Current and Future States of the DIA Bayesian Scientific Working Group Education Effort

Mat D Davis, PhD

BASS Conference

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DIA DEVELOP INNOVATE ADVANCE

Outline

- DIA BSWG introduction
- Bayesian survey
- Case examples
- Future state

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DIA Bayesian Scientific Working Group (BSWG)

- Group of representatives from Regulatory, Academia, and Industry, engaging in scientific discussion/collaboration
  - facilitate appropriate use of the Bayesian approach
  - contribute to progress of Bayesian methodology throughout medical product development

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DIA BSWG Activities

- Sub-teams
  - Safety (Karen Price/Amy Xia)
  - Use of historical data/prior specification (John Zhong)
  - Non-inferiority (Mani Lakshminarayanan)
  - Reporting/Tools (Mani Lakshminarayanan/Melvin Munsaka)
  - Joint Modeling (Larry Gould)
  - Program-wide Decision Making (Bin Yao/Karen Price)
  - Missing Data (Frank Liu/Stacy Lindborg)
  - Education (Fanni Natanegara/Mat Davis)
  - Pediatric (joint with Pediatric community and ADSWG)
  - Medicine Adaptive Pathway to Patients (Zoran Antonijevic/Larry Gould/Bob Campbell)
- Each sub-team has mini-charter and meets regularly

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DIA BSWG Education Subteam

- **Goal**: provide and coordinate Bayesian educational support for medical product developers in the use of Bayesian methods where appropriate
  - WHO: identify the main groups of people that are in need
  - WHAT: identify the group-specific needs
  - HOW: describe available and potentially missing group-specific educational material, identify channels for knowledge transfer and to make information available
- **Team members:**

- Mat Davis (Teva)
- Meg Gamalo (FDA)
- Isabella Ghement (Ghement Consulting)
- Cory R. Heilmann (Eli Lilly)
- Nelson Kinnersley (Roche)
- Fanni Natanegara (Eli Lilly)
- Beat Neuenschwander (Novartis)
- David Ohlssen (Novartis)
- Lucy Rowell (Roche)
- Matilde Sanchez (Arena)
- John W. Seaman, Jr. (Baylor University)
- Laura Thompson (FDA)
- Cindy Yang (FDA)
- Ying Yang (FDA)

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Bayesian Survey

- In 2012, we conducted an industry-wide Bayesian survey
  - first industry-wide survey to collect information on the use of Bayesian methods amongst statisticians working in medical product development
  - results and recommendations were published in Pharmaceutical Stats, 2014
- Winkler (2001): Why Bayesian analysis hasn't caught on in healthcare decision making
  - Case for why Bayesian analysis should be more widely used
  - Philosophical vs practical aspects
  - Need for Bayesian training, tools/procedures to make Bayesian analysis easier to understand/use, education for decision makers

