



EFSPI Integrated Data Analysis SIG

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Basel



IDA SIG Charter

- To form **working groups** to review current methodology and practice, and where necessary develop new methods or practices for the integration of data, in the areas of
 - **Efficacy Data in Phases II and III**;
 - **Safety Data** (maintaining links with the Epidemiology and Safety SIG);
 - Health Technology Assessment and **Network Meta-Analysis** (maintaining links with the Health Technology Assessment SIG);
 - Greater **data transparency** on the part of the industry.
- **To write position papers** and engage in public debate by making presentations at public meetings and conferences.

Brief History of IDA SIG

- First announced in June 2013.
- 30+ volunteers joined the SIG (from USA, UK, Europe).
- Representatives from:
 - Amgen, Astellas, Astra Zeneca, Bayer, GSK, Eli Lilly, Mylan, Novartis, Pfizer, Roche, Sanofi, UBC
 - University of Bristol, University of Goettingen.
- Now settled into 6 working groups:
 - Efficacy
 - Safety (x3)
 - Network Meta Analysis(x2)
 - Data Transparency

Working Groups

- **Efficacy:**

- *Data integration to support development decisions*

- **Safety:**

- *Analysis of safety data with rare events*
- *Reporting adverse reactions in product labels*
- *Integration of data in networks of observational databases (for active safety surveillance)*

- **Network Meta Analysis:**

- *Practice*
- *Methodology*

- **Data Transparency**

Communication/Record Keeping: Lilly Box maintained by Brenda Crowe (Eli Lilly)

- Initially TCs fortnightly, now monthly for whole SIG.
- As required for Working Groups

LILLY BOX

The screenshot displays the OneDrive interface for the 'Lilly Box'. The top navigation bar includes the 'Lilly' logo, a search bar labeled 'Search Files', and an 'Upgrade' button. Below the navigation bar, the breadcrumb path is 'All Files > EFSPi IDA'. The main content area shows a list of folders with the following details:

Folder Name	Updated	By	Count	Notes
NMA subteam	Jun 4, 2014	Byron Jones	3	Byron Jones leading.
Efficacy subteam(s)	Jun 4, 2014	Byron Jones	7	
Safety Subteams	May 28, 2014	Jean Crowe	51	Each safety subteam will have their own folder.
Full team	May 17, 2014	Byron Jones	7	
Data Transparency subteam	Feb 5, 2014	Byron Jones	1	Sally Hollis proposed as leader.

On the right side, the 'Collaborators' section lists 41 collaborators. The visible list includes:

- Box Admin (OWNER)
- Brenda Crowe (CO-OWNER)
- Co-Admin (CO-OWNER)
- MARIE-ANGE PAGET (CO-OWNER)
- Byron Jones (EDITOR)
- Amy Xia
- Jean Crowe
- Richard Nixon

Below the list, it states '33 more collaborators' and a button that says 'Invites are unavailable'.

Efficacy Working Group

Data integration to support development decisions

- **Leader: Georgina Bermann (Novartis)**

- **Members:**

Tim Auton (Astellas), Frank Bretz (Novartis), Christy Chuang-Stein (Pfizer), Tim Friede (Univ of Goettingen), Guenter Heimann (Novartis), Byron Jones (Novartis), Qi Jiang (Amgen), Hui Quan (Sanofi), Jane Temple (GSK).

Issues of data integration: Decision making at the Phase II/Phase III transition

- The available data up to the end of Phase II presents challenges for adequate extrapolation to Phase III results due to substantive differences in, e.g.,
 - Studied subjects (HV and patients who are often more homogeneous and closely followed than Phase III patients)
 - Endpoints
 - Length of exposure
 - Safety (limited data)
 -
- How can these data be effectively integrated to allow teams to explore the full range of potential results given the observed data (and external information)?

Objectives of Efficacy Working Group

- To develop tools using data integration techniques to improve decision making.
- To develop generic case studies to evaluate these tools.

