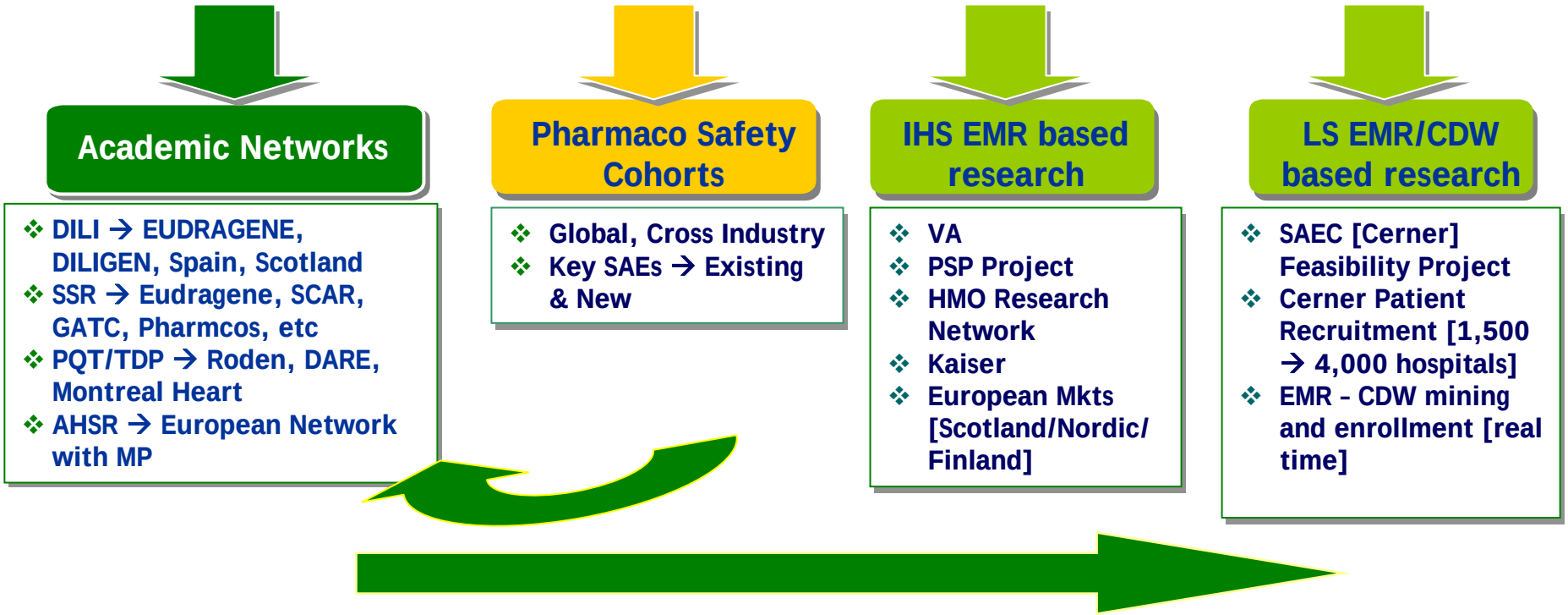
- *http://www.saeconsortium.org*





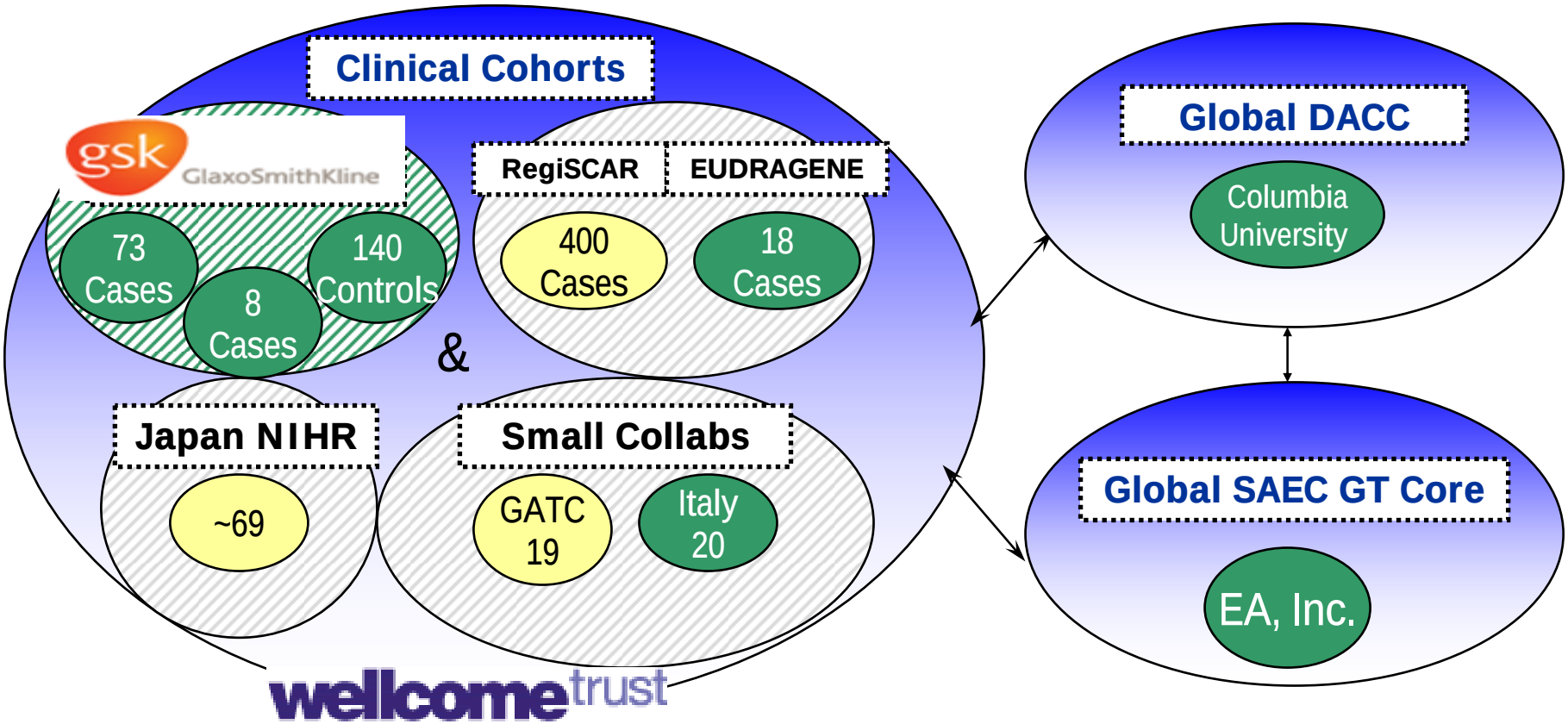
"Pathways" to SAE Cases and Controls

SAE Research → Discovery, Validation and Outcomes