BAYESIAN SURVEY: Background and Results

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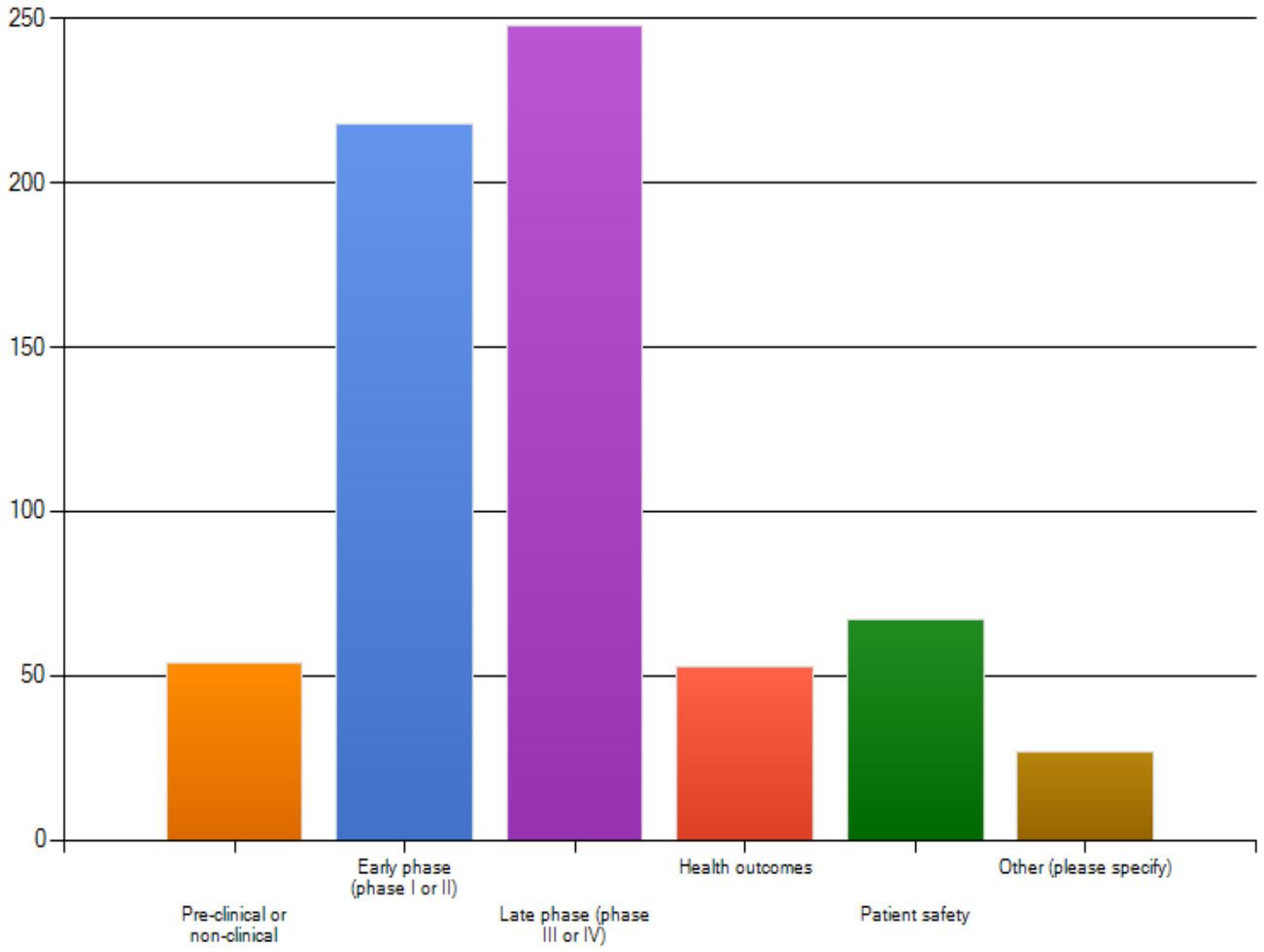
Bayesian Survey

- Sent out on April 30, 2012 to 17 organizations
- Closed on June 8, 2012
- Survey consist of 10 questions
  - Demographic (medical product phase, disease state, role, Bayesian background, education)
  - Implementation (hurdles, helpful factors, preferred education venue, topics of interest)
  - Open ended question
- Survey responders: 384 statisticians
  - 74% pharmaceutical
  - 13% each in regulatory and contract/medical research organizations

Which phase of medical product development do you work in? Please choose all that apply.



Survey respondents could give multiple responses to some questions hence percentages sum to greater than 100%; percentages are calculated based on the number of respondents who answered the respective question.

