



# Pharsight Perspective: Sharing Knowledge to Improve Clinical Development

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Jonathan K. Wagg, M.D., Ph.D., Senior Consultant  
[jwagg@pharsight.com](mailto:jwagg@pharsight.com)

Pharsight Corporation  
Strategic Consulting Services



# Overview of Presentation

- **Pharsight SCS Perspective**
  - Business model
  - How we currently share models
  - Drivers of M&S
  - Overview of models
  - Use of public-domain information
- **Case Study**
- **Implications for Model Sharing Consortium**
  - What might a consortium look like and what would it do
  - Potential roles/responsibilities
  - Challenges
  - Questions/concluding thoughts

# Pharsight SCS Business Model

- **Strategic Consulting Services (SCS)**
  - 25+ PhD/MD consultants (USA, Europe, Japan, Australia)
- Generates approximately half of annual revenue
- Vast majority of clients are Biopharmaceutical companies
- Typical consulting project:
  - Prospective, driven by short-term phase II/III development decisions
  - Often follow-on from earlier work prompted by availability of new data
  - Spans 2-3 months
- Scope of work usually defined by explicit work plan
  - Milestone-based fixed price with a “Per Diem” for unanticipated “out-of-scope” work
- Business relationship defined by “Master Services Agreement” covering confidentiality and intellectual property issues
  - In general, all project work completed under the MSA is the intellectual property of the client
- **Pharsight Meta-database Group**
  - “In-house” group dedicated to extracting information from the public-domain and transforming this information into “model-ready” datasets
  - Leveraged by SCS consultants and/or clients for specific projects

# Key development decisions drive the approach to M&S

Preclinical	Early Phase (I/IIa)	Late Phase (IIb/III)	Post-Approval (IV)
<p><i>“What candidate should we take forward to human clinical trials?”</i></p> <p><i>“Should we in-license this compound?”</i></p> <p><i>“What is the probable clinical dose-response in humans?”</i></p>	<p><i>“Is there a clinical trial design that will show PoC and find the best dose?”</i></p> <p><i>“What’s the probability of success in Phase 3?”</i></p> <p><i>“Is this treatment likely to be as good as the competition?”</i></p> <p><i>“What is the optimal patient population for this drug?”</i></p> <p><i>“What is an optimal regulatory strategy?”</i></p> <p><i>“What’s the best dose and schedule?”</i></p>	<p><i>“Should we continue this development program?”</i></p> <p><i>“Which indication should we go into first to maximize the value of the program?”</i></p> <p><i>“What are the most important attributes of a 2nd generation compound?”</i></p>	<div data-bbox="1522 479 1891 561" style="background-color: yellow; border: 1px solid black; padding: 5px; text-align: center;"><b>ILLUSTRATIVE</b></div> <p><i>“Is it worth developing a new dosage form?”</i></p> <p><i>“What are additional indications?”</i></p>

# Collective SCS experience spans all major therapeutic areas and all phases of development including preclinical

## Cumulative Experience by Therapeutic Area and Phase

Therapeutic Area	Phase I	Phase II	Phase III	Phase IV
Anti-Infectives (includes HIV & HCV)	✓	✓	✓	✓
Anti-inflammatory	✓	✓	✓	
Cardiovascular	✓	✓	✓	✓
Central Nervous System	✓	✓	✓	✓
Dermatology			✓	
Endocrine (includes diabetes & HRT)	✓	✓	✓	
Gastro-intestinal (GI)		✓	✓	
Genito-urinary (GU)	✓	✓	✓	
Immunomodulation (includes allergies)	✓	✓	✓	
Oncology (includes Hematology)	✓	✓	✓	✓
Ophthalmology	✓			
Pain (includes anesthetics)	✓	✓	✓	
Respiratory			✓	

# Pharsight models have been applied to development decisions across most high prevalence diseases & syndromes

<b>Therapeutic Area</b>	<b>Disease State/Indications</b>
Cardiovascular	Congestive Heart Failure (CHF), Hypertension, Hyperlipidemia/Dyslipidemia, Hypercholesterolemia, Thrombosis & others
Central Nervous System	Depression, Schizophrenia, Sleep Disorders, Alzheimers Disease, Parkinsons Disease, Pain of various aetiologies (Neuropathic, migraine) & others
Endocrine	Type II Diabetes, Obesity & others
Gastro-intestinal	Gastro-esophageal reflux disease (GERD) & others
Anti-infectives	HIV, HCV, antimicrobials
Respiratory	Asthma, Chronic Obstructive Pulmonary Disease (COPD) and others

Typically develop empirical models to describe placebo/natural disease progression and active comparator arm changes over time as a function of patient characteristics as measured by one or more accepted clinical/surrogate endpoints and/or biomarkers.