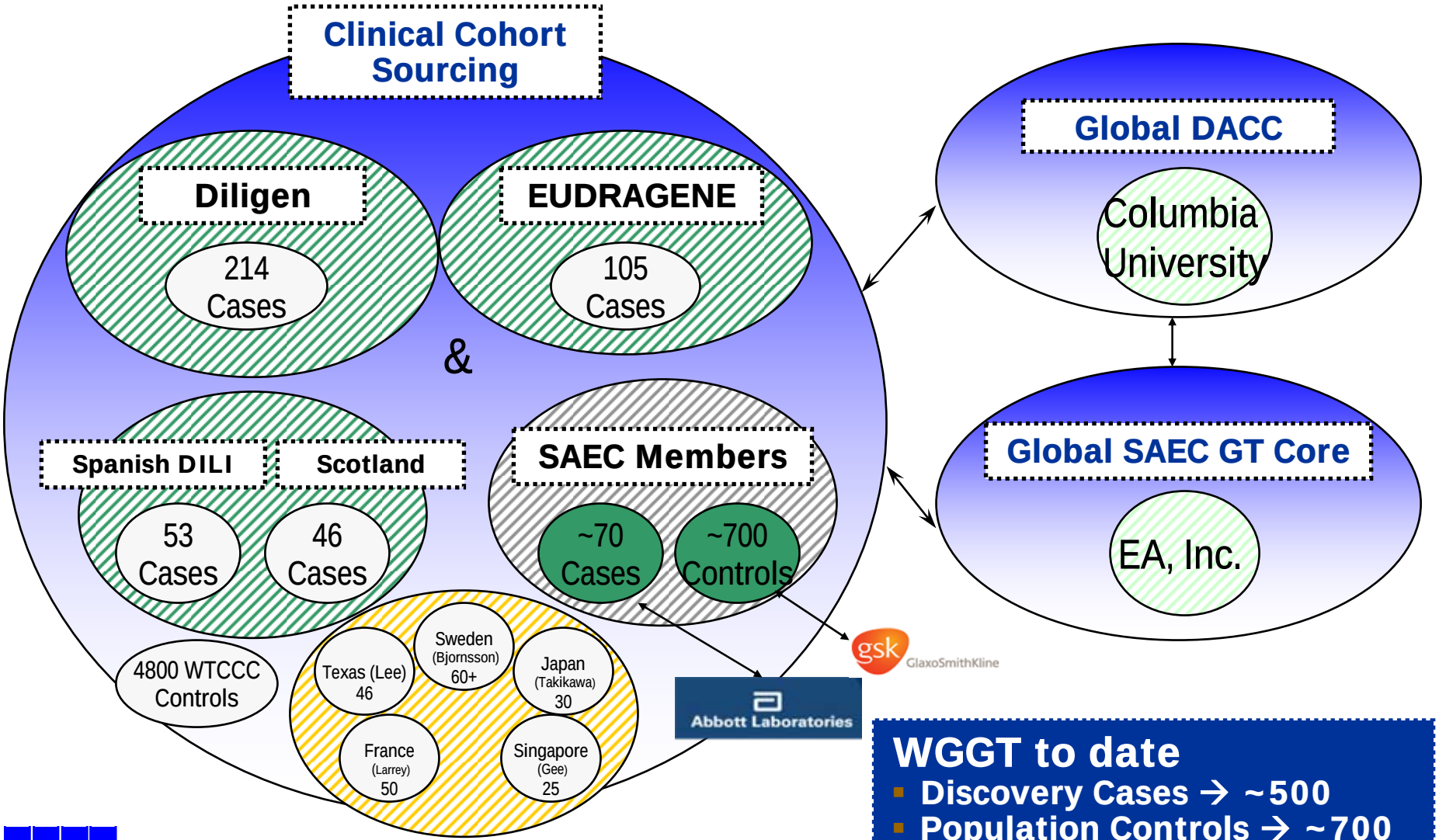
Scalability & Breadth of Safety PGx Research

Phase 1 SSR Discovery Project – June`09



- **Discovery Cohort → 81**

Phase 1 DILI Discovery Project – as of 06/09



