Interactions with Regulators in EU

PD Dr. Christoph Gerlinger
EFSPI regulatory chair

Paris 2016-07-05

EFSPI/PSI Regulatory Affairs Committee

- Co-ordinates review of regulatory guidance within EFSPI members

- Chair Anna Berglind (PSI), co-chair Christoph Gerlinger (EFSPI)

- Members

  - UK: Chrissie Fletcher, Daniel Evans, Frances Lynn, Jon Blatchford, Julie Anderson, Jürgen Hummel, Kerry Gordon, Lesley France

  - FR: Maylis Coste; SE: Anna Berglind, Per Larsson; DE: Christoph Gerlinger, Ruthild Sautermeister; BE: Anne Daniau; IE: Erika Daly; CH: Kaspar Rufibach

  - Companies: Amgen, AZ, Bayer, BI, BioMarin, Grünenthal, GSK, Icon, Medicomp, Novo, PDD, Pfizer, Quintiles, Roche, Servier

- 7 countries represented (+3 from last year)

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Key activities in the past year

Meeting with MHRA statisticians 2015-09-14

  Summary to be published

Meeting with BSWP 2015-10-09

  Summary plublished in EFSPI newsletter

Contributed to EMA workshop on extrapolation 2016-05-17/18

  Co-organized by Christoph

  Presentation by Marisa

Upcomming activities

Meeting with MHRA statisticians (tbd Nov/Dec)

Meeting with BSWP (Sep 30th)

Expert groups to prepare for commenting

    Estimands

    Extrapolation

    Statistics in CMC

1st EFSPI regulatory statistics workshop

1st EFSPI regulatory statistics workshop

- Scientific Committee: Norbert Benda, Egbert Biesheuvel, Hans Ulrich Burger, Tim Friede, Christoph Gerlinger, Armin Koch, David Wright and Emmanuel Zuber
- Venue Biozentrum Basel

1st EFSPI regulatory statistics workshop

- Session 1: Estimands, upcoming guidelines
  - Thomas Permutt (FDA), Norbert Benda (BfArM), Mouna Akacha (Novartis)

- Session 2: Implications of Estimands Selection on Labeling
  - Ann-Kristin Leuchs (BfArM), Kaspar Rufibach (Roche), Chrissie Fletcher (Amgen), Christoph Gerlinger/Michael Kunz (Bayer)

- Session 3: Extrapolation (e.g. from adults to children)
  - Jacob Brogren (MPA), Kristina Weber/Armin Koch (MH Hannover), Michael Looby (Novartis)

- Session 4: Risk Benefit assessments
  - David Wright (MHRA), George Quartey (Roche), Alexander Schacht (Lilly)

- Session 5: Statistics in Quality and Quality Attributes
  - Jens Lamerz (Roche), Bruno Boulanger (Arlenda), EU regulatory statistician (tbd)

- Session 6: Short topics discussions [debate]

Your input please:

What are your hot topics to discuss with regulatory statisticians?

Topics for discussion with BSWP needed by July 7th

Update on data sharing

PD Dr. Christoph Gerlinger
EFSPI regulatory chair

Paris 2016-07-05

Key Activities

5 papers from EFSPI working party on data sharing in BMC Medical Research Methods (scheduled for July 8th)

Commented on ICMJE data sharing proposal

Participated at Data Sharing Conference Wellcome Trust / MRCT Center of BWH and Harvard

Uptake of data sharing

not many requests for 3019 studies listed

Number of Research Proposals submitted up to 31 May 2016		218
Data Analysis	In process	93
	Withdrawn by the requestor	1
	Complete	1
Publication	In process	0
	Published and/or results summary received View details of these research proposals	1
	No publication or results summary (18 months after data access closed)	0

ClinicalStudy
DataRequest.com

As of 2016-07-01

Update on ICH E9(R1) Estimands and Sensitivity Analyses

Chrissie Fletcher

EFPIA lead for E9 WG

Paris 2016-07-05

Seeking harmony: estimands and sensitivity analyses for confirmatory clinical trials

Devan V Mehrotra[1], Robert J Hemmings[2], Estelle Russek-Cohen[3], on behalf of the ICH E9/R1 Expert Working Group

Abstract

In October 2014, the Steering Committee of the International Conference on Harmonization endorsed the formation of an expert working group to develop an addendum to the International Conference on Harmonization E9 guideline ("Statistical Principles for Clinical Trials"). The addendum will focus on two topics involving randomized confirmatory clinical trials: estimands and sensitivity analyses. Both topics are motivated, in part, by the need to improve the precision with which scientific questions of interest are formulated and addressed by clinical trialists and regulators, specifically in the context of post-randomization events such as use of rescue medication or missing data resulting from dropouts. Given the importance of these topics for the statistical and medical community, we articulate the reasons for the planned addendum. The resulting "ICH E9/R1" guideline will include a framework for improved trial planning, conduct, analysis, and interpretation; a draft is expected to be ready for public comment in the second half of 2016.