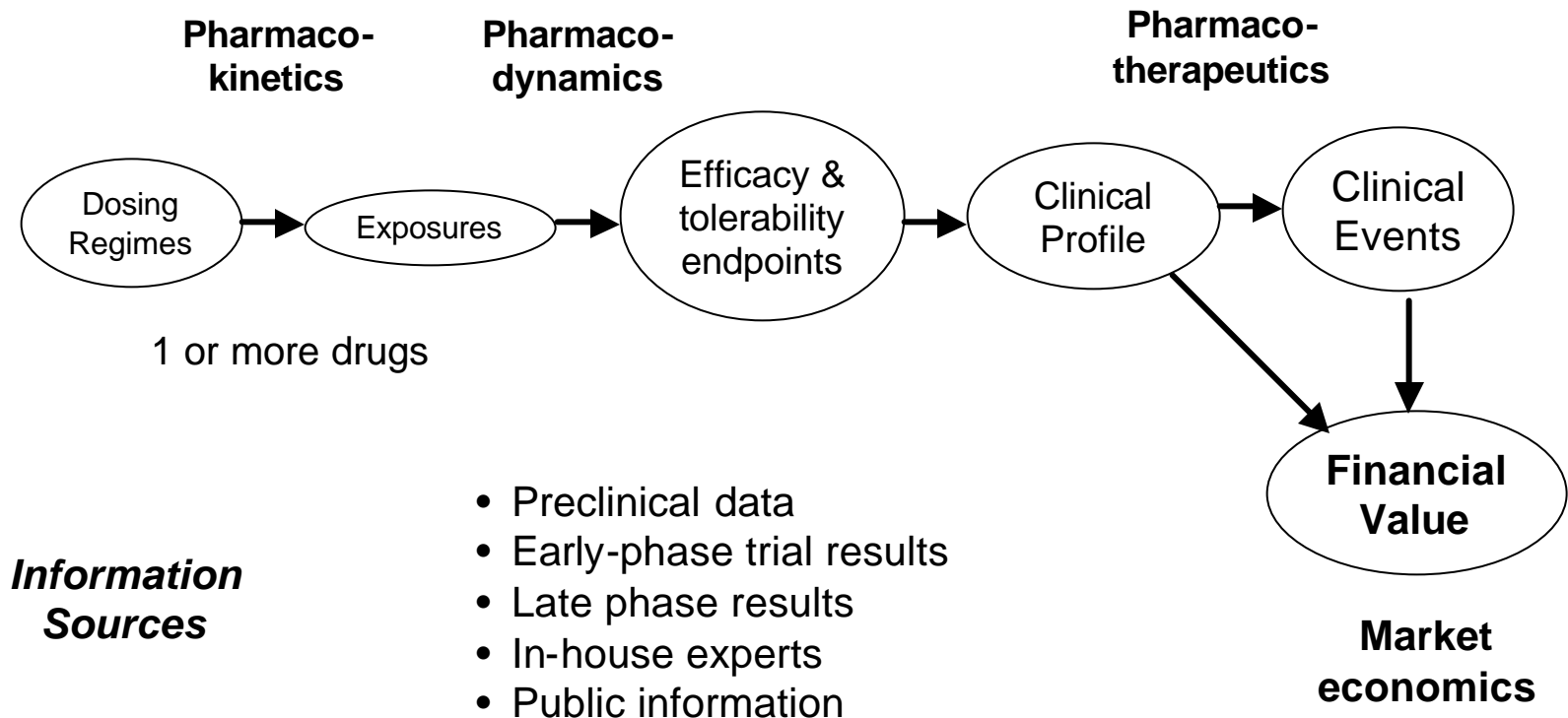
# Models provide rational framework for integration and organization of disparate compound/biologic knowledge

Model-based drug development = An integrated, data-driven, model-based decision-making methodology:

Integrate all relevant public and proprietary data spanning from discovery to clinical, from in-house data to competitors' information, and from healthy volunteers to patients into a probabilistic model of the compound's attributes and product profile in the context of a competitive landscape

