The Changing Environment for Drug Development and Drug Licensing in Europe after ICH

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- My History with regulatory science
- Emerging Health Technology Assessments in Europe
  - NICE
  - IQWiG
- My German experience
  - How it works in general
  - Three examples
  - Outlook

MyHistory, starting back in the Eighties

Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services

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Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR THE FORMAT AND CONTENT
OF THE CLINICAL AND STATISTICAL SECTIONS OF AN APPLICATION

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July 1988

July 1988

CPMP 1993

BIOSTATISTICAL METHODOLOGY IN CLINICAL TRIALS

Guideline Title	Biostatistical Methodology in Clinical Trials
Legislative basis	Directive 75/318/EEC as amended
Date of first adoption	May 1993
Date of entry into force	October 1993
Status	Last revised May 1993
Previous titles/other references	*Biostatistical methodology in clinical trials in applic.* *for Marketing Authorisations for Medicinal Products* III/3630/92,

ICH E9, 1998

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9

Dated 5 February, 1998

European Statistical Activities following ICH E9

- 2000 Points to Consider on Switching between Superiority and Non-inferiority
- 2001 Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study
- 2001 Missing data in confirmatory clinical trials, draft 2009
- 2002 Points to Consider on Multiplicity Issues in Clinical Trials
- 2003 Points to Consider on Adjustment for Baseline Covariates
- 2005 Choice of a Non-Inferiority Margin
- 2007 Methodological Issues in Confirmatory Clinical Trials planned with an adaptive design
- 2010 Concept Paper on Subgroup Analyses

Recently FDA released Guidance

- 2010 Noninferiority Clinical Trials
- 2010 Adaptive Design Clinical Trials for Drugs and Biologics
- 2013 Oversight of Clinical Investigations – A Risk based Approach to Monitoring

Regulatory disharmonies

- Jorgen Seldrup reports discussion from MCP 2011
  - Does the FDA care if EMA wants something different?
  - FDA-representative: ”No”
  - visa-versa: propably „No“
- New treatment T, placebo P and activ control C, and one region wants T v. P as primary and the other wants T v. C
  - Consequences on patient accrual in respect to placebo arm
- Designing multiregional clinical trials with
  - Different inclusion criteria
  - different regional required primary endpoints
  - …
- **When do differences begin to make a difference?**

Diverging Developments even in the ICH Regions.

More Divergence through Foundation of National Health Technology Assessment Agencies

HTA is represented in this talk by
- NICE (UK) and
- IQWiG (Germany)

National Institute for Health and Care Excellence
NICE increasing responsibilities over the years

- in 1999 founded
  - as the National Institute for Clinical Excellence,
  - to reduce variation in the availability and quality of NHS treatments and care.
- In 2005,
  - began developing public health guidance to help prevent ill health and promote healthier lifestyles.
  - name changed to National Institute for Health and Clinical Excellence.
- In April 2013
  - responsibility for developing guidance and quality standards in social care
  - National Institute for Health and Care Excellence

Institute for Quality and Efficiency in Health Care - IQWiG

- Objective: To examine objectively the advantages and disadvantages of medical interventions for patients.
- Since 2004
  - Institute for Quality and Efficiency in Health Care (IQWiG for short).
- The Institute produces independent, evidence-based reports, e.g. on:
  - drugs
  - non-drug interventions (e.g. surgical procedures)
  - diagnostic tests and screening tests
  - clinical practice guidelines (CPGs) and disease management programmes (DMPs)

NICE /IQWiG

- On the first glance: Similar objectives
- NICE appraises in addition cost effectiveness
- NICE can delegate review and appraisal to groups outside (usually academic institutions).
  - Four standing Appraisal Committees (each about 20 members including biostatisticians)
- IQWiG includes outside experts into its review team but retains key positions
- IQWiG receives its tasks from G-BA (Joint Federal Committee) and prepares and proposes decisions.
  - Decisions are solely made by G-BA.
  - G-BA has 13 voters from Health Insurance, Hospitals, Physicians Unions,…
    - (no biostatisticians, currently a majority of economists).

Guidances, Guidances, Guidances

- NICE
  - Guides to the Methods of Technology appraisal (2008)
  - Technical reports:
    - introduction to evidence synthesis for decision making
    - for pairwise and network meta-analysis of RCTs
    - …
- IQWiG
  - General Methods 4.0 in 2011
  - Aktualisierung (draft 2013)
  - General methods to evaluate cost and benefit (2009)
  - …

My German experiencs with HTA

GB-A/IQWIG-Problem Areas all of which have close relations with biostatistical methodology

- Definition of comparators
- Subgroups
- Endpoint definition
- Type I error control
  - Multiple testing
  - Predefined analyses
- Categorisation/dichotomisation