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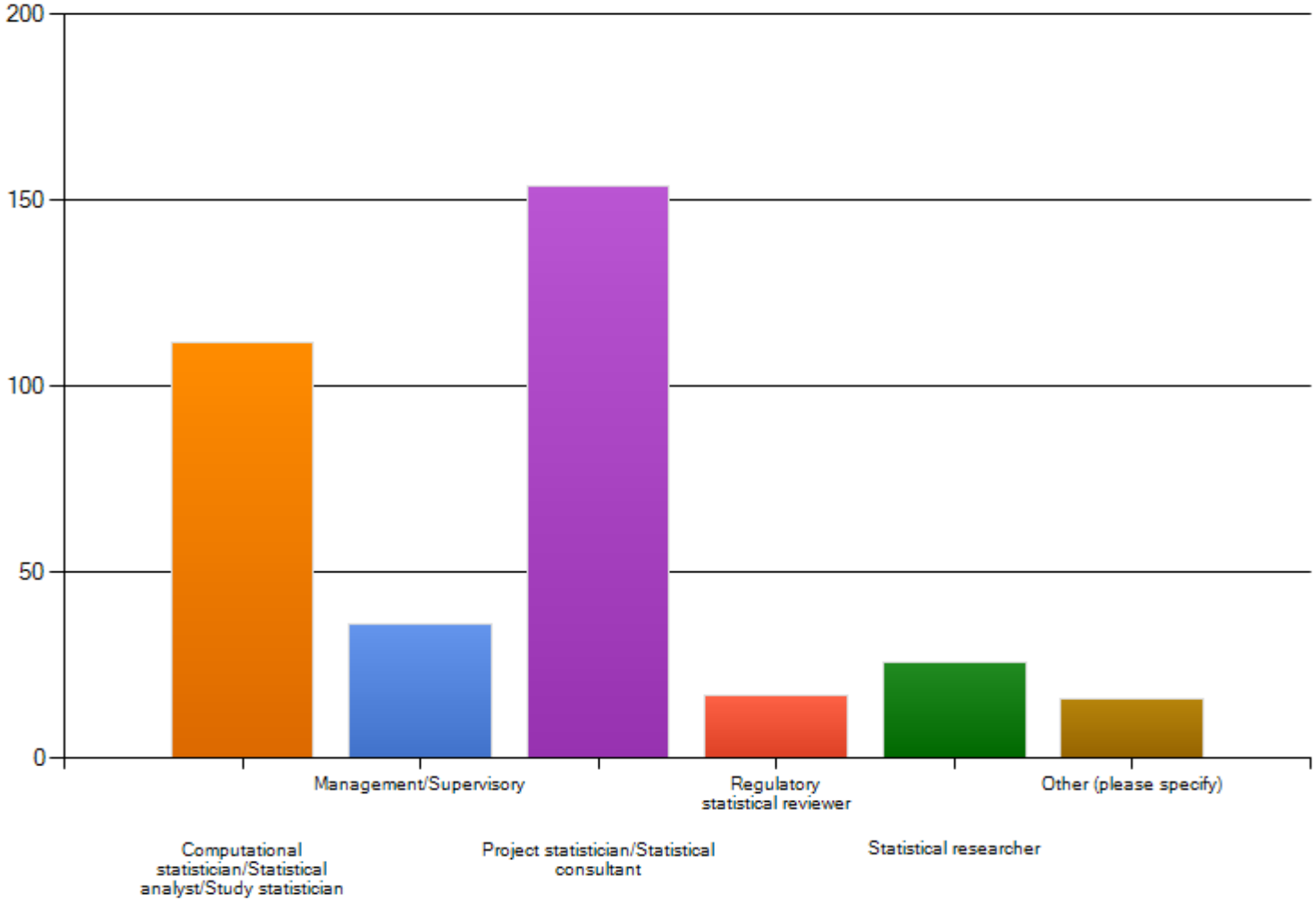
Which of the following best describes your current role?



