



Science For A Better Life



The Estimands Concept - Experiences when Introducing the Concept in a Global Development Organization

PSI One Day Meeting: Estimands – Examples for Statisticians! – Reading, UK

2017-09-27 / PD Dr. Christoph Gerlinger, Dr. Michael Kunz



Agenda

- Introduction and Problem Statement
- Statisticians' working group
- Literature review and white paper
- Pilot workshops with clinicians
- Plans for Roll-Out
- Summary



Acknowledgements & Disclaimer

Part of this presentation is work in progress and the talk represents the current thinking of the authors and are not to be considered as official positions of BAYER.

Thanks to all the members of the BIC group on Estimands

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Introduction

The new estimands framework laid out in draft ICH-E9 (R1) has major implications on almost all aspects of drug development trials.

- *“The construction of the estimand(s) in any given clinical trial is a multi-disciplinary undertaking including clinicians, statisticians and other disciplines involved in clinical trial design and conduct.” Draft ICH-E9 (R1), lines 290-1.*

Estimands framework laid out in ICH-E9 (R1) not (yet?) reflected in other guidances, e.g. on content of protocols or clinical study reports

Despite being a multidisciplinary topic it is often perceived as an exclusively statistical topic in adjacent functions like medical, project management, or regulatory affairs.

Problem Statement Influencing an Organization



Who?

Statisticians, Clinicians, Regulatory Affairs, Project Management

What?

Introductory material, examples, templates

When?

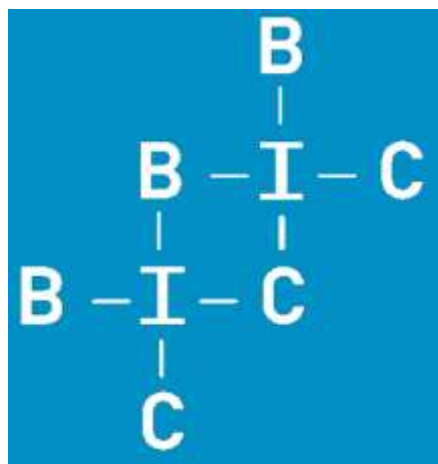
In which order?

Bayer's Approach to Biostats Innovation

No dedicated „Statistical Methods Group“ of full-time innovators

Instead: virtual Biostatistics Innovation Center, founded in 2011

- Voluntary work groups of statisticians on any topic relevant to Bayer
- Groups across organizational units and locations
- Work is recognized by BIC steering committee
- 20 BIC groups currently active



Kulmann et al. The Biostatistics Innovation Center at Bayer.
Biopharmaceutical Report 23(3) 2016.

https://higherlogicdownload.s3.amazonaws.com/AMSTAT/fa4dd52c-8429-41d0-abdf-0011047bfa19/UploadedImages/BIOP%20Report/2016_Fall_BR.pdf
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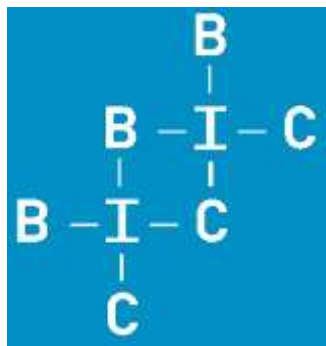


The BIC group on estimands

Founded early 2016

Largest BIC group to date:
18 members from 3 sites and all
statistics functions.

Mandate: To prepare the statisticians
and the whole company for the
changes in the way we plan, run, and
analyze clinical trials in the future.



How did we get started?

Read and discuss the relevant papers

- Summarize the papers on a few slides

Discuss first examples from our work

- Oral contraceptives: relevant difference in efficiency between *treatment policy* (failure rate ~4% regardless of intake failure) and *principal stratum* (failure rate <1% if taken according to label)
- Pelvic pain due to endometriosis: how to handle the intercurrent event „intake of additional pain killers (rescue medication)“

Develop white paper on the topic

Summaries of key publications

15 key papers summarized in 5-10 slides

Papers and summaries

- discussed in BIC group
- Made available to
 - all statisticians
 - clinicians on demand

White paper

Intended for adjacent functions

Real examples from Bayer

1st draft reviewed by interested clinicians

4 pages

What you always wanted to know about “Estimands” but never dared to ask

Christoph Gerlinger, Vivian Lanius, Michael Kunz, Richard Vonk 2016-10-21

Why is this topic important for me?

A new buzzword is around in clinical development: "estimand" (that which is to be estimated). This

White paper content

Why is this topic important for me?

„42“ is the answer, but what exactly was my question?

Now that I know what the question is, how can I define the estimand?