# To simulate development scenarios of interest a number of sub-models are developed and integrated

- Sub-models differ in focus, mechanistic-depth, required disciplinary expertise, the quantity and quality of data they are developed from, and, the extent to which they serve to summarize proprietary client data



# Model/data sharing is a day-to-day element of SCS business operations

- **Dedicated, secure, computational infrastructure**
  - Access to project level information on a “need-to-know” basis
- **Pharsight project team members**
  - Patient-level data, S-Plus/NONMEM code & Trial Simulator Models, simulation results
- **Share with clients**
  - S-Plus/NONMEM code, Trial Simulator Models, simulation results, etc..
    - Interactive, iterative discussion
  - Training workshops focused around specific projects (SCS group)
  - Formal training workshops focused on specific products (Trial Simulator)
- **M&S community**
  - Publications in the scientific literature
  - Abstracts and conference proceedings
  - Case studies
    - Blinded / Non-blinded
  - Webinar and related Internet-accessible materials
  - Informal-interactions
- **Future: Participation in a model-sharing consortium?**

# Observations Relevant to Model Sharing

- Models developed by one group for one purpose may not be useable by another group
  - Differences in the intended use/focus of the model, i.e., problem domain
  - Quality and quantity of available data
  - Ease with which it may be integrated with other models
- M&S practices vary across clients
  - Different corporate cultures/philosophies
  - Preferences and approaches to M&S
    - Richness of contextual information
      - Clinical, biological and mathematical assumptions/rationale for M&S approach
      - What was the model developed for? What does it do well?
      - Limitations and caveats
- Software is rarely backwards compatible
  - Executables and code have an increasingly short shelf-life
- Mathematically explicit model descriptions that are implementation independent may have a longer shelf-life

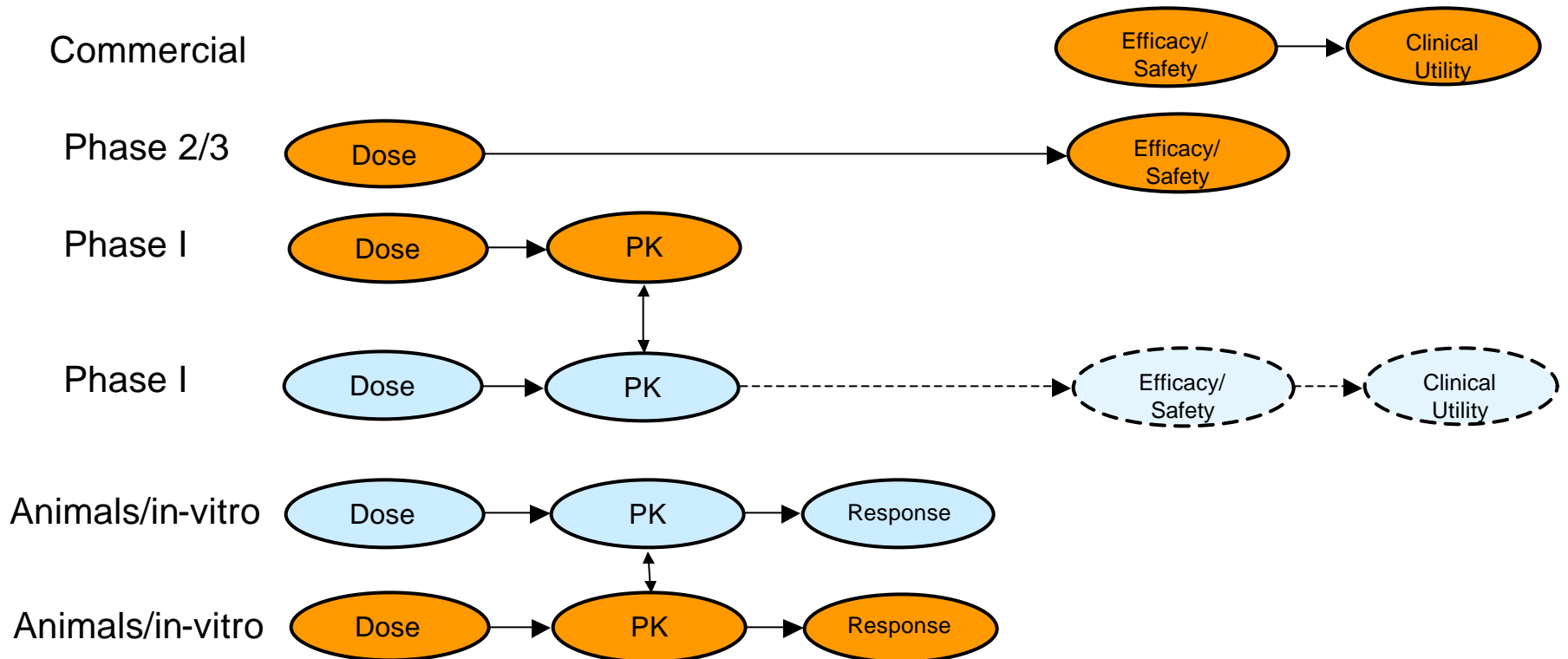
# Public-domain information/data is utilized to some extent in the majority of projects