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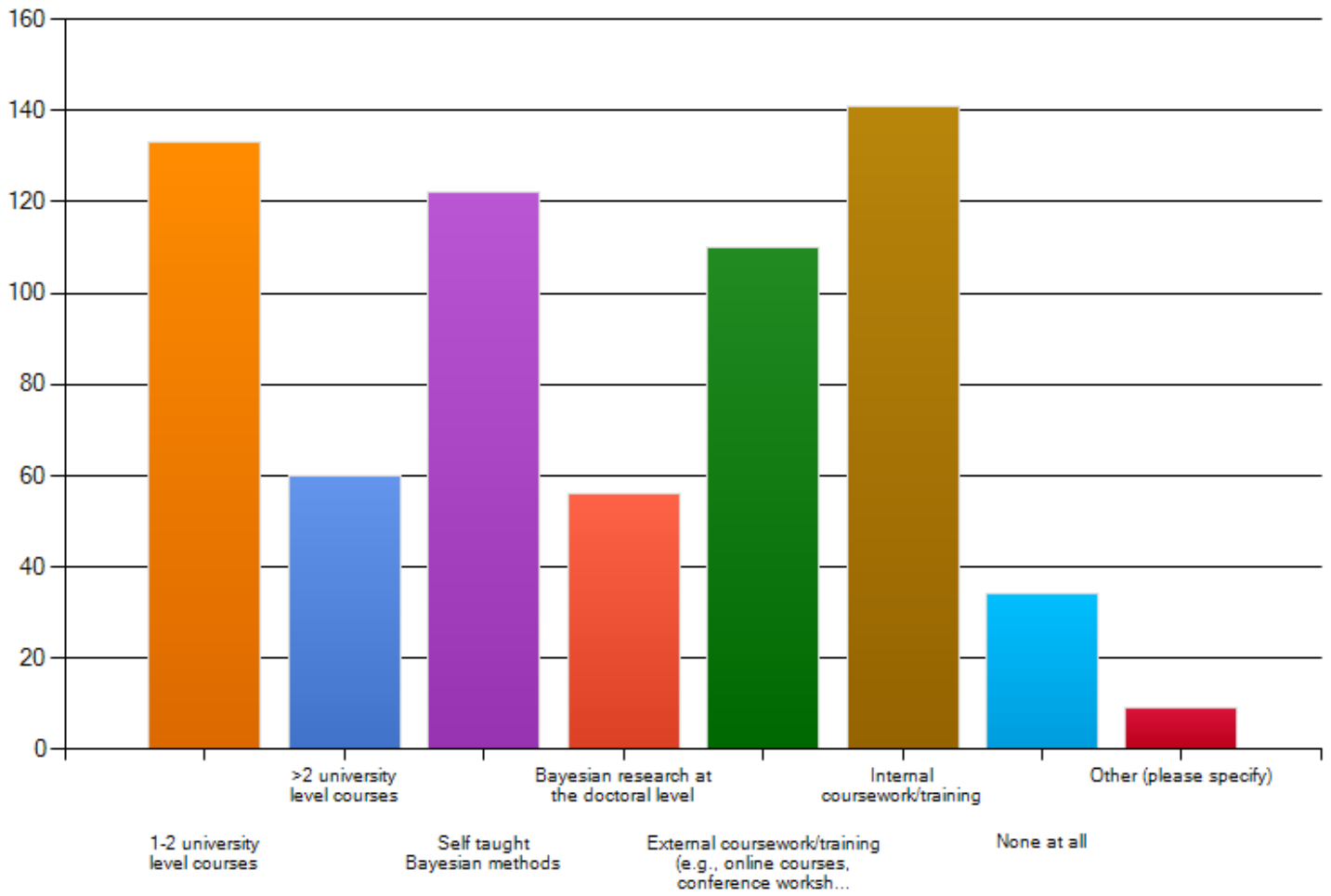
I have the following background/training in Bayesian approach. Please choose all that apply.



Survey respondents could give multiple responses to some questions hence percentages sum to greater than 100%; percentages are calculated based on the number of respondents who answered the respective question.

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Implementation Hurdles

- Insufficient knowledge of the Bayesian approach, particularly on the practical level
- Lack of clarity of the regulatory position and/or lack of guidance and experience
- Lack of tools including case examples and user-friendly software
- Company-internal difficulties (lack of time, lack of support/guidance, general reluctance from team members to accept the Bayesian approach)

HOW TO IMPROVE THE PROGRESS ON BAYESIAN APPLICATION IN MEDICAL PRODUCT DEVELOPMENT?

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Recommendation #1: Bayesian education

- Internal and external forums
  - Internal live training is preferred
- Central repository of literature (books/articles) organized by topics to be made available
- Learning process is continuous!

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Recommendation #2: Case Example Repository

- The goal of the case example working group of the DIA BSWG is to create a case example repository to make Bayesian examples available to the general public
  - Also provides an opportunity to receive case examples from the general public
- Case examples are to be categorized by methodology
- Currently discussing where to house the case example repository
- http://www.diaglobal.org/en/resources/tools-and-downloads#Bayesian-Case-Studies

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Bayesian Case Studies

The Bayesian case example repository, supported by the DIA Bayesian Scientific Working Group, contains a series of case studies demonstrating examples of the use and value of Bayesian statistics in medical product development.