WGGT to date

- Discovery Cases → ~500
- Population Controls → ~700
- WTCCC Controls → ~4800

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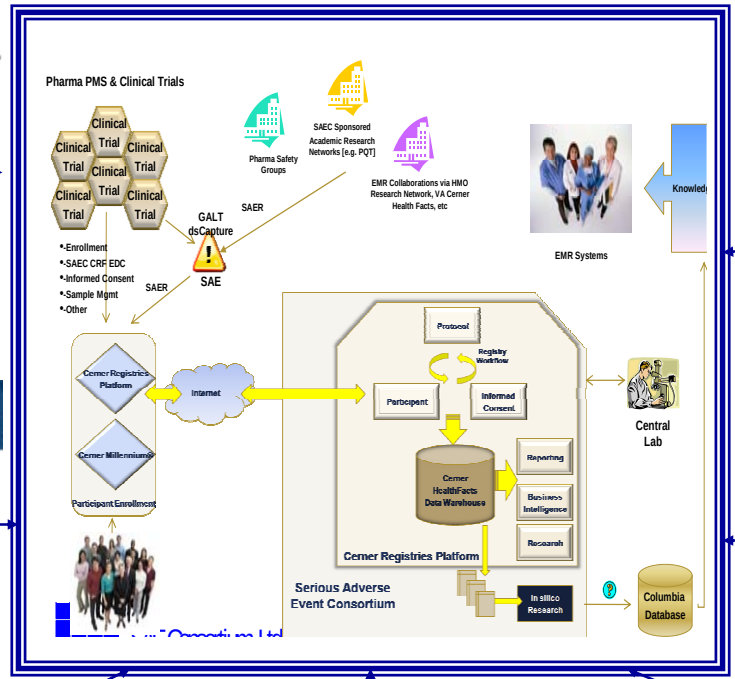
Pharmacos Sourced SAE Cohorts