Questions for Leaders on Efficacy topic

- What are the most important contributors to decision making at the Phase II/III transition point:
 - Efficacy?
 - Safety?
 - Competitive landscape?
 - Probability of Success? (Success for what?)
 - What quantitative data are needed?
 - Portfolio optimization? (NPV?)

- Can you help provide a/some case studies to focus our thoughts and help develop better (statistical) tools?

Safety Working Group #1

Analysis of Rare Events

- **Leaders:**

Sally Hollis (AZ) and David Ohlssen (Novartis)

- **Members:** Georgina Bermann (Novartis), Andreas Brueckner (Novartis), Christy Chuang-Stein (Pfizer), Tim Friede (University of Goettingen), Sally Lettis (GSK), Byron Jones (Novartis), Qi Jiang (Amgen), Hui Quan (Sanofi), Amy Xia (Amgen).

Background

- Driven by FDA White Paper “**Meta-Analysis of Randomized Controlled Clinical Trials for Evaluation of Risk To Support Regulatory Decisions**” and the FDA Public Meeting called to discuss it (November, 2013).
- Invited panel members for Public Meeting included: Byron Jones, David Ohlssen and Christy Chuang-Stein.

[See Appendix for complete list of panel members and information on White Paper.]

Statistical Methods discussed at Public Meeting

- Is either a **fixed- or random-effects** model preferable?
- How should **individual studies that have large influence** on the meta-analysis due to their size or number of events be handled in the meta-analysis?
- **Cross-validation methods**. Recommendations regarding this approach?
- **Frequentist and Bayesian** methods in the present context?
- What methods are preferred for **sparse events**?

Objectives: Concentrate on IPD data

Write a paper

- What are the advantages of using IPD data.
- Analysis of sparse data.
- Combining IPD and summary data.
- Handling missing and censored data.
- Multiplicity/multiple outcomes.
- Pooling short and long exposures.

Questions for Leaders on Analysis of Rare Safety Events topic

- How do you do this in your company?
 - How do you deal with studies in a meta-analysis that have no events on one or both arms?
- Are you using Bayesian methods?
- How are you preparing for the expected release of the FDA guidance on meta-analysis?
- Does your company conduct safety meta analysis regularly to integrate knowledge as studies are completed?

Safety Working Group #2: Reporting Adverse Reactions in Product Labels

- **Leader: Brenda Crowe (Lilly)**

- Members: Christy Chuang-Stein (Pfizer), Andreas Brueckner (Novartis) , Byron Jones (Novartis), Sally Lettis (GSK)

Topics for consideration

- 1. Rare events: How to analyze and present them.
 - Improvement on “Rule of 3” – take account of exposure, Bayesian

- 2. Better ways to make/report direct comparisons.
 - How to utilize Chuang-Stein and Beltangady methods.
 - How to do a better job of reporting ~~accrued or exposure-adjusted~~ incidence rates.

- 3. Causality Assessment
 - Methods for flagging adverse events that need further assessment.
 - Role of multiplicity adjustment, p-values

Objective: Write paper

- Working title:
“Reporting Adverse Reactions in Product Labels”

- **Sections:**
 - Introduction
 - The problems with current reporting practice
 - Possible solutions
 - When there are regional differences in reporting adverse events
 - Discussion

Questions for Leaders on Reporting Adverse Events topic

- Do you also have concerns in the way safety information is reported in drug labels, either in Europe or in the US?
- Can you share any examples of how your company decides on what to put in the safety information?
- Do you see a difference between the EU and other countries in the way safety information is reported?

Safety: Working Group #3:

Integration of data in networks of observational databases (for active safety surveillance)

- **Leader: Andrew Bate (Pfizer)**

- **Members:**

- Christy Chuang-Stein (Pfizer), Andreas Brueckner (Novartis), Byron Jones (Novartis), Kai Vogtlaender (Bayer)

Active Safety Surveillance: Background

- Lots of recent work in the development of **networks of observational databases** covering hundreds of millions of patients. [With much opportunity for heterogeneity.]
- Examples: **EU-ADR project** and FDA-sponsored, **Mini-Sentinel project**. [Other examples of large databases are given in the Appendix.]
- A key focus has been the use of such networks for **rapid analyses, often with rapid ensuing dissemination**.
- Lots of statistical issues [See Appendix.].

