BBS
Basler Biometric Section

BBS Seminar

Safety monitoring during the life cycle of a drug

Introduction

Conny Berlin
Global Head Quantitative Safety & Epidemiology
29 November 2016

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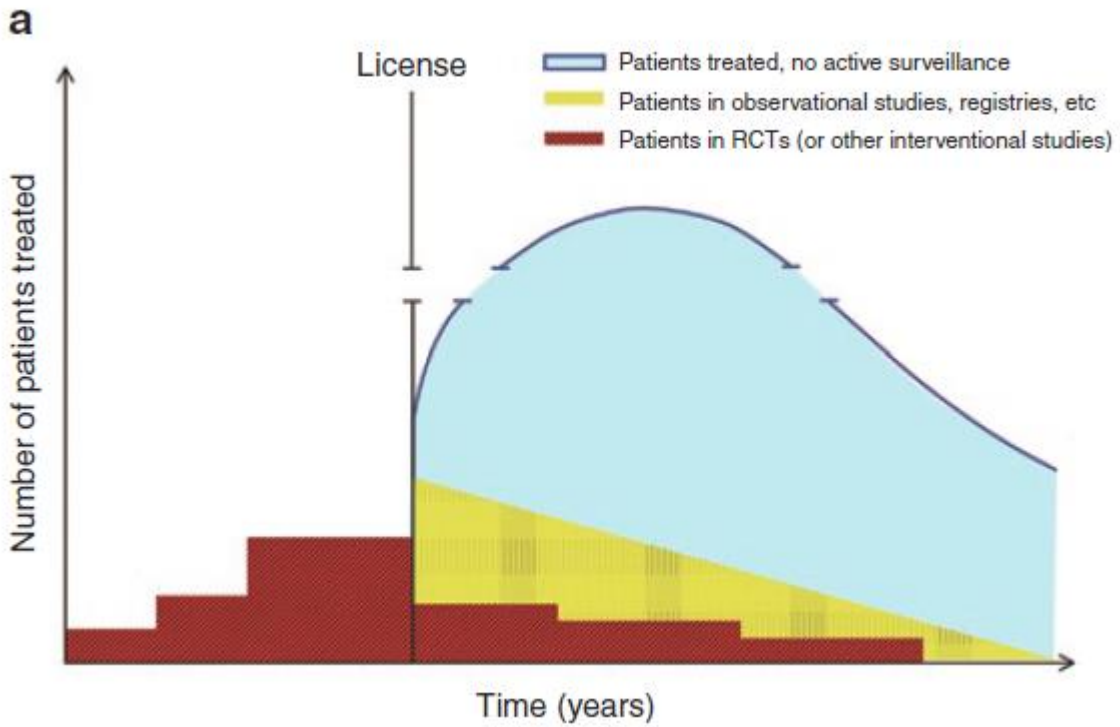
Increasing amount of safety data over time



H-G Eichler et al, «Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval", Clin Pharm&Techn 2012, 91 (3), 426-437

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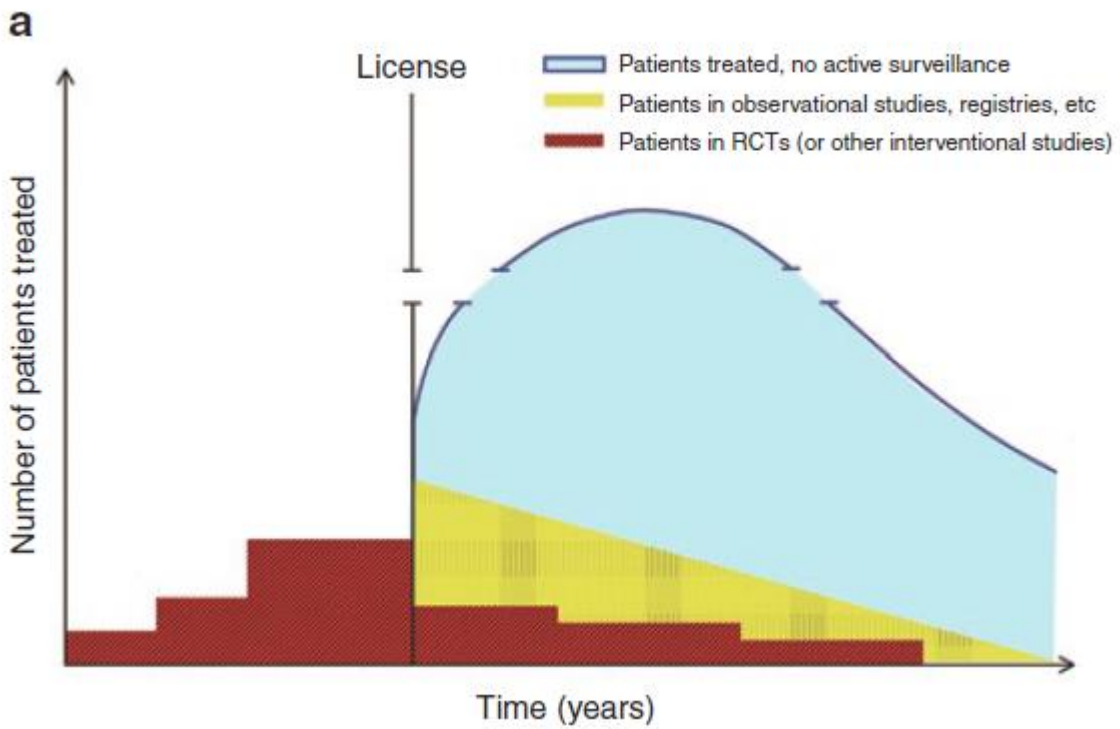
Increase in safety knowledge