CLINICAL DATA

Agranulocytosis Pharmaco 1 Cohort



wellcome trust

Control Cohorts (2)

gsk GlaxoSmithKline

Abbott Laboratories

DILI Pharmaco 5 Potential Cohorts

AHSS Pharma Cohorts (TBD)

gsk GlaxoSmithKline

PQT/TDP Pharmaco 1 Cohort

gsk GlaxoSmithKline

SSR Pharmaco 1 Cohort

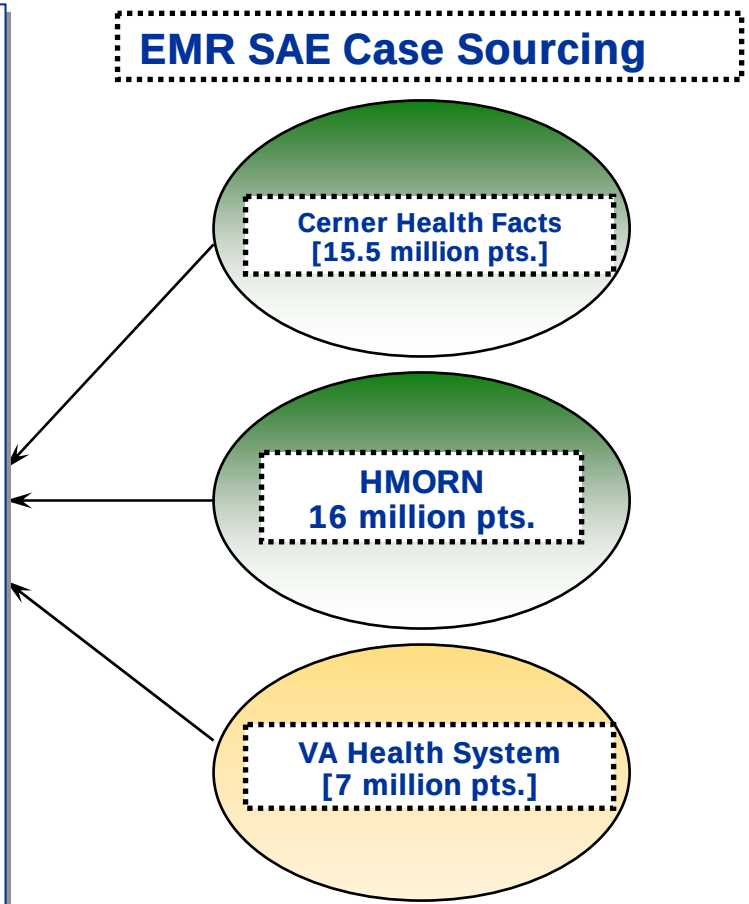
sanofi aventis

Angio-Edema Pharmaco 1 Cohort

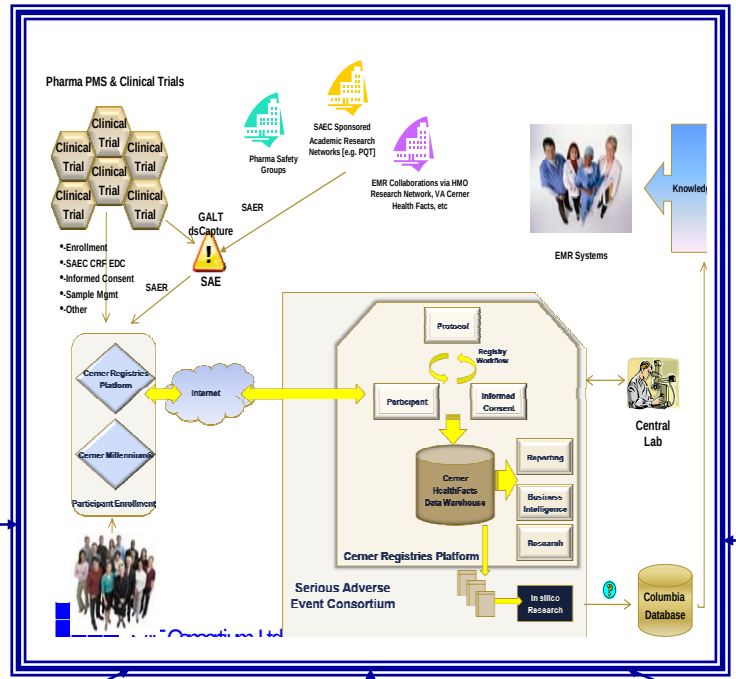
SAE Consortium

Sourcing SAE cases via Providers & EMRs
Phase 1 Feasibility Project

- 2009-10 Feasibility Projects
- Focus: Using EMR and associated research systems to determine the feasibility of yielding high quality SAE cases.
- SAE targets / 3 / collaboration [*of joint interest*]
  - Cerner → Hepatotoxicity, TdP / PQT, and SSR
  - HMORN → Hepatotoxicity, EWG, and SSR
  - VA → Hepatotoxicity and Rhabdo / Myopathy
- Standardized phenotype translated into EMR data ontology – feasibility of (retrospective) case detection in CDW
- Determine how many potential cases and key clinical data gaps



HMORN Sourced SAE Cohorts (Pilot)



Geisinger

EWG-Anti Psych