- To identify candidate disease models
  - Model structures, parameter values, boundary conditions
  - Adapted/modified to best suit a particular problem domain
    - Reducing model complexity, estimating compound and/or patient population specific parameters
- To quantify the efficacy/tolerability profile of established standards of care across target therapeutic areas
  - Pharsight Meta-database group
- To help predict the likely clinical profile of an entity in the early states of clinical development
  - nth-in-class (Meta-database group) and first-in-class

# Public information can be used to predict dose-response

 = competitor and analogues

 = NCE



There is a wealth of modeling data in the public domain. However, it is challenging to identify prior work directly applicable to a given development issue

The screenshot shows a Microsoft Internet Explorer browser window with the address bar displaying the search URL: <http://www.google.com/search?hl=en&lr=&q=%22model%22+%22glucose+dynamics%22+&btnG=Search>. The search results are for the query "model" "glucose dynamics".

**Web** Results 1 - 10 of about 9,880 for "model" "glucose dynamics". (0.06 seconds)

**Optimal insulin infusion resulting from a mathematical model of ...**  
File Format: PDF/Adobe Acrobat  
simplified mathematical **model** of blood **glucose dynamics** to derive in- sulin infusion programs for the control of blood glucose levels in dia- ...  
[ieeexplore.ieee.org/iel1/110/704/00018755.pdf?arnumber=18755](http://ieeexplore.ieee.org/iel1/110/704/00018755.pdf?arnumber=18755) - [Similar pages](#)

**Welcome to IEEE Xplore 2.0: Recursive least-squares identification ...**  
Recursive least-squares identification of **glucose dynamics** ... is based on the method of computing a discrete-time mathematical **model** of blood glucose and ...  
[ieeexplore.ieee.org/xpls/abs\\_all.jsp?arnumber=609687](http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=609687) - [Similar pages](#)

**Repeatability of 2 methods for assessment of insulin sensitivity ...**  
Both the euglycemic-hyperinsulinemic clamp(EHC) and minimal **model** ... and repeatability of measures of **glucose dynamics** and insulin sensitivity in horses ...  
[cat.inist.fr/?aModele=afficheN&cpsid=17279723](http://cat.inist.fr/?aModele=afficheN&cpsid=17279723) - [Similar pages](#)

**Epinephrine effects on insulin-glucose dynamics: the labeled IVGTT ...**  
Epinephrine effects on insulin-**glucose dynamics**: the labeled IVGTT two-compartment minimal **model** approach. Paolo VICINI, Angelo AVOGARO, Mary E SPILKER, ...  
[cat.inist.fr/?aModele=afficheN&cpsid=13771791](http://cat.inist.fr/?aModele=afficheN&cpsid=13771791) - [Similar pages](#)

