Multiregional Trials

Main features and issues raised

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Multiregional Clinical Trials

Definition and Motivation

- A single clinical trial that is conducted simultaneously in multiple geographical regions under a common protocol
- Increasingly, clinical trials are run using patients from various regions worldwide.
  - More patients needed to demonstrate treatment advantages, as new treatments may have only incremental benefits vs existing therapies.
  - Local health authorities would like to see representation / evidence within their domains.
  - Varied settings may enhance confidence in observed effects.
  - Expanded markets interest trial sponsors.

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Multiregional Clinical Trials

Advantages

- Advantages *(Ando, Y. , ICSA/ISBS Conference, 2013)*
  - Prevents unnecessary duplication of clinical trials
  - Makes drug development more efficient and cost-effective
  - Enables simultaneous global drug submission and approval
  - Gets effective and safe drugs to patients faster.

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Example: multiregional trial

679 study centres

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Example of an MRCT

- 7,216 patients were enrolled from 5 geographical regions, 39 countries and 679 study centers.
- 3,581patients were randomized to the drug group and 3,635 to the placebo group.

Region	Number of countries	N	Drug (n)	Placebo (n)	Treatment difference	Standard error	P-value
Asia	5	441	214	227	-6.97	1.675	<.0001
Europe	20	3819	1889	1930	-5.43	0.531	<.0001
Latin America	9	1229	630	599	-3.96	0.991	<.0001
North America	2	1525	750	775	-4.93	0.829	<.0001
Other	3	202	98	104	-3.18	2.258	0.16
Global	39	7216	3581	3635	-5.10	0.391	<.0001

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Regulatory Guidance

ICH E5 and ICH E5 Q&A

Guidance for Industry

E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2006
ICH

Revision 1

A11. **A multi-regional trial ...**

The objectives of such a study would be:
(1) to **show that the drug is effective in the region** and
(2) **to compare the results of the study between the regions** with the intent of establishing that the **drug is not sensitive to ethnic factors.**

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What is a region?

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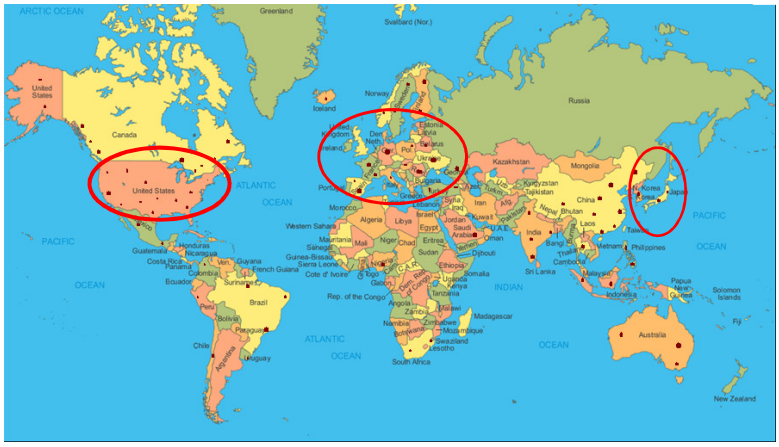
What is a region?

Is it based on geography?



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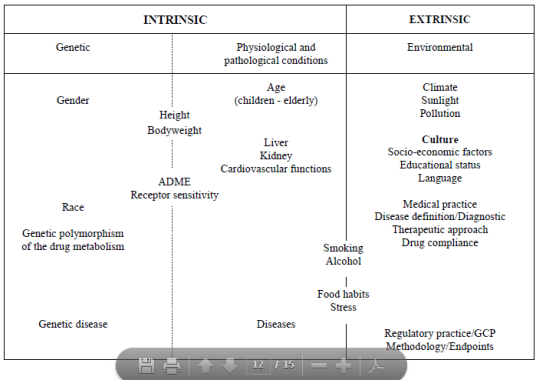
What is a region?

Not necessarily defined by location

- "*... region should not be limited to geographic boundaries but should take into consideration relevant intrinsic genetic and physiological or pathological factors as well as extrinsic factors such as medical practice*" ICH E5.