Main Problem Areas I – G-BA/IQWIG

- Definition of different comparators in subpopulations
  - Results in unforeseeable partitition („slicing“) of RCTs
  - Increased need for indirect comparisons. However, subpopulation characteristics (mean, std, etc) rarely contained in publications.
  - Makes randomisation dependent on post hoc variable selection.
- Subgroup analyses
  - Disregarding of post hoc character
  - Mechanistic use of interaction tests
- Endpoint definition
  - Preferred GB-A views result in unplanned endpoints
  - Necessitates own IQWiG (post-hoc) calculations (sometimes with errors)

Main Problem Areas II – G-BA/IQWIG

- Type I error Control
  - Is more or less abandoned
  - Is replaced by rather intransparent methods on aggregation of information
- General technique: Categorisation – One size fits all
  - Categorisation of uncertainty
    - 3 categories: Hint (clue); indication(suggestion); proof (substantiation)
  - Categorisation of additional clinical benefit
    - 3 categories: Gering(Small); beträchtlich(important); Erheblich(major)

Examples

- Ticagrelor – Brilinta (ACS)
- Fingolimod – Gilenya (MS)
- Sitagliptin (DM)

Example I – Ticagrelor (FDA wording)

- The disease: BRILINTA is a P2Y12 platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction).
- Endpoint: BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel.
- Some details: The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

Example I – Ticagrelor (EMA wording)

- the CHMP considered by consensus that the risk-benefit balance of Brilique co-administered with acetylsalicylic acid (ASA) in the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with ACS
  - (unstable angina,
  - non ST elevation Myocardial Infarction [NSTEMI] or
  - ST elevation Myocardial Infarction [STEMI])
    - including patients managed medically,
    - and those who are managed with percutaneous coronary intervention (PCI)
    - or coronary artery by-pass grafting (CABG)
- was favourable and therefore recommended the granting of the marketing authorisation.

Example I Ticagrelor (NICE)

- You should be able to have ticagrelor if you:
  - have a condition called ST-segment elevation myocardial infarction (major heart attack) that your cardiologist intends to treat with a procedure to widen your narrowed artery (called primary percutaneous coronary intervention)
  - a condition called non-ST-segment elevation myocardial infarction (mild heart attack) **or**
  - have been admitted to hospital with unstable angina.

Example I – Ticagrelor (G-BA/IQWiG)

- G-BA: Partitition ("slicing") of the pivotal PLATO study into 4 different (disjoint) populations
  1. Unstabil Angina pectoris and myocardial infarction without ST-elevation (IA/NSTEMI),
  2. Myocardial infarction with ST-elevation (STEMI) managed medically
  3. Patients with STEMI managed with PCI
  4. Patients with STEMI, managed with CABG
- IQWiG Assessment: Additional benefit (proof for medium effect in mortality) only in population 1,
- no additional benefit in 2, 3 or 4 due to lack of data , failure to show superiority in an indirect comparison (Prasugrel, population 3) or small sample sizes.

Example II – Fingolimod (FDA wording)
RRMS – Relapsing Remitting Multiple Sclerosis

- GILENYA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

Example II – Fingolimod (EMA wording)

- Patients with high disease activity despite treatment with a beta-interferon.
  - These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon.
  - …..
  - A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year,
- or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

Example II Fingolimod (NICE)

- Fingolimod is recommended as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if:
  - they have an unchanged or increased relapse rate **or** ongoing severe relapses compared with the previous year despite treatment with beta interferon,
  - **And** the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.
  - NICE recommended fingolimod because it is a valuable new oral treatment for patients with multiple sclerosis.

Example II Fingolimod (IQWiG/G-BA)

- G-BA: Partitition of the study population of the (only) pivotal trial TRANSFORMS (n=1292) into 3 (disjoint) subpopulations
  1. Patients with highly active RRMS, complete pre-treatment with IFN-ß (comparator Glatirameracetat)
  2. Patients with highly active RRMS, incomplete pre-treatment with IFN-ß (comparator IFN-ß 1a))
  3. Patients with rapidly evolving severe RRMS (comparator IFN-ß 1a).
- IQWiG Assessment: None of the 3 subpopulations showed an additional benefit regarding improvement of RRMS.
- In a subpopulation (n=57) a “significant“ reduction regarding of flulike symptoms (non serious AE) led to stating a hint for a small additional benefit [1/27 versus 9/30).