- Bayesian approach to conduct sensitivity analysis for missing data
- Bayesian approach to equivalence study of medical device
- Bayesian Adaptive, Dose-Finding, Seamless Phase 2/3 Study of a Long-Acting Glucagon-Like Peptide-1 Analog (Dulaglutide)
- The utility of Bayesian predictive probabilities for interim monitoring of clinical trials

Electronic Document Management Reference Model

DIA Community for Document and Records Management developed an initiative aimed at developing a taxonomy/metadata reference model that can ultimately be shared by biopharmaceutical organizations as a common starting point for building sustainable, shareable EDM repositories.

DOWNLOAD MODEL

DOWNLOAD GUIDE

Case Example: Pravigard PAC

Case Example Author: Meg Gamalo-Siebers

Original Author: Donald A Berry

Berry, Donald A. "Bayesian clinical trials." *Nature reviews Drug discovery.* 5.1 (2006): 27-36.

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Background

- Medicinal product of interest: Pravigard Pac (Bristol-Myers Squibb)
  - Pravigard is a co-packaging of pravastatin 40 mg (Pravachol; Bristol-Myers Squibb), a cholesterol-lowering drug, with aspirin 81 or 325 mg.
  - Indication: reduce the occurrence of cardiovascular events, including death, myocardial infarction or stroke, in patients who have clinical evidence of cardiovascular and/or cerebrosvascular disease.
- There was no clinical study submitted for this combination
  - Five secondary prevention protocols for pravastatin (PLAC I, PLAC II, REGRESS, LIPID and CARE) in which pravastatin had been randomized and aspirin use had been recorded but not randomized.
- FDA's approval was based on the Bayesian posterior probability that the combination is more effective than either agent alone.
  - Five inter-related outcomes were analyzed: composite of CHD death, non-fatal MI, myocardial revascularization procedures or ischemic stroke; composite of CHD death, non-fatal MI or myocardial revascularization procedures ; composite of CHD death or non-fatal MI; composite of fatal or non-fatal MI; ischemic stroke
  - Safety information was assessed from the same cohort in the five studies.

Bayesian justification

- Indication overlap. Aspirin's vascular indication includes prevention of recurrent MI, unstable angina pectoris, and chronic stable angina which is related to pravastatin's indication of increased risk for atherosclerotic related clinical events, e.g., secondary prevention of cardiovascular events.
- The Bayesian approach is ideally suited for synthesizing information from multiple heterogeneous sources.
- The Bayesian approach focuses on probabilities of hypotheses for existing data makes it ideal for retrospective analyses.

Statistical analysis plan

- Three Bayesian meta-analytic models for addressing the benefit of the combination of pravastatin and aspirin [AP] relative to that of the individual agents [A] and [P], i.e., [AP]>max{[A], [P]}
- Models use Cox proportional hazards structures for the covariates assuming a hierarchical distribution for trial effects; Model 1 have constant hazard rate over time; Model 2 have piecewise hazard; Model 3 drops the proportional hazards assumption
- Covariates include any CAD, Gender, Smoking, Aspirin use, Age, LDL-C, HDL-C, TG, SBP, DBP

Tools <Code>

- Metropolis-Hastings step for the complete conditional distributions were coded in Fortran
- Complete conditionals were provided in supplementary paper but not the code

Efficacy Model

- Likelihood: hazard function and survival function
- Prior: non-informative/vaguely informative for fixed effects parameters; moderately informative for the random effect parameter (trial effect)
- Posterior:

Table 4. Model 3 Posterior Probabilities for the Indicated Possibilities Cumulated to the End of the Indicated Years

Possibility	*Year 1*	*Year 2*	*Year 3*	*Year 4*	*Year 5*
Antagonistic	.0318	.0072	.0012	.0002	.0008
Cooperative	.2050	.1162	.0444	.0414	.0660
Synergistic	.7632	.8766	.9544	.9584	.9332