Appendix A: Classification of intrinsic and extrinsic ethnic factors



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Inconsistency in the definition of regions

Review of 60 FDA Advisory Committee Meetings 2008-2010

- 90% of submissions were multiregional.
  - "Region was most often defined based on geography, and specifically continent ..."
- "No trends or consistency was observed in how regions were defined within or across therapeutic areas nor any rationale for the definition of region ..."
- "We propose that adequate justification of the definition should take into consideration factors such as race or ethnicity, disease epidemiology, medical practice, and geographic proximity, among others."

Tanaka et al. (2011)
[The PhRMA MRCT Key Issue Team]

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PhRMA MRCT KIT Perspective on Region

- "... regions should be predefined in the designs stage and properly documented."
- "... Geography alone may not be adequate when defining regions. ... Intrinsic and extrinsic factors should be considered."
- " Country and site selection should be considered at the design stage as part of predefining regions..."
- Analytical approach to defining regions (e.g., factor analysis, principal components).
- The number of regions should not be large.

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Analysis models for multiregional clinical trials

Fixed or Random effects for regions/centres

Recall: Multicentre Trials

- Fixed-effects Model [centre is a fixed factor]
  - The centers have been specifically chosen. Conclusions reached here only apply to the centers considered and can not be extended to other centers that are not in the trial
- Random-effects Model [centre is a random factor]
  - The centers are a random sample from a large population of centers. Conclusions reached here can be extended to all the centers in the population

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For MRCTs: Are regional estimates fixed or random?

- Surely “region” is a fixed-effect – cannot think of a random sample of regions?
- Possible model might assume centres are randomly nested within the levels of a fixed regional factor.
- However, this are differing opinions in the literature.

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MTCT: fixed or random effects?

Random: Chen, Hung and Hsiao (2012)

- Chen, Hung and Hsiao (2012) define a random effects model for the true treatment difference that applies to region i, i=1,2, ..., M.
- They derive the global estimate of the treatment difference by applying well-known results for the random-effects estimator obtained from a meta-analysis, using the DeSimonian and Laird (1986) estimator of the between region variance.
- Give sample size formula based on global estimate.

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Shrinkage estimates of regional treatment effects

Qui et al. (2013). Statistics in Medicine

- Recommend :
  - fixed-effects model to estimate global effect and
  - estimates of individual region treatment differences using an empirical shrinkage estimator based on a random effects model
  - Individual region estimates borrow strength from other regions' estimates.

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Consistency

Are individual region estimates similar to the global estimate?

- It is (or should be) a basic premise of an MRCT that that there is no, or at most only a small amount of, regional variation
  - Regional variation can be reduced by good design and by inclusion of region-specific covariates in models for the response.
- Should testing for such *consistency* be part of the analysis plan?
  - Sponsor more interested in global estimate
  - Regulator more interested in local estimate for their region
  - Ideally, global estimate of treatment difference is significantly different from zero **and** all regional estimates are significantly different from zero.
  - Sample size implications are different for the two situations.

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Two well-known examples of possible **inconsistency**

- PLATO trial
- MERIT trial

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PLATO Trial

PLATlet inhibition and patient Outcomes trial (Wallentin, et. al., 2009)

- Compare ticagrelor (novel) vs clopidogrel (standard)
- Patients with ACS (acute coronary syndomes)
- Primary endpoint: CV death, MI, stroke
- 18624 patients, followed for a year.

Endpoint	ticagrelor	copidogrel	HR	P-value
Primary	9.8%	11.7%	0.84	<0.001
Death	4.5%	5.9%	0.78	<0.001

- Very strong evidence that ticagrelor is superior.
- BUT...