H-G Eichler et al, «Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval", Clin Pharm&Techn 2012, 91 (3), 426-437

- Investigator Brochure
- Development Safety Update Report (DSUR)
- Summary of Clinical Safety (SCS)
- Labeling (Package Insert)
- Risk Management Plan (RMP)
- Periodic Safety Update Report (PSUR)

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Adverse Drug Reactions Section
(FDA ADR guidance 2006)

... **Exhaustive lists of every reported adverse event,** including those that are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy **should be avoided**.

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Informative package leaflet

2. What you need to know before you take Ciprofloxacin tablets

Do not take Ciprofloxacin if you:

- are allergic (hypersensitive) to the Ciprofloxacin, to any other quinolone drugs or to any of the other ingredients of Ciprofloxacin tablets (see section 6).
- are taking tizanidine (see Section 2: Taking other medicines).

Warnings and precautions:

Talk to your doctor, pharmacist or nurse before taking Ciprofloxacin Tablets if:

- you suffer from 'fits' or epilepsy or any other neurological conditions.
- you have ever had kidney problems because your treatment may need to be adjusted
- you have a history of tendon problems during previous treatment with antibiotics such as

4. Possible side effects

Like all medicines, ciprofloxacin can cause side-effects, although not everybody gets them.

You may suffer an allergic reaction, symptoms of which include rash, itching, difficulty in breathing or swelling of the face, lips, throat or tongue. If this happens to you, stop taking the tablets immediately and seek medical help.

STOP taking the tablets immediately and seek medical help if any of the following occur:

- muscle pain and/or weakness, inflammation of the joints and joint pain, increased muscle tone and cramping, inflammation of the tendons or tendon rupture, particularly affecting the large tendon at the back of the ankle (Achilles tendon). If

IMI PROTECT - Signal detection in Clinical Trial Data, Spontaneous Reports, Observational Data

Drug Saf
DOI 10.1007/s40264-016-0405-1

SPECIAL ARTICLE

Good Signal Detection Practices: Evidence from IMI PROTECT

Antoni F. Z. Wisniewski[1] · Andrew Bate[2] · Cedric Bousquet[3,4] · Andreas Brueckner[5] · Gianmario Candore[6] · Kristina Juhlin[7] · Miguel A. Macia-Martinez[8] · Katrin Manlik[9] · Naashika Quarcoo[10] · Suzie Seabroke[11] · Jim Slattery[6] · Harry Southworth[12] · Bharat Thakrar[13] · Phil Tregunno[11] · Lionel Van Holle[14] · Michael Kayser[15] · G. Niklas Norén[7]

Signal detection in Clinical Trial Data

PROTECT

imi efpia

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Statistical signal detection in Clinical Trial data

Christiane Ahlers, Andreas Brueckner, Anngret Mallick, Nils Opitz, Vlasta Pinkston, Bruno Tran, Janet Scott, Harry Southworth, Bruno Tran, Lionel Van Holle, Nicola Wallis

PROTECT Symposium February 19-20 2015

Journal of Biopharmaceutical Statistics, 21: 1006–1029, 2011

ISSN: 1054-3406 print/1520-5711 online
DOI: 10.1080/10543406.2010.520181

Taylor & Francis
Taylor & Francis Group

Statistical Methods in Medical Research 2004; **13**: 227–238

Use of the false discovery rate for evaluating clinical safety data

Devan V Mehrotra and **Joseph F Heyse** Merck Research Laboratories, Blue Bell, PA, USA