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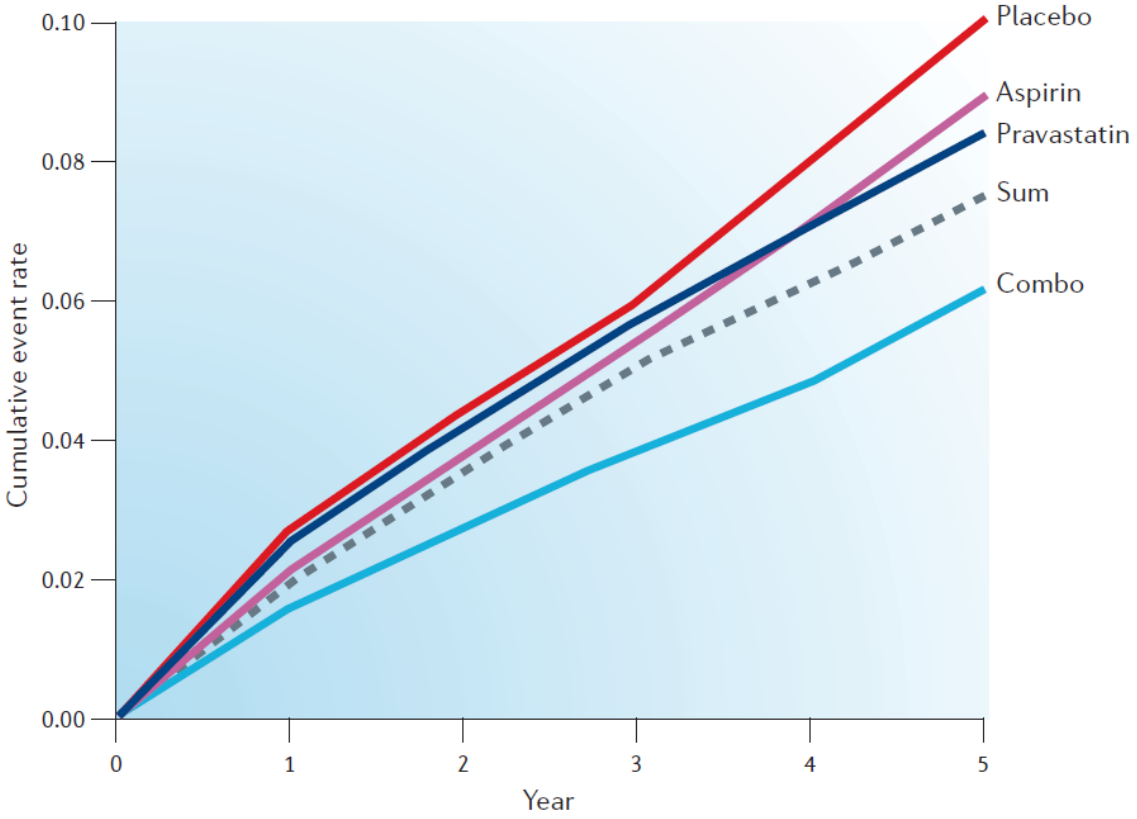
Efficacy Result



Probabilities that the combination is better than either individual drug and also of synergism

Comparison	Year 1	Year 2	Year 3	Year 4	Year 5
Combo best	0.968	0.993	0.999	0.999	0.999
Synergism	0.763	0.877	0.954	0.958	0.933

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Sensitivity Analyses

Table 5. A Sensitivity Analysis for the Prior Distribution of σ_ϕ^2 Within Model 3