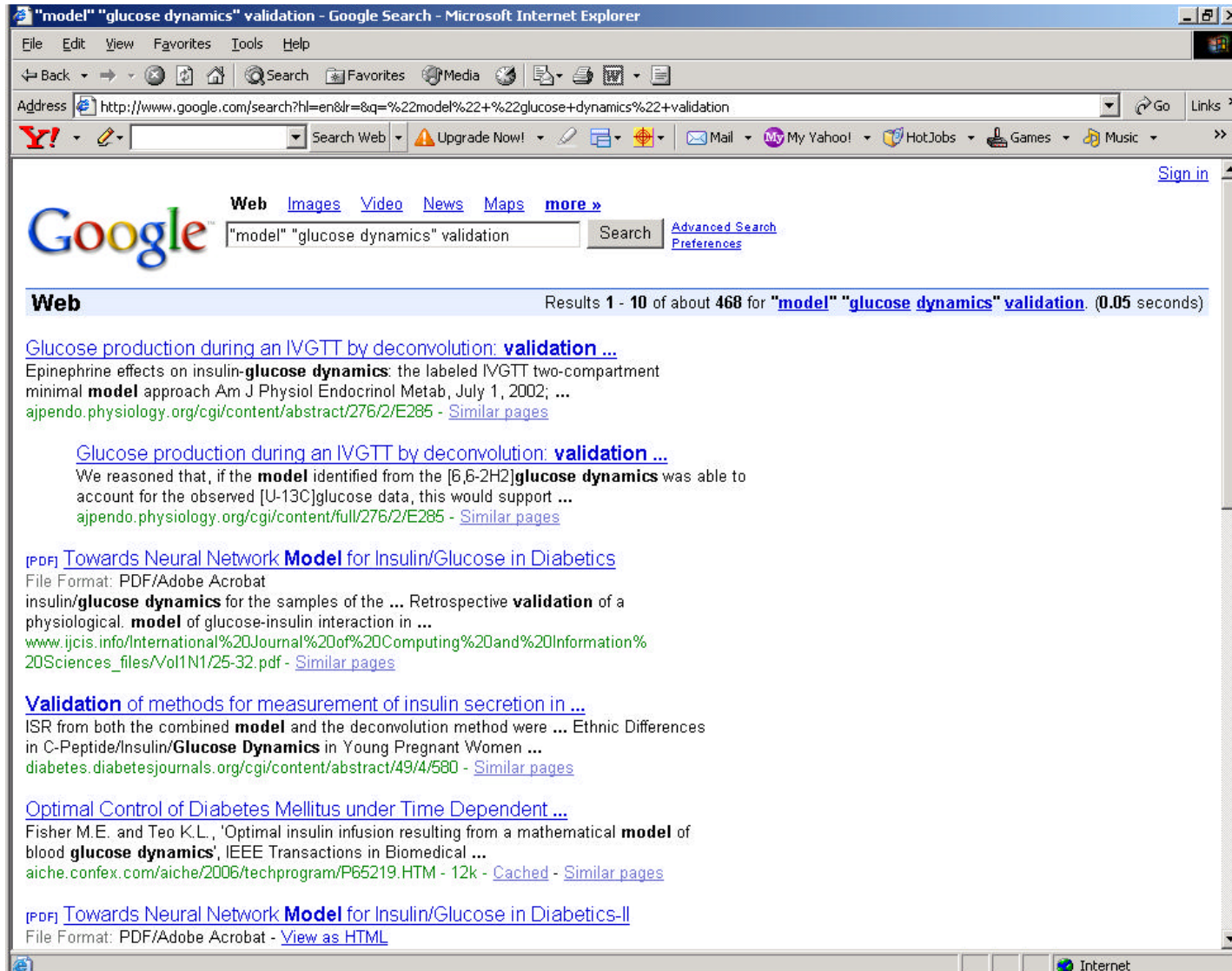
**Repeatability of 2 methods for assessment of insulin sensitivity ...**  
Both the euglycemic-hyperinsulinemic clamp (EHC) and minimal **model** ... of 2 methods for assessment of insulin sensitivity and **glucose dynamics** in horses. ...  
[www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list\\_uids=16355685&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=16355685&dopt=Abstract) - [Similar pages](#)

**Optimal insulin infusion resulting from a mathematical model of ...**  
Mathematical optimization techniques are applied to a simplified mathematical **model** of

**Sponsored Links**

- [Glucose](#)  
Why Blood Glucose Test?  
Feel Better When You're In Range.  
[OneTouchMeters.com](http://OneTouchMeters.com)
- [Blood Glucose Meters](#)  
Find the right meter and find your confidence in diabetes management.  
[www.accu-chek.com](http://www.accu-chek.com)
- [Do I Have Diabetes?](#)  
Easy tips for diagnosing yourself.  
Expert advice on treatment options.  
[www.EverydayHealth.com](http://www.EverydayHealth.com)

# Contextual information is critical to model selection including model validation – but is generally difficult to obtain