Health Partners

DILI

Group Health Cooperative

Kaiser

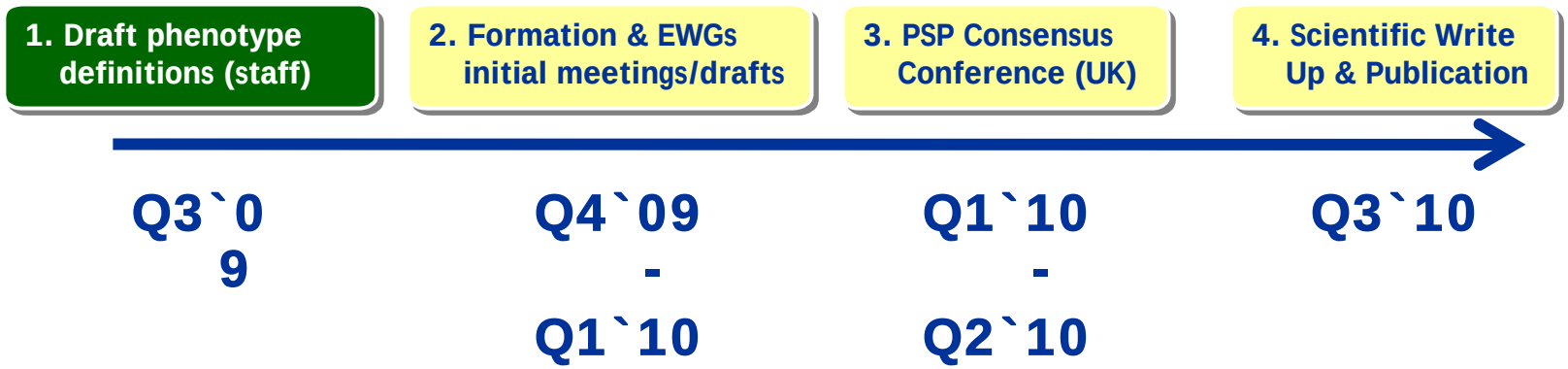
SSR

Marshfield

SAE Consortium

SAE PSP Project Phase 1 – EMR ID of SAE Cases

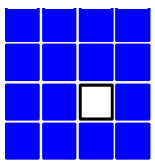
- ADR research challenges → lack of phenotype standards and "coding" into EMR data ontologies
- PSP 1 Focus: Immunologic Related SAEs (SSR, DILI & AHHS) and TdP/PQT
- 2009-10 Project → Munir Pirmohamed, Chairman; Julian Arbuckle, Project Consultant
- EWG Steering Committee → Munir Pirmohamed (Liverpool), Ann Daly (Newcastle), Paul Watkins (UNC), Guru Aithal (Nottingham), Dan Roden (Nashville) & Dr. Elijah Behr (London)
- Organizing committee → Arthur Holden (SAEC), Michael Dunn (WT), Munir Pirmohamed (Clinical Chairman), and ShaAvhree Buckman (FDA)
- Expert Working Committees (3) → AHHS/SSR, DILI, and TdP/PQT
- Q4`09 – Member CRF inputs solicited; representative involvement in 2010 consensus conference
- Pooled funding → SAEC project management and working group meetings, WT 2010 consensus conference, and FDA scientific writing consultants for proceedings write-up