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Current practices in choosing estimands and sensitivity analyses in clinical trials: Results of the ICH E9 Survey

C. Fletcher*[1,2], S. Tsuchiya[3,4], D. Mehrotra[5] on behalf of the ICH E9(R1) Working Group

[1]Amgen Ltd., 240 Cambridge Science Park, Milton Road, Cambridge CB4 0WD, UK

[2]Clinical Development Expert Group, European Federation of Pharmaceutical Industries and

Submitted and under review by TIRS
(DIA Journal)

[5]Merck Research Laboratories, 351 N. Sumneytown Pike, North Wales, PA 19454, USA

*email: fletcher@amgen.com (phone: +44 1223 436264)

Abstract

An addendum to the International Conference on Harmonisation E9 guidance document (Statistical Principles for Clinical Trials) is currently under development. The aim of the addendum is to promote harmonised standards on the choice of estimand (well defined measure of the treatment effect that is being estimated) in clinical trials, and describe a consensual framework for planning,

E9 WG Progress

- Detailed technical discussions what defines an estimand and which estimands can be estimated
  - Causal Inference (Rubin) versus Statistical Inference (Lehmann)
  - 'Classes' of estimands, 'valid' estimands
- How best to update E9?
  - Addendum has major impact to analysis sets, missing data, and sensitivity analyses
- Preliminary case studies shared of impact of E9(R1) on protocol writing
- Impact of E9(R1) to other E documents (e.g. E3, E6, E8)

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E9 WG Key Milestones

- Finalise technical document (addendum) for sign-off by ICH Assembly at next ICH conference (7-10th Nov 2016)

- Long public consultation period anticipated

- Developing technical appendix

- Continue local consultations
  - EFSPI
  - EFPIA
  - Others?

IMI Update

Survey results

Paris 2016-07-05

Q37: In which of the following initiatives is your team involved
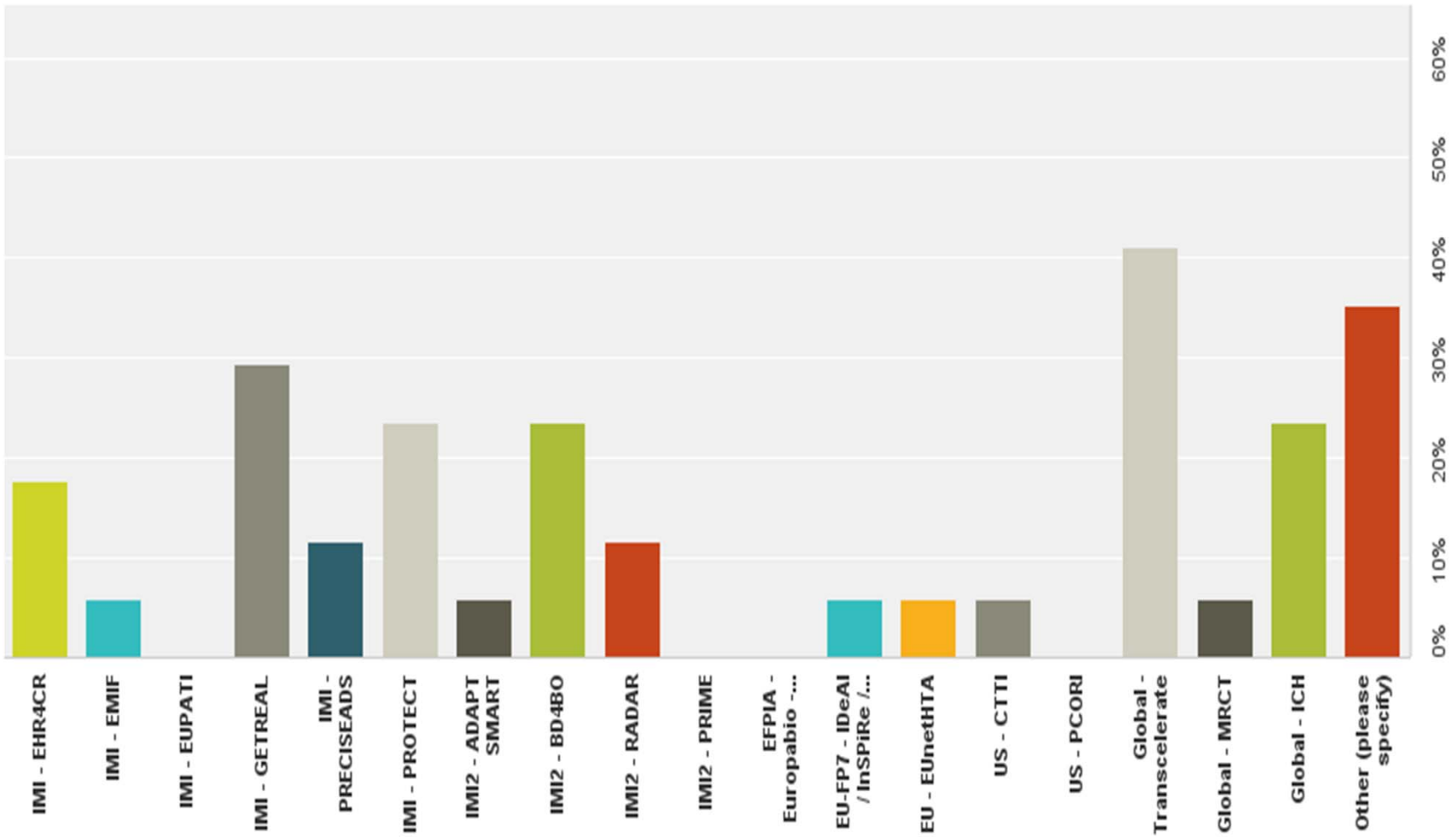
IMI GetReal