Objective: Write paper

- **Develop a position paper on lessons learnt from RCTs** that would be of value and importance to the further development of routine processes for the analysis of networks of observational databases.

Questions for Leaders on Active Surveillance topic

- Do you agree that there is a lot we can share from good practice on the design and analysis of RCTs?
- Are there statisticians/epidemiologists in your company with experience/interest in this topic?
- Have you any experience or expertise to share?

Network Meta Analysis

- **Leaders: Chrissie Fletcher (Amgen) and Byron Jones (Novartis)**
- **Members:** Georgina Bermann (Novartis), Kevin Carroll (kjc Statistics), Yovanna Castro (Roche), Maria Costa (GSK), Omar Dabbous (GSK), Sophia Dias (University of Bristol), Tim Friede (University of Goettingen), Ekkehard Glimm (Novartis), James Roger (GSK), Martin Scott (Numerus), Anna Wiksten (Novartis).
- Joint effort by PSI/EFSPI HTA SIG and EFSPI IDA SIG

Network Meta Analysis (NMA)

Objective: Write two papers

■ Individual Patient Data (IPD)

- We expect IPD to be used more in NMAs in the future.
- Is current methodology adequate for the needs of the pharmaceutical industry (current [academic/public sector] practice emphasises the use of aggregate data)?

■ Quality of reporting of NMAs in published literature

- Explosion in number of reports of NMA results.
- Are these papers giving a fair summary of the conclusions?
- Is undue emphasis being put on parts of the network of evidence?
- How to bridge the (perceived/actual) gap between statisticians and health economists?

Questions for Leaders on NMA topic

- Are you concerned about the quality of NMA publications?
- Do you have statisticians actively working on NMA in your company?
- Are they closely integrated with health economic functions?
- Do you contract out your NMA activities?
- Does your company have expertise in the analysis of IPD data for NMA?

Data Transparency

- **Leader: Byron Jones (Novartis)**

Members: Andy Kenwright (Roche), Sally Hollis (AZ), Rachel Hodge (GSK)

Objective: Support EFSPI Data Transparency SIG

Question: How best can we do this?

END OF PRESENTATION

Appendix

IDA SIG Charter

- To create a forum for individuals interested in integrated data analyses **to share experiences, develop best practices, work with experts in the field and collaborate with other interested parties on integrated data analysis in drug development.**
- **To be aware of regulatory initiatives** of relevance to integrated data analysis and to **assess their potential impact** on industry practice.
- **To develop an industry position on how data in the private and public domains should be integrated and presented,** particularly with respect to how such data will be considered by regulatory agencies.

FDA White Paper

- Focuses specifically on **meta-analyses** conducted for purposes of safety evaluation using data **from randomized controlled clinical trials** (RCTs).
- ... the planned guidance will **provide a consistent framework** for how meta-analyses should be designed, analyzed, reported, and interpreted in the context of product safety regulation:
 - ... when FDA requires **industry sponsors or other non-FDA entities** to conduct a meta-analysis for submission and review,
 - when **FDA conducts its own meta-analysis**, and
 - when **FDA evaluates an unrequested meta-analysis** that is submitted by sponsors or published in the peer review literature.

FDA White Paper

FDA White Paper

- ... the guidance will be directed to industry, researchers and FDA staff, so that all are aware of the expectations and criteria against which meta-analyses will be judged and to encourage the use of best practices when planning, conducting and reporting meta-analyses to FDA.
- Specifies that the availability and use of patient-level data versus study-level data increases the value of evidence of a meta-analysis in most cases.
- However, few published examples of IPD meta-analysis of safety data which fully consider the potential advantages and pitfalls.