Once I know what the estimand is, how can I determine the trial design and the plan for statistical analysis?

This paper in just five lines:

The new ICH estimands framework will change our clinical studies profoundly. It particularly affects how we define trial objectives, how we define “the treatment effect”, how we collect and interpret data, and how we subsequently label drug effects. The new framework will introduce more clarity for all parties involved and will also help to streamline our development in the sense that we can minimize the risk of not having the necessary data to show the difference for the patient.

Strategy meeting in Q4'2016

BIC-Group on Estimands: Where Do We Want to Go? Where Should We Go?



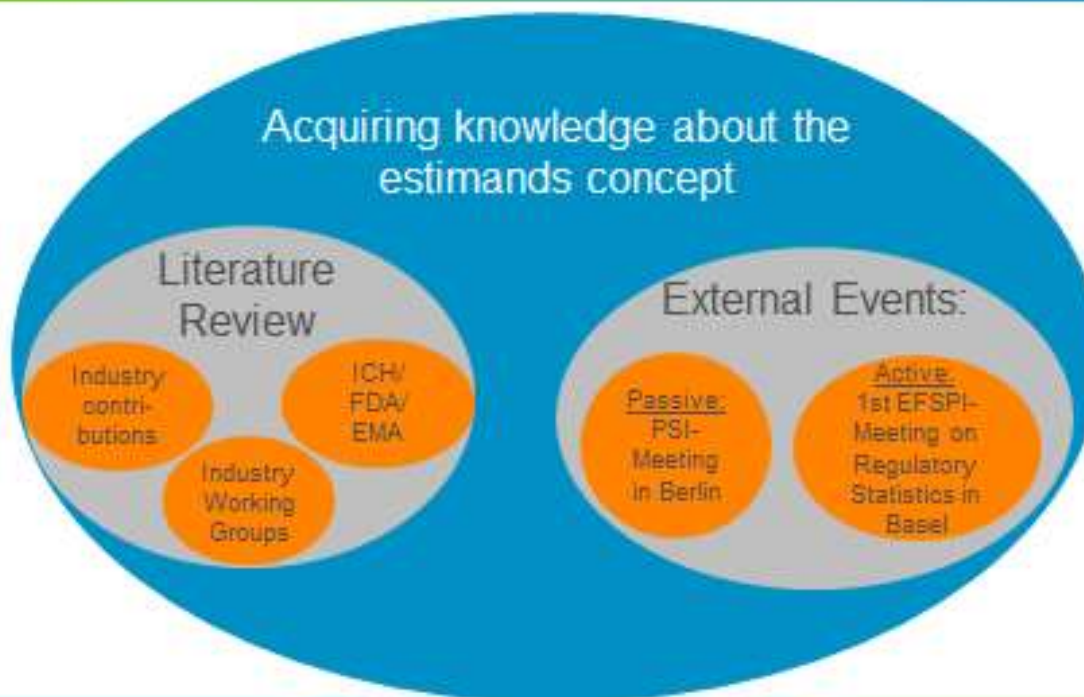
Goals:



When Does BAYER expect contributions from us?

Literature and Conferences

BIC-Group on Estimands:
Where Do We Want to Go? Where Should We Go?



Page 6

Pilot projects



BIC-Group on Estimands:
Where Do We Want to Go? Where Should We Go?



Getting first experiences with the
application/ communication of the
estimands concept - Pilots