Overall objectives

GetReal aims to show how robust new methods of RWE collection and synthesis could be developed and considered for adoption earlier in pharmaceutical R&D and the healthcare decision making process. This will require companies, healthcare decision makers and other stakeholders to work together to generate a consensus on best practice in the use of RWE in regulatory and reimbursement decision-making.

Alternative evidence generating strategies will deliver more focused research in pharmaceutical R&D, and allow healthcare decision makers to be more certain when providing patients with access to new treatments.

Example GetReal Outputs

Methods
- Detection of bias
- Adjustment of bias
- Aggregate RWD in NMAs
- Individual patent RWD in NMAs

Original research
- Drivers of effectiveness
- Analytical methods
- Prediction models
- Methodological guidance

Tools
- Software
- Checklists & templates
- Design options for pragmatic clinical trials

Summaries
- Study types
- Sources of data
- Methods
- Literature reviews

Case studies
- Retrospective analyses of relative effectiveness issues
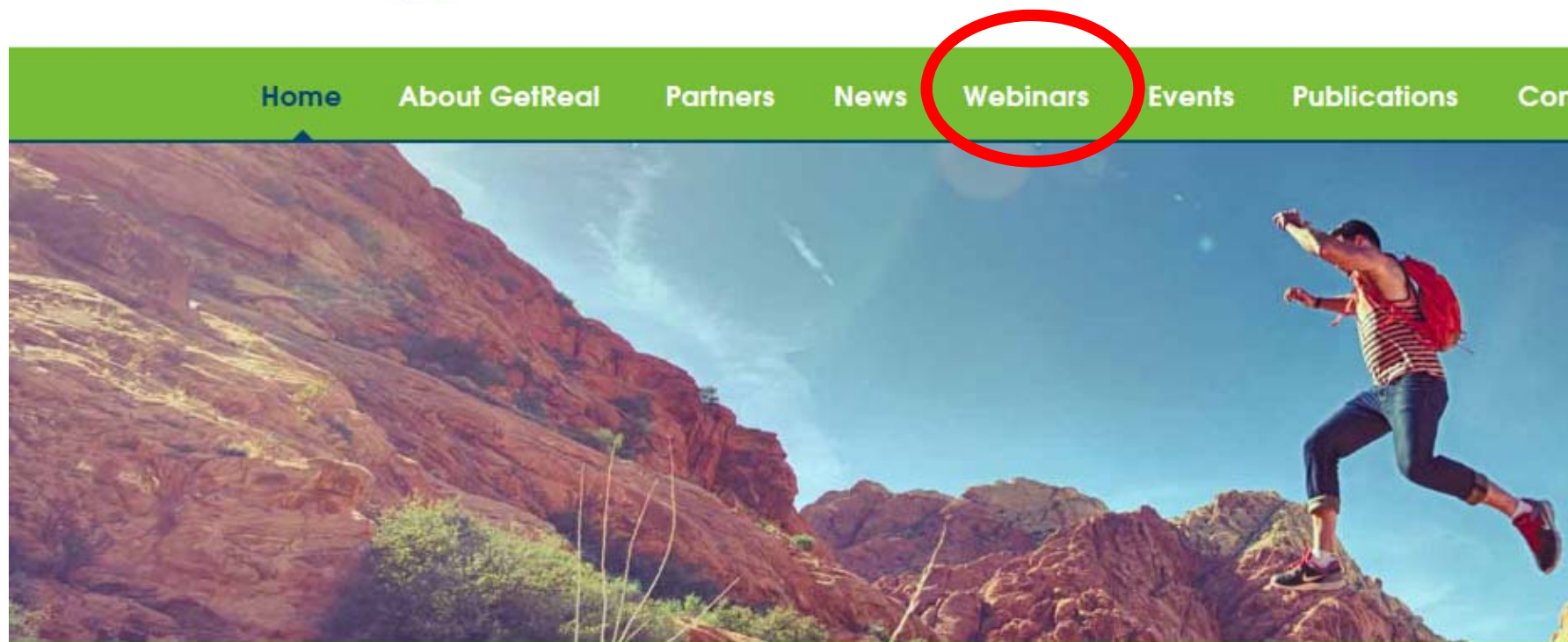- Disease area specific issues
- Stakeholder views