FDA Panel Meeting: Participants

- **Robert Ball**, M.D., Deputy Director, Office of Surveillance and Epidemiology, CDER/FDA
 - **Greg Campbell**, Ph.D., Director, Division of Biostatistics, OSB/CDRH
 - **Aloka Chakravarty**, Ph.D., Director, Division of Biometrics 7, OB/OTS/CDER/FDA
 - **Lisa M. LaVange**, Ph.D., Director, Office of Biostatistics, OTS/CDER/FDA
 - **Mark Levenson**, Ph.D., Deputy Director, Division of Biometrics 7, OB/OTS/CDER/FDA
 - **Robert O'Neill**, Ph.D., CDER Statistical Advisor, OTS/CDER/FDA
 - **Estelle Russek-Cohen**, Ph.D., Director, Division of Biostatistics, OBE/CBER/FDA
 - **Robert Temple**, M.D., Deputy Center Director for Clinical Science, CDER/FDA
 - **Douglas C. Throckmorton**, M.D., Deputy Center Director for Regulatory Programs, CDER/FDA
 - **Ram Tiwari**, Ph.D., Associate Director Office of Biostatistics, OTS/CDER/FDA
- Non-FDA**
- **Eric B. Bass**, M.D., MPH, Professor of Medicine and Health Policy & Management, Director, Evidence-based Practice Center, Johns Hopkins University
 - **Jesse Berlin**, Ph.D., Vice President, Pharmacoepidemiology, Johnson and Johnson Pharmaceutical
 - **Christy Chuang-Stein**, Ph.D. Vice President and Head of Statistical Research and Consulting Center at Pfizer
 - **Amy Cutrell**, Ph.D., Director, Clinical Statistics, Infectious Diseases, GlaxoSmithKline
 - **Kay Dickersin**, Ph.D., Director, Center for Clinical Trials, Johns Hopkins Bloomberg, School of Public Health
 - **Stephen Evans**, Professor of Pharmacoepidemiology, Dept. of Medical Statistics, London School of Hygiene & Tropical Medicine
 - **Dean Follmann**, Ph.D., Chief, Biostatistics Research Branch, DCR, NIAID, NIH
 - **Nancy L. Geller**, Ph.D., Director, Office of Biostatistics Research, NHLBI, NIH
 - **Steve Goodman** M.D., Ph.D., Professor of Medicine and Health Research Policy, Stanford School of Medicine
 - **Byron Jones**, Ph.D., Senior Biometrical Fellow/Executive Director, Novartis
 - **Sanjay Kaul**, M.D., Director, Cardiology Fellowship Training Program at Cedars-Sinai Medical Center
 - **David Ohlssen**, Ph.D., Sr Expert Methodologist, Novartis
 - **Mike Proschan**, Ph.D., Mathematical Statistician, National Institute of Allergy and Infectious Diseases, NIH
 - **Christopher Schmid**, Ph. D., Professor of Biostatistics, Brown University
 - **CAPT. Anne E. Trontell**, MD, MPH, Center for Outcomes and Evidence, AHRQ

Active Surveillance: Examples of observational databases

Database	Country	Characteristic	Population Size
THIN	UK	GP primary care database	10.5 M ¹
Danish National Health Service Register Database	Denmark	Healthcare registry of care	5.5 M ²
Premier	US	Clinical data from the hospitals	130 M+ patient discharges ³
Normative Health Information (NHI) Database	US	Transactional claims records of a commercial health insurer	60 M+ ⁴
Health Insurance Review and Assessment Service (HIRA)	Korea	Insurance Claims from near universal national system	48 M ⁵

Active Surveillance: Statistical Issues (some examples)

- Pooled analyses across observational databases held remotely (lack of access to IPD: covariates, etc.).
- Hypothesis generation and testing in the same network of data sets.
- Multiple testing.
- Transparency.
- Not implementing (high) standards of RCTs expected for regulatory submissions.