	Prior				
Parameter	*IG(3, 1)*	*IG(1, 1)*	*IG(−.5, 1000)*	*IG(5, 5)*	*IG(10, 10)*
Prior percentiles for σ_ϕ					
5th	.398	.578	—	.147	.080
50th	.612	1.201	—	.207	.102
95th	1.106	4.415	—	.319	.136
Posterior summaries					
Study mean (μ_ϕ^2)	.004	.035	−.001	−.087	−.150
Study st. dev. (σ_ϕ^2)	.601	.873	.858	.257	.121
LIPID (ϕ_2)	−.430	−.430	−.438	−.423	−.386
PLAC-I (ϕ_3)	.476	.546	.478	.222	−.022
PLAC-II (ϕ_4)	.347	.383	.316	.070	−.095
REGRESS (ϕ_5)	−.366	−.351	−.362	−.323	−.254
Posterior probabilities					
Pr(antagonistic)	.0008	.0014	.0012	.0010	.0010
Pr(cooperative)	.0660	.0688	.0772	.0682	.0692
Pr(synergistic)	.9332	.9298	.9216	.9308	.9298

Conclusion

- Analysis described provided basis for the efficacy portion of the submission; the scientific objective is to compare the benefit of combining pravastatin and aspirin with benefits of individual drugs
- Bayesian methods are inherently synthetic and are ideally suited for combining results of different trials designs
- Help directly answer the question of interest

Additional Case Examples

Utility of Bayesian Predictive Probabilities for Interim Monitoring of Clinical Trials

- Presented at the KOL Lecture series November 2015 by Ben Saville, PhD, Berry Consultants
- Demonstrates the utility of predictive probability of success for declaring efficacy or futility in interim analyses
- Hypothetical examples of utility of the method
- Comparisons between Bayesian and frequentist methodology
- Challenges and benefits of implementation

Bayesian Approach to Conduct Sensitivity Analysis for Missing Data

- Provided by G. Frank Liu, Baoguang Han, Michael J Daniels, Xin Zhao and Qun Lin
- Specified pattern mixture, selection and Bayesian non-parametric models to handle missing data
- Applied these models as sensitivity analyses to the primary endpoint in a Schizophrenia trial
- Provides guidance on tools used for analysis
- Compares Bayesian results to frequentist results

Dulaglutide phase 2/3 Study

- Information obtained from Geiger et. Al. (2012)[2]
- The first adaptive, dose-finding, inferentially seamless phase 2/3 trial
- Study divided into two stages
  - Stage 1: Bayesian adaptive, dose-finding design to lead to dose-selection (up to 2 of 7 doses) or early termination for futility
  - Stage 2: Continued evaluation of selected doses
- Trial accepted and served as a pivotal trial for dulaglutide

2. Geiger et. Al. An Adaptive, Dose-Finding, Seamless Phase 2/3 Study of a Long-Acting Glucagon-Like Peptide-1 Analog (Dulaglutide): Trial Design and Baseline Characteristics.

J Diabetes Sci Technol 2012;6(6):1319-1327

Additional Case Examples

- Pravigard Pac Approval, Data Synthesis
- Non-Inferiority
- Selection of Priors
- Assessment of Inhibitor Risk in Studies of Factor VIII Concentrates
- I-Spy II Trial Design
- Safety Signal Detection
- Safety Analysis
- Joint Modeling
- Sensitivity Modeling for Missing Data
- Reporting Tools
- Application to Pediatric Studies

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Call for Case Examples

- We need additional case examples for the repository
- As the repository grows, we hope that others will continue to contribute case examples
- The case example template will be made public
- For now, case example ideas can be submitted to Fanni and Mat
  - Fanni: natanegara_fanni@lilly.com
  - Mat: matthew.davis07@tevapharm.com

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Recommendation #3: Internal Bayesian infrastructure

- A group of statisticians with dedicated time for focusing on Bayesian methods
  - allow systematic training of statisticians and non-statisticians
  - recruitment of statisticians with thorough Bayesian training
  - collaboration with other functions

Recommendation #4: Interaction between Bayesian and frequentist statisticians and other stakeholders

- Bilingual approach
  - Good understanding of Bayesian and frequentist methods
- Focus should be on the problem and not the methods
  - convey balanced opinions when presenting a Bayesian approach to a problem

Hurdles/needs identified from Joint Conference (Feb, 2015)

- Transform culture
  - More transparency from sponsors on use of Bayes/AD
  - Internal resistance to change
  - No clear path for timely communication with regulators regarding technical aspects associated with AD and/or Bayesian approaches
  - Lack of acceptance for use of Bayesian methods in confirmatory study as basis of approval
- Apply method appropriately
  - Acceptance of control of type 1 error via simulation (including characterization of the null space)
  - Formal use of prior knowledge
  - Limited expertise regarding AD and Bayesian methods (computation, methods, knowledge of designs, etc.)
  - Need guidance/template/good practice document etc (refer to Bayesian guidance

What are we doing now?