The screenshot shows a Microsoft Internet Explorer browser window displaying a Google search results page. The search query is "model" "glucose dynamics" validation. The page shows the first 10 results out of 468. The results are as follows:

- Web** Results 1 - 10 of about 468 for "model" "glucose dynamics" validation. (0.05 seconds)
- [Glucose production during an IVGTT by deconvolution: validation ...](#)  
Epinephrine effects on insulin-**glucose dynamics**: the labeled IVGTT two-compartment minimal **model** approach Am J Physiol Endocrinol Metab, July 1, 2002; ...  
[ajpendo.physiology.org/cgi/content/abstract/276/2/E285](#) - [Similar pages](#)
- [Glucose production during an IVGTT by deconvolution: validation ...](#)  
We reasoned that, if the **model** identified from the [6,6-2H2]**glucose dynamics** was able to account for the observed [U-13C]glucose data, this would support ...  
[ajpendo.physiology.org/cgi/content/full/276/2/E285](#) - [Similar pages](#)
- [Towards Neural Network Model for Insulin/Glucose in Diabetics](#)  
File Format: PDF/Adobe Acrobat  
insulin/**glucose dynamics** for the samples of the ... Retrospective **validation** of a physiological. **model** of glucose-insulin interaction in ...  
[www.ijcis.info/International%20Journal%20of%20Computing%20and%20Information%20Sciences\\_files/Vol1N1/25-32.pdf](#) - [Similar pages](#)
- [Validation of methods for measurement of insulin secretion in ...](#)  
ISR from both the combined **model** and the deconvolution method were ... Ethnic Differences in C-Peptide/Insulin/**Glucose Dynamics** in Young Pregnant Women ...  
[diabetes.diabetesjournals.org/cgi/content/abstract/49/4/580](#) - [Similar pages](#)
- [Optimal Control of Diabetes Mellitus under Time Dependent ...](#)  
Fisher M.E. and Teo K.L., 'Optimal insulin infusion resulting from a mathematical **model** of blood **glucose dynamics**', IEEE Transactions in Biomedical ...  
[aiche.confex.com/aiche/2006/techprogram/P65219.HTM](#) - 12k - [Cached](#) - [Similar pages](#)
- [Towards Neural Network Model for Insulin/Glucose in Diabetics-II](#)  
File Format: PDF/Adobe Acrobat - [View as HTML](#)

# It is harder to assess model qualification – how well suited is a model for its intended purpose? The art of modeling – past experience, judgment – knowing what is essential

The screenshot shows a Microsoft Internet Explorer browser window with the address bar containing the search URL: <http://www.google.com/search?hl=en&lr=&q=%22model%22+%22glucose+dynamics%22+qualification&btnG=Search>. The search results are displayed on the Google search page, showing the search query "model" "glucose dynamics" qualification and the number of results (1-10 of about 27). The results list several PDF documents related to glucose dynamics and model qualification, including:

- Continuous glucose monitoring and closed-loop systems**  
File Format: PDF/Adobe Acrobat  
After sensor **qualification**, the Clarke error grid showed 90 and ... **glucose dynamics** after subcutaneous insulin injection. Diabetes. Care 1989; 12: 725-736. ...  
[www.blackwell-synergy.com/doi/pdf/10.1111/j.1464-5491.2005.01672.x](http://www.blackwell-synergy.com/doi/pdf/10.1111/j.1464-5491.2005.01672.x) - [Similar pages](#)
- Blackwell Synergy: Diabetic Med, Vol 23, Issue 1, pp. 1-12 ...**  
After sensor **qualification**, the Clarke error grid showed 90 and 10% of ... Recording of subcutaneous **glucose dynamics** by a viscometric affinity sensor. ...  
[www.blackwell-synergy.com/doi/abs/10.1111/j.1464-5491.2005.01672.x](http://www.blackwell-synergy.com/doi/abs/10.1111/j.1464-5491.2005.01672.x) - [Similar pages](#)
- PS 71 Devices**  
File Format: PDF/Adobe Acrobat  
number of **qualifications** exceeding the admissible tolerance of error of ... rapidly rising and falling **glucose dynamics** (hyperglycemic clamps) and by ...  
[87.234.226.93/easd/customfiles/easd/18IDF/abstracts/PS71.pdf](http://87.234.226.93/easd/customfiles/easd/18IDF/abstracts/PS71.pdf) - [Similar pages](#)
- Development and testing of a simple algorithm for a glucose clamp**  
File Format: PDF/Adobe Acrobat  
1 Linear two-compartment **model** of **glucose dynamics** used. in the computer simulations ... postgraduate computing **qualifications**. He has ...  
[www.springerlink.com/index/7L7W35W12H0155Q8.pdf](http://www.springerlink.com/index/7L7W35W12H0155Q8.pdf) - [Similar pages](#)
- THE DESIGN AND TESTING OF A PERSONAL HEALTH SYSTEM TO MOTIVATE ...**  
File Format: PDF/Adobe Acrobat - [View as HTML](#)  
is any structure within **glucose dynamics** that suggests predicting is a meaningful exercise. ... The participants in the Game Group had a **qualification** ...  
[www.media.mit.edu/~kumar/VSK\\_MDThesisFinal.pdf](http://www.media.mit.edu/~kumar/VSK_MDThesisFinal.pdf) - [Similar pages](#)