Clinical adverse experience (AE) data are routinely evaluated using between group *P* values for every AE encountered within each of several body systems. If the *P* values are reported and interpreted without multiplicity considerations, there is a potential for an excess of false positive findings. Procedures based on confidence interval estimates of treatment effects have the same potential for false positive findings as *P* value methods. Excess false positive findings can needlessly complicate the safety profile of a safe drug or vaccine. Accordingly, we propose a novel method for addressing multiplicity in the evaluation of adverse experience data arising in clinical trial settings. The method involves a two-step application of adjusted *P* values based on the Benjamini and Hochberg[1] false discovery rate (FDR). Data from three moderate to large vaccine trials are used to illustrate our proposed 'Double FDR' approach, and to reinforce the potential impact of failing to account for multiplicity. This work was in collaboration with the late Professor John W. Tukey who coined the term 'Double FDR'.

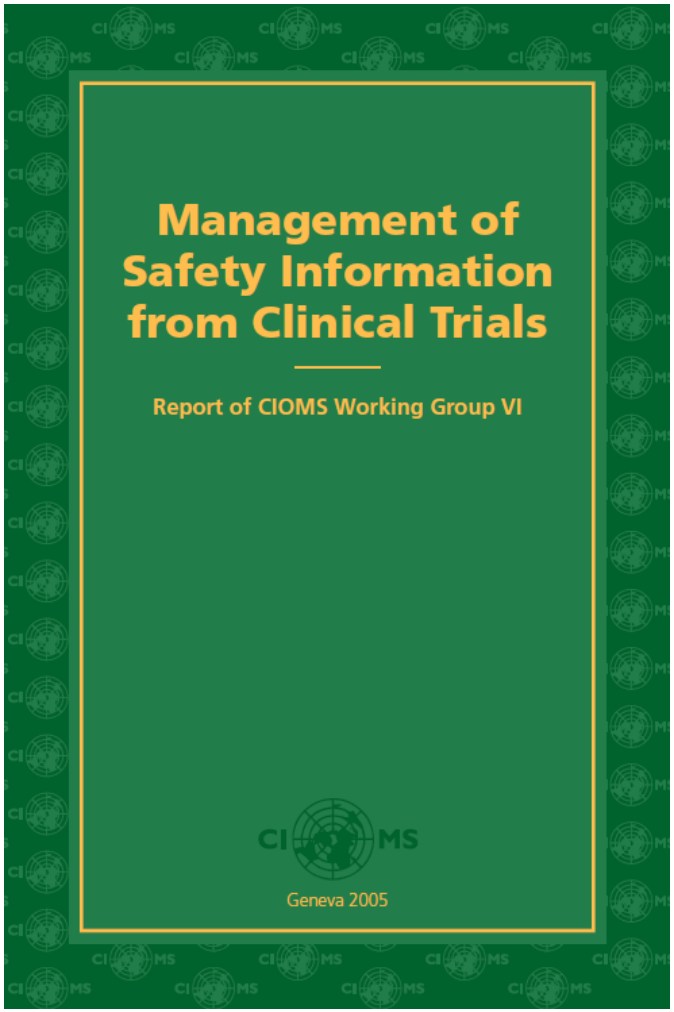