Endometriosis

Project X

Project Y

Project Z

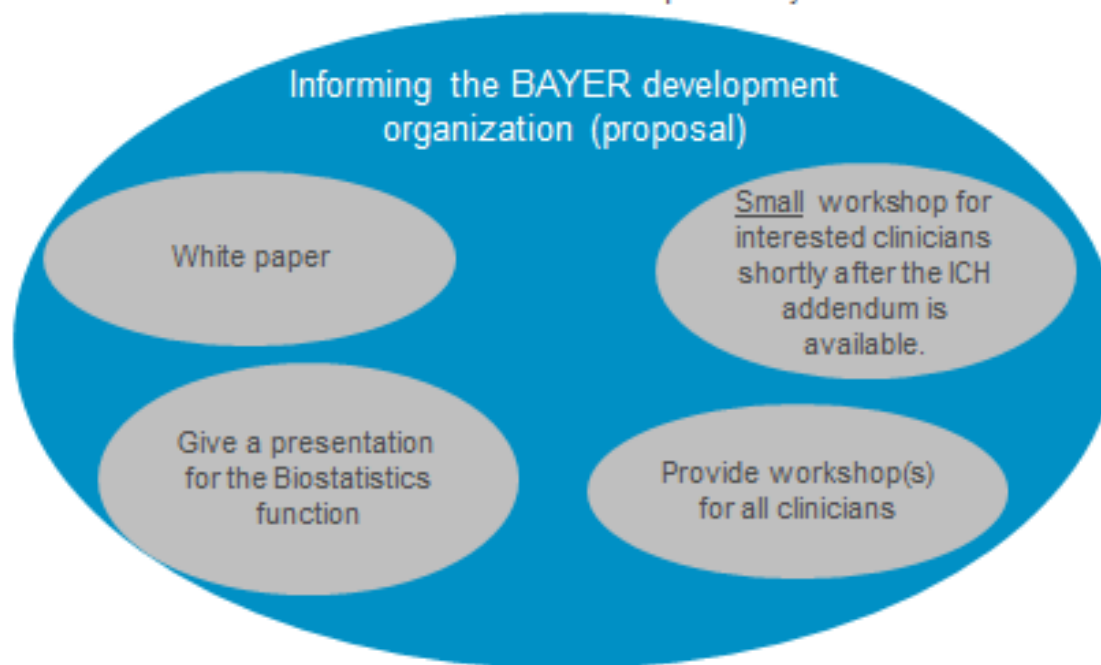
Page 9

Inform the development organization

BIC-Group on Estimands: Where Do We Want to Go? Where Should We Go?



- The first draft of the ICH-E9 addendum is expected by the end of 2016.



Acquiring knowledge

Summaries of the key publications

Creation of a white paper

Conference / Meeting attendance

- Esp. EFPIA/EFSPI workshops in Uxbridge

Engagement in statistical community

- Presentations at industry statisticians meetings (EFSPI in Basel, ASA in US, SSL in Finland, PSI)
- Presentations at academic statisticians meetings (Berlin and Hannover, Germany)

Pilot studies

Applied estimands framework to two studies in two therapeutic areas

- One pilot in early development.
- One pilot in late development

Worked well in late development, less in early development

Many „technicalities“, e.g. where to fit the estimands into the protocol

Time consuming discussions, not only due to novelty of framework

Regulatory consultation is pending

Pilot workshops

Two pilot workshops (EU and US)

- Lunch-and-Learn face-to-face meetings
- Aimed at clinical leads interested in methodology

Concept adapted from EFSPI/EFPIA workshop in January 2017 (Thanks to Chrissie Fletcher, Frank Bretz, et al.!!)

- shortened to 3 hours
- White paper as pre-read
- Examples from Bayer indications
- Clinicians „randomized“ to breakout group discussing example from other area
- Small breakout groups 3-4 clinicians + moderator from BIC group

Agenda of pilot wokshop



Agenda

10:30h	Welcome
10:35h	Introduction to the Estimands Concept
11:45h	Split into Breakout Groups and Fingerfood Lunch
12:45h	Summary
13:15h	Closure of the Workshop

Page 12 | Estimands Workshop, 03 May 2017



Learnings from pilot workshops

Very good attendance, not only from clinicians

Short pre-read and one hour introduction well received

Examples from Bayer indications were very helpful

Good idea to „randomize“ to example from other therapeutic area (do not get lost in details of your own study)

Time for breakout session perceived too short but 3 hours lunch-and-learn

- perceived as long before the workshop
- perceived as short after the workshop

Plans to roll out the estimands concept

Plan to have a second worldwide F2F meeting of BIC group in Q4'17 to

- Discuss draft ICH E9 (R1) text
- Update white paper
- Detailed plans for roll-out
 - Within the statistics department
 - Within adjacent functions (clinical, medical, regulatory, medical writing, project management, ...)

Training for statisticians

Read draft ICH-E9 (R1) and summarize for (clinical) statisticians

Address „technicalities“, e.g. where to fit the estimands into the protocol template

Develop training on principal stratification methods

Workshops for adjacent function

Revised version of the pilot workshops with a mix of functions

- Clinical development
- Medical affairs
- Regulatory affairs
- Medical writing
- Project management
- ...

Summary

Preparing for ICH E9 (R1) is a huge effort

- For statistics
- For the adjacent functions

Discussing estimands takes more time than discussing objectives in clinical teams

Measures taken at Bayer seem to work well

- White paper
- Workshops

References



- C. Gerlinger and M. Kunz 'Some Thoughts on Estimands in a Chronic Pain Indication', 1st EFSPi-Workshop on Regulatory Statistics, September 2016
- Christoph Gerlinger, Vivian Lanius, Michael Kunz, Richard Vonk. *What you always wanted to know about "Estimands" but never dared to ask*. September 2016
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Thank you!