- Case example locator tool publicly available
  - For statisticians, by statisticians
- Best practice paper: Bayesian trial design simulations to demonstrate control of type 1 error including documentation of operating characteristics and rationale of parameters
- Medical and regulatory colleagues and scientists involvement
  - Develop education materials for physicians
  - CE course in medical/scientific conferences
  - Publication in medical journals
- Website: www.bayesianscientific.org

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http://www.bayesianscientific.org/

Bayesian Scientific Work Gr...

Bayesian Scientific Work Group

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Bayesian Scientific Working Group

Group Overview

The DIA Bayesian Scientific Working Group (BSWG) was formed in 2011 with the vision to ensure that Bayesian methods are well-understood and broadly utilized for design and analysis throughout the medical product development process and to improve industrial, regulatory and economic decision making. The group is comprised of individuals from academia, industry and regulatory authorities.

Subteams

Resources

90%

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What are we doing now?

- **Medical outreach effort**
  - Bayesian methods are becoming more pervasive among statisticians
  - More willingness from statistical reviewers and regulators to accept Bayesian methods
  - Now, the conversation needs to change to educate physicians and non-statistical regulators
- Team currently being developed
- One identified goal is to provide Bayesian training at a key medical conference
- Statistician's opportunity for leadership

What are we doing now?

- **Bayesian Best Practices Paper**
  - Individuals who know Bayesian methods and can design Bayesian clinical trials may not know all that is needed to formally submit and support a Bayesian design
  - Lack of clarity and guidance on what should be submitted
  - Intention of the paper is to provide guidance on best practices for design and submission
  - Will provide another resource for novice Bayesian statisticians to support the use of Bayesian methods

Future State

- Increased acceptance could transform the future of drug development, but there are some key barriers that currently result in limited uptake
- Bayesian survey: need for Bayesian education, tools, infrastructure, moving beyond Bayesian vs Frequentist

  "T*he past was combative, the present is competitive and the future will be cooperative*" - Jack Lee
- In Jul 2015, US House of Rep passed the 21st Century Cures Act , nonpartisan effort to help streamline, modernize and personalize health care, encourage greater innovation and research
  - Calls for guidance documents, public meetings, and a pathway to discuss technical aspects related to innovative designs and analyses including Bayesian and AD

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How to get involved?

- Call for case examples
  - natanegara_fanni@lilly.com
  - matthew.davis07@tevapharm.com
- Join DIA BSWG sub-teams
  - safety, prior, non-inferiority, reporting/tools, joint modeling, program-wide decision making, missing data, education, pediatric
  - price_karen_lynn@lilly.com

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BACK UP

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Survey Summary 1: Case Examples and Templates

- Most helpful factor
- Currently we have no publicly available repository of case examples
- Templates would be helpful
- "I feel pretty familiar with the Bayesian methodology and principles. However, I have problems in the technical implementation of specific cases…."

Survey Summary 2: Software Availability

- Need for user-friendly software/packages
- Currently available: BUGS, BugsXLA, SAS, R packages, JAGS, Stan
- Use of any of these packages requires solid knowledge of Bayesian methods

Survey Summary 3: Bayesian Training

- Majority of respondents (90%) have some Bayesian training ranging from self-taught methods to multiple university courses and dissertation research
- Top hurdles: insufficient knowledge and difficulty in explaining Bayesian analyses to others
- Very little literature discussing this as an integral part of medical product development

Survey Summary 4: Perception of Regulatory Acceptance

- Top helpful factor for broader use
- Work in progress, trend is promising
  - FDA CDER approved Pravigard Pac, used to treat high cholesterol and lower the risk of heart complications
  - FDA CBER observed an increasing number of Bayesian protocols submitted for review
  - FDA Guidance on Bayesian methods for medical device
  - In EU, applications in HTA