BAYESIAN HIERARCHICAL MODELING FOR DETECTING SAFETY SIGNALS IN CLINICAL TRIALS

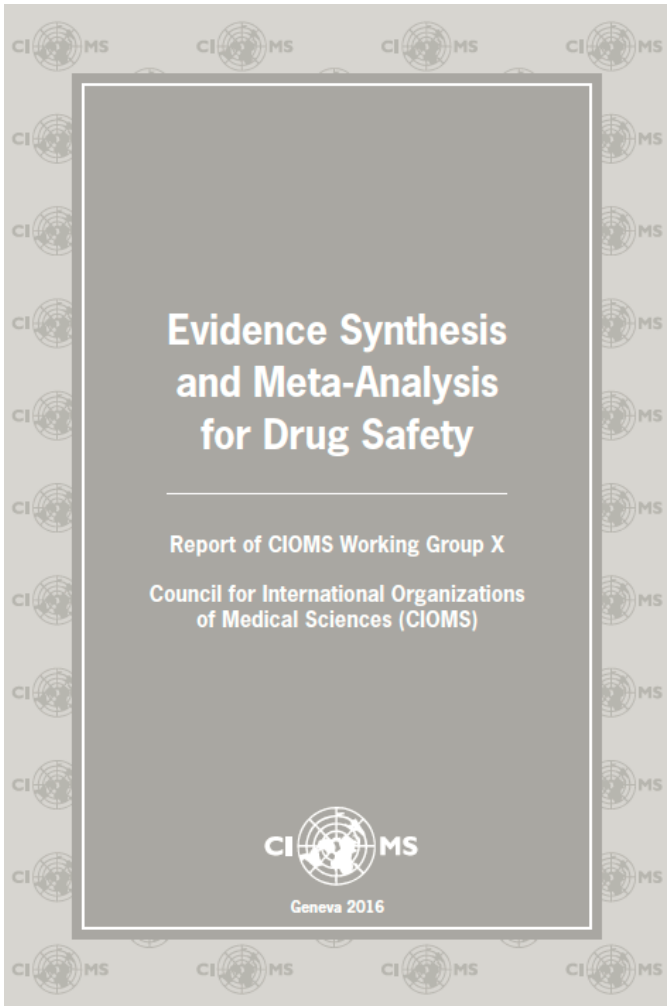
H. Amy Xia[1], Haijun Ma[1], and Bradley P. Carlin[2]
[1]*Amgen, Inc., Thousand Oaks, California, USA*
[2]*University of Minnesota, Twin Cities, Minnesota, USA*

Detection of safety signals from clinical trial adverse event data is critical in drug development, but carries a challenging statistical multiplicity problem. Bayesian hierarchical mixture modeling is appealing for its ability to borrow strength across subgroups in the data, as well as moderate extreme findings most likely due merely to chance. We implement such a model for subject incidence (Berry and Berry, 2004) using a binomial likelihood, and extend it to subject-year adjusted incidence rate estimation under a Poisson likelihood. We use simulation to choose a signal detection threshold, and illustrate some effective graphics for displaying the flagged signals.

Key Words: Bayesian hierarchical models; Clinical trials; Drug safety; Multiplicity; Signal detection.

Safety evaluation of Clinical Trial Data





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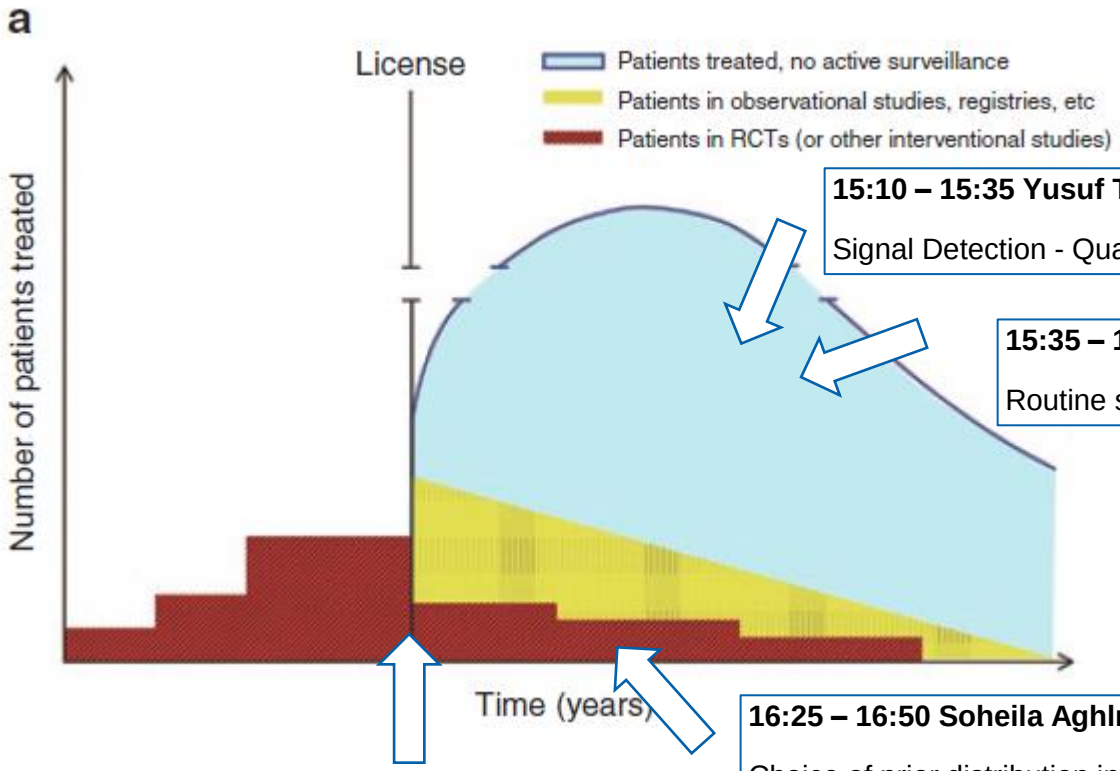
Today's agenda