SAE Consortium

Key Points from SAEC's Phase 1

1. Genomic technology and the scope of the SAEC's collaborative networks are helping to enable basic genomic research on drug induced SAEs … a significant public health and drug industry/FDA challenge … faster and more efficiently.
2. Robust statistical inference is possible from relatively small SAE cohorts [e.g. DILI research] and larger, well constructed control cohorts
3. DNA variants may be useful in predicting and mitigating SAE risk for some drugs in some patients → certainly supportive of safety PGx studies as part of clinical development or post market surveillance studies
4. There are important genetic effects at root of many SAEs, but many of these effects will likely be drug and ethnicity specific, and vary in terms of their predictability and clinical utility
5. At the same time, we are finding genetic risk alleles [e.g. HLA B*5701] that predispose certain individuals to drug induced SAEs [e.g. SSR, Acute hypersensitivity reaction, or DILI] across multiple drugs.



SAEC Evolutionary Perspective

Phase 1
SAE Research Feasibility & PGx Infrastructure

- DILI GWAS
- SSR GWAS
- Other GWASs
- Limited Rx/ethnicities

- SAEC GWAS/Clinical Database I
- Publications (~5)
- IP filings (5 -- ~ 200+ markers)

Phase 2
SAE Research Feasibility & PGx Infrastructure

- Immunologic based SAEs
- AHSS, DILI, & SSR
- Causal Drugs → Targeted & member recommended
- Technology→ Web-based/EMR based ID & enrollment
- GWAS & Sequencing Pilot(s)

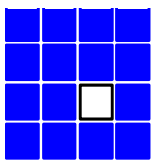
- SAEC GWAS/Clinical Database II
- SAE Healthcare Partnerships
- Publications (~TBD)
- IP filings (10 -- ~ 300+ markers)

"LT Assets"
Enhanced Pharmaco SAE Research Partners, Data & Capabilities

- SAE Research /PV Channels (HMORN, EMRs, SAE CRO?)
- SAE Clinical /Genetic Database (Wellcome Trust)
- ADR/SAE Academic Partners (Sanger, Columbia, Duke, etc.)
- ADR/SAE IP Cache (~300+ SAE Markers)

2007-2009 **2010-2012** **2012+**

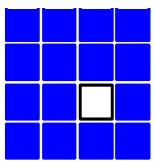
SAEC Era **Post SAEC**



SAE Consortium

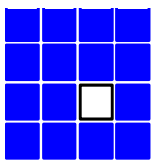
EMR based drug safety PGx science

- "Standardization" of phenotype
- "Functional/ compatible" ontology/ies
- Drug and ethnic diversity
- High quality phenotyping → real time
- Adequate case & control numbers (e.g. 50 cases X drug X ethnicity/3X control)
- Supporting genomics skills and infrastructure
- Committed partners, with "results orientation"



The SAEC Has Established an Ideal Collaborative Framework for SAE Research [1]

- ☑ Global orientation to deal with ethnic diversity
- ☑ Driving standardized phenotyping across SAE/ADRs
- ☑ Strong research design skills via Scientific Management Committee
- ☑ Strong network development skills → adequate size cohorts & optimal controls [*from academia, providers and companies*]
- ☑ Strong genomics "core"
- ☑ Excellent Data Analysis & Coordinating Center *[@ Columbia*] with state-of-the-art analysis pipeline and public website for data release
- ☑ Efficient IP pipeline to ensure all discovered markers are placed unencumbered into the public domain
- ☑ Strong, focused management
- ☑ Strong integration → industry, academia, providers & regulators



1. Giacomini et at, *Nature*, Volume 446,4/07.