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- Drivers of M&S
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- Case Study

- Implications for Model Sharing Consortium

- What might a consortium look like and what would it do
- Potential roles/responsibilities
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# What might a Modeling Consortium look like?

Model Consortium  
Executive Committee

FDA/EMEA/JMHW --3 votes  
Sponsors--3 votes  
Neutral Academic--1 vote

- Evaluate and authorize projects
- Set sponsor contribution level
  - Financial
  - Data, models
- Approve bylaws, SOPs for confidentiality, etc

Sponsors

- Propose projects
- Contribute data, models
- Contribute agreed annual funding
- Receive Model Consortium benefits

Modeling Vendor  
(e.g., Pharsight)

- Execute authorized projects
  - Pharsight staff
  - Model Consortium interns
- Provide Agreed Consortium Services
- Contribute expertise

FDA/EMEA/JMHW

- Propose projects
- Make data available as authorized by joint agreement
- Outsource development of global modeling resources

# What Might a Modeling Consortium Do?

## Three Components of Deliverables

### Data

- Model Libraries including pedigrees, e.g.,
  - NONMEM
  - S Plus
  - Trial Simulator 2
- Response models
  - Placebo
  - Gold standard therapy
  - Safety assessments
- Compliance models
- Physiological parameters
- Master datasets from contributing sponsors, literature

### Knowledge Services

- Model development, maintenance
- Archiving/hosting
- Federate cross-sponsor data
- Prepare tutorials and examples
- Prepare treatises on model standards
- Develop and disseminate modeling strategy treatises, e.g., population modeling strategies
- Validate utilities and subroutines
- Publish models to DMX for visualization

### Tools

- Collaboration environment
- Links to meetings and publications
- Model List Serve
- Model Blog
- Links to technical resources
- Parallel/Grid capability

# Examples of Information That Could Be Shared

- Leveraging of repetitive modeling and simulation work that recurs across multiple projects including
  - Disease progression
  - Placebo response
  - Patient compliance
  - Dropouts
  - “Gold standard” therapeutic responses
  - Standard safety analyses (e.g., QT interval)

Note: The FDA is probably in the best position to develop (or provide information needed to develop) many of these models.

# Questions to Consider

- What is the optimal structure for a consortium?
- Are consortium activities best structured around specific, focused, development questions?
  - e.g., the QTc prolongation properties of a new class of compounds
- What can we learn from the SNP consortium and others?
- Could initial efforts support the objectives of other groups such as the serious adverse event consortium?
- Who will solicit and secure funding?
- Who will act as fiduciary to the contributors to ensure that their money is well spent?
- How will (should?) broad public health aims be taken into account in setting modeling priorities?
- If there is to be potential liability for the activities of the Modeling Consortium, is an independent board of directors needed to provide overall guidance to the Executive Committee?

# Concluding Thoughts

- A Modeling Consortium must overcome a number of issues involving organizing itself, funding, data contribution, and project execution
  - It would probably require Executive-level oversight, a board, and an administrative structure to ensure that member goals are balanced and achieved
    - This is a significant undertaking
    - This will take time and money to put in place
- Some barriers to establishing a consortium could be reduced by:
  - Focusing initial consortium efforts on a limited number of problems for which collaboration is least problematic such as:
    - Collation and modeling of public-domain data and/or pooling of placebo data for patient populations of common interest
    - To dove-tail with and add value to an independent consortium such as the Serious Adverse Event Consortium