15:10 – 15:35 Yusuf Tanrikulu, Roche

Signal Detection - Quantitative analysis of safety data

15:35 – 16:00 Gianmario Candore, EMA

Routine signal detection at EMA

16:25 – 16:50 Soheila Aghlmandi, University Bern

Choice of prior distribution in rare-events meta-analysis

16:00 – 16:25 Pritibha Singh, Novartis

ADR screening in Clinical Trials

16:50 – 17:00 Marisa Bacchi, Actelion

Discussion

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Possible topics for future BBS seminars

New FDA Regulation to Improve Safety Reporting in Clinical Trials

Rachel Behrman Sherman, M.D., M.P.H., Janet Woodcock
Cheryl Grandinetti, Pharm.D., and Robert J. Temple, M.D

As part of an initiative designed to modernize the clinical trial enterprise, the Food and Drug Administration (FDA) recently published a regulation establishing a new safety-reporting paradigm for drugs being studied under investigational new drug applications (INDs).[1] This rule — published last September and effective as of March 28, 2011 — is one in a series of steps the FDA is taking to enhance the protection of human subjects and improve trial conduct by streamlining the regulatory procedures for clinical trials.

Monitoring patient safety during clinical trials is a critical component of the drug-development process. Such monitoring is a dy-

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vestigators, r
trial sponsor
ing to the FDA, all investigators, and institutional review boards (IRBs) of serious new adverse reactions. Although safety databases are scrutinized when applications for marketing approval are submitted, ongoing safety analyses during trials are critical in ensuring that serious adverse events are discovered as soon as possible. Safety data from ongoing clinical trials influence the clinical care of patients enrolled in those and other trials of a given drug; if the drug is already on the market, these data may affect its clinical

responsibilities of clinical investigators and IND sponsors with respect to the reporting and analysis of serious, unexpected events

Signal detection in ongoing clinical trials

DIA DEVELOP INNOVATE ADVANCE

Original Research

Statistical Analysis of Cumulative Serious Adverse Event Data From Development Safety Update Reports

Brian Davis, MBChB[1], and Harry Southworth, PhD[2]

Therapeutic Innovation & Regulatory Science
1-7

sagepub.com/journals/Permissions.nav
DOI: 10.1177/2168479015602735
tirs.sagepub.com

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Possible topics for future BBS seminars

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 February 2014
EMA/204715/2012

Guideline on good pharmacovigilance practices (GVP)

Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators

Draft finalised by the Agency in collaboration with Member Stat submitted to ERMS FG	
Draft agreed by ERMS FG	
Draft adopted by Executive Director	
Released for consultation	
End of consultation (deadline for comments)	
Revised draft finalised by the Agency in collaboration with Mem States	
Revised draft agreed by ERMS FG	29 January 2014
Revised draft adopted by Executive Director as final	21 February 2014
Date for coming into effect	1 March 2014

How to measure effectiveness of additional Risk Minimization Measures?

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Possible topics for future BBS seminars

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022

1. Advancing Postmarketing Drug Safety Evaluation Through Expansion of the Sentinel System and Integration into FDA Pharmacovigilance Activities

FDA will use user fee funds to conduct a series of activities to systematically implement and integrate Sentinel in FDA pharmacovigilance practices. These activities will involve augmenting the quality and quantity
improving methods for determining
comprehensive training of review st

Signal detection in observational data

a. FDA will work toward e
enhancing the system's c

b. FDA will enhance its communication with sponsors and the public regarding general methodologies for Sentinel queries, including what the Agency has learned regarding the most appropriate ways to query and use Sentinel data. This can be done through enhancement of existing mechanisms and/or greater frequency of such mechanisms.

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What are you interested in ?

BBS Seminar on

Safety monitoring during the life cycle of a drug

29 November 2016

Please give us your feedback

1. "Safety monitoring" is a relevant topic for me

☐ Yes

☐ No

2. I got valuable insights by today's seminar

☐ Yes

☐ No

3. I'm interested in future seminars about "Safety monitoring"

☐ Yes

☐ No

4. These are topics I'm interested in

_____

_____

_____

My professional role is (e.g. statistician, physician in drug safety)

_____

Please fill the survey or send me an e-mail

conny.berlin@novartis.com

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