Illustrative examples – not a complete list of GetReal outputs

Evidence synthesis and predictive modelling

- Involvement of statisticians in network meta-analyses / indirect comparisons
  - Following best practices
  - HTA agencies note some NMA applications poor quality
- Methodology and approaches are evolving
  - RCT and Non-RCT expertise
- Use of modelling and risk algorithms increasing
  - Opportunities for statisticians

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https://www.imi-getreal.eu/

WP4 webinar - Synthesis and integration of real-world evidence in network meta-analyses and outcome prediction

10 May, 2016 - 15.00-16.00 CET (14.00-15.00 UK time)

Download the webinar slide pack

Bridging efficacy to effectiveness: The IMI GetReal project

Meta-analyses, outcome prediction, evidence synthesis and modelling

WP4 Webinar 10 May 2016

Read the webinar report

WP4 webinar report

GetReal Events

Save the date!

This WP4 webinar is part of a series of outputs on IMI GetReal foreseen throughout 2016:

SPEAKERS

Matthias Egger
Director of the Institute

Christine Fletcher
Executive Director

Eva-Maria Didden
Postdoctoral research

Georgia Salanti
Research group leader at

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On behalf of GetReal, Workpackage 4 (WP4) invites you to our Stakeholder Workshop:

Evidence Synthesis and Predictive Modelling of Relative Effectiveness

PAVING THE WAY TO BEST PRACTICE

Date: 15th September 2016 (9.30 – 16.30 BST)

Venue: Thistle Holborn, The Kingsley, Bloomsbury Way, London WC1A 2SD

EFPIA Update

Paris 2016-07-05

New model has simpler structure with clearer decision-making responsibilities

	Board				
BSCs	**Patient Access**	**Innovation**	**International**	**Finance/ Operations**	**Director-General**
Priority WGs (cross-functional)	HTA	IMI Strategy	U.S. & Canada		Ethics & Compliance
	LoE Biologics**^	Clinical Trials	Growth Markets		Communications
	Orphan Drugs***	Data Protection	Global Health*		Brussels Advocacy
	Supply Chain	Adaptive Models			
	Health Systems	ATMPs**			
	Pricing/ Reimbursement	Personalised Meds**			
Expert WGs (functional)	Competition	Intellectual Property	International Regulatory		Patient Think Tank
		EU Regulatory			PIE****
		Preclinical Development			
		Pharmacovigilance			
		Clinical Development			
		Regulatory IT			
		Technical Development			
		Envi Health & Safety			
		Animal Welfare			
		EFPIA Security Forum			
		IMI Operational Group			

← 2+ statisticians

European Markets Committee (EMC)	
CEE Taskforce	
Greece Taskforce	

Notes: *Coordinated with IFPMA/ PhRMA; **With EBE; ***With EBE/ Europabio; ****With AESGP/ EGA; ^Covering Access, not Regulatory; **BSC** = Board-Sponsored Committee; **WG** = Working Group; **ATMP** = Advanced Therapy Medicinal Product; **LoE** = Loss of Exclusivity; **PIE** = Pharmaceuticals in Environment; **HTA** = Health Technology Assessment; **IMI** = Innovative Medicines Initiative;

efpia

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