Example II Fingolimod – the role of the regulatory agencies in HTA evaluations

- CHMP had intensive discussions about a potential wordings in the label (see EPAR). It involved several ad-hoc committees and required twenty or more post-hoc subgroup analyses to be submitted by the applicant.
- Finally CHMP decided for the identical wording as for Tysabri (Natalizumab).
- It remained unclear which part of study population really was covered by the final wording of the label.
- Wording has great impact on HTA evaluations
- There are earlier occurrences of discussions in the literature about the wording of the label in relation to the study population [e.g. JUPITER study, contributions by Ridger (Author), Temple(FDA), Day(EMA), Breckenridge(Canada), Clinical Trials 2011]

Example III
Diabetes Mellitus - Sitagliptin (only G-BA/IQWiG)

G-BA:

- 5 different groups/comparators were performed depending on whether Sitagliptin was used as mono or in combination with various other
- Of interest here is the comparison Sitagliptin + Metformin versus Glipizid+Metformin

IQWiG Asssessment: A hint for a strong additional benefit was stated based on a “significant“ finding on mortality

Example III
Diabetes Mellitus - Sitagliptin (only IQWiG).
Discrepancy between p-value and upper CI limit

Dossierbewertung A13-02 — Version 1.0
Sitagliptin – Nutzenbewertung gemäß § 35a SGB V — 27.06.2013

Tabelle 13: Ergebnisse (dichotome Endpunkte) – RCT, direkter Vergleich: Fragestellung A, Sitagliptin vs. Glipizid (Studie P063, Monotherapie mit Sitagliptin, relevante Teilpopulation)

Studie Endpunktkategorie Endpunkt	Sitagliptin		Glipizid		Sitagliptin vs. Glipizid
	N	Patienten mit Ereignissen n (%)	N	Patienten mit Ereignissen n (%)	RR / Peto-Odds Ratio[a] [95 %-KI]; p-Wert[b]
P063					
Mortalität					
Gesamtmortalität	149	0 (0)	154	4 (2,6)[d]	0,14 [0,02; 0,98][c,d] 0,051

Inconsistency: 95%CI: [0.02;0.98], but p-value equals 0.051

Example III
Diabetes Mellitus - Sitagliptin (only IQWiG)

Tabelle 36: Ergebnisse – RCT, direkter Vergleich: Kombination Sitagliptin plus Metformin vs. Glipizid plus Metformin

Studie Endpunktkategorie Endpunkt	Sitagliptin plus Metformin		Glipizid plus Metformin		Sitagliptin plus Metformin vs. Glipizid plus Metformin
	N[a]	Patienten mit Ereignissen n (%)	N[a]	Patienten mit Ereignissen n (%)	RR / Peto-OR[b] [95 %-KI]; p-Wert[c]
P024[d]					
Mortalität					
Gesamtmortalität	588	1 (0,2)	584	8 (1,4)	0,21 [0,06; 0,77]; 0,021

IQWiG Statement: hint for a strong additional benefit

Example III
Diabetes Mellitus - Sitagliptin (only IQWiG)

Kombination Sitagliptin plus Metformin vs. Glipizid plus Metformin — Tabelle 36

Studie Endpunkt Merkmal Subgruppe	Sitagliptin plus Metformin		Glipizid plus Metformin		Sitagliptin plus Metformin vs. Glipizid plus Metformin	
	N[a]	Patienten mit Ereignissen n (%)	N[a]	Patienten mit Ereignissen n (%)	RR / Peto-OR[b] [95 %-KI]	p-Wert[c]
P024						
Gesamtmortalität						
Geschlecht						
Männer	336	1 (0,3)	358	8 (2,2)	0,22 [0,06; 0,82]	0,024
Frauen	252	0 (0)	226	0 (0)	n. b.	n. b.
					Interaktion	n. b.

a: Alle Patienten wie behandelt (APaT-Population: All patients as treated).
b: Angabe des Peto-Odds Ratio statt Relatives Risiko bei Ereigniszahlen ≤ 1 % in mindestens einer Zelle.
c: eigene Berechnung, unbedingter exakter Test (CSZ-Methode nach [11]).
d: Daten aus den Patienten Listings nach Preferred Term.
e: Berechnung basierend auf RR.
f: Berechnung basierend auf Peto-OR.

IQWiG Statement: hint for a strong additional benefit only in men

IQWiG proposal for measuring clinical benefit (categorisation)

IQWiG: Upper limits of the 95%CI for the relative risk (RR) have to fall below the indicated thresholds in order to claim the respective category of additional benefit

Additional benefit	Mortality	•Serious Symtoms/ADRs •Quality of Life	Non serious Symptoms/ADRs
major	0.85	0.75	Not possible
important	0.95	0.90	0.80
small	1.00	1.00	0.90

Looking into the Future of ICH Achievements

Dark clouds at the horizon;

I am not amused

Actually, there are many more Players around, not just NICE and IQWiG:

- Members of EUnetHTA – the Umbrella Association

- · **Austria**
- · **Belgium**
- · **Bulgaria**
- · **Croatia**
- · **Cyprus**
- · **Czech Republic**
- · **Denmark**
- · **Estonia**
- · **Finland**
- · **France**
- · **Germany**
- · **Greece**
- · **Hungary**
- · **Ireland**
- · **Italy**
- **Latvia**
- · **Lithuania**
- · **Malta**
- · **Netherlands**
- · **Norway**
- · **Poland**
- · **Portugal**
- · **Romania**
- · **Slovakia**
- · **Slovenia**
- · **Spain**
- · **Sweden**
- · **Switzerland**
- · **United Kingdom**