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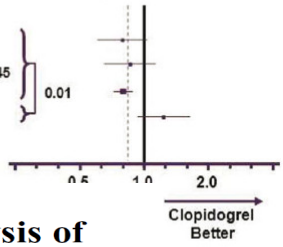
PLATO trial

"Ticagrelor works, except if you're an American" – Stuart Pocock (LSHTM)

Characteristic	Total Patients	KM at Month 12 Tic	KM at Month 12 Clop	HR (95% CI)	Interaction p-values
Geographic Region					
Asia / Australia	1714	11.4	14.8	0.80 (0.61, 1.04)	0.045
Cent / Sth America	1237	15.2	17.9	0.86 (0.65, 1.13)	
Euro / Md E / Afr	13859	8.8	11.0	0.80 (0.72, 0.90)	0.01
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	



Statistical Evaluation and Analysis of Regional Interactions: The PLATO Trial Case Study

02

Kevin J. CARROLL and Thomas R. FLEMING

Statistics in Biopharmaceutical Research
May 2013, Vol. 5, No. 2
DOI: 10.1080/19466315.2013.783878

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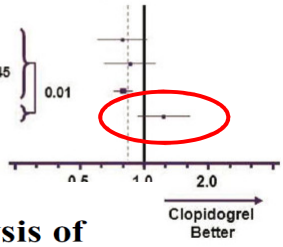

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PLATO: A chance result?

- Given 31 subgroup analyses were done, can this significant interaction be due to chance alone?
- The chance of a "reversal" in sign of estimated treatment difference is not negligible.
- But "region" is a special subgroup and will be of interest to US regulators (FDA).
- Can this "chance" finding be explained?
- Is it caused by the Aspirin (ASA) loading dose and long-term maintenance dose that patients received on day of randomization to treatment?

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Does Aspirin use explain the interaction (?)

Factor	df	Log HR	SE	χ^2	Pr > χ^2
Randomized treatment	1	0.238	0.1638	2.11	0.1459
Country (US and non-US)	1	0.159	0.1264	1.58	0.2095
Country x Randomized treatment	**1**	**-0.443**	**0.1708**	**6.73**	**0.0095**

Significant Treatment by Country interaction

Factor	df	Log HR	SE	χ^2	Pr > χ^2
Randomized treatment	1	-2.735	0.8390	10.63	0.0011
Country (US and non-US)	1	0.289	0.1619	3.19	0.0743
Country x Randomized treatment	**1**	**0.028**	**0.2271**	**0.02**	**0.9023**
Median ASA dose	1	0.196	0.1109	3.12	0.0773
Median ASA dose x Randomized treatment	**1**	**0.542**	**0.1528**	**12.60**	**0.0004**

Region by Country interaction lost when ASA allowed for

ASA by Treatment interaction significant

ASA × treatment interaction explains 1-{0.028/-0.443} ≈ 100% of the country × treatment interaction

Figure 5. ASA dose largely accounts for the U.S./non-U.S. regional interaction.

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MERIT-HF trial

Metoprolol Controlled –Release Randomised InterventionTrial in Heart Failure

Challenges of subgroup analyses in multinational clinical trials: Experiences from the MERIT-HF trial

Hans Wedel, PhD,[a] David DeMets,[c] PhD, Prakash Deedwania, MD, PhD,[d] Björn Fagerberg, MD, PhD,[b] Sidney Goldstein, MD,[e] Stephen Gottlieb, MD,[f] Ake Hjalmarson, MD, PhD,[b] John Kjekshus, MD, PhD,[g] Finn Waagstein, MD, PhD,[b] and John Wikstrand, MD, PhD,[b] on behalf of the MERIT-HF Study Group *Göteborg, Sweden, Madison, Wis, Fresno, Calif, Detroit, Mich, Baltimore, Md, and Oslo, Norway*

American Heart Journal
September 2001

American Heart Journal
Volume 142, Number 3

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MERIT-HF trial in heart failure

Overall results

Endpoint Death	Metoprolol	Placebo	HR	P-value	95% CL Lower limit	95% CL Upper limit
Sample size	1990	2001				
Total deaths	145	217	0.66	0.00009		

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MERIT-HF trial in heart failure

Make USA a subgroup

Endpoint Death	Metoprolol	Placebo	HR	P-value	95% CL Lower limit	95% CL Upper limit
Sample size	1990	2001				
Total deaths	145	217		0.00009		
USA	51	49	1.05		0.71	1.56
Other countries	94	168	0.55		0.43	0.70

Interaction test: P = 0.003

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Break out deaths by country and treatment

country	metoprolol	placebo
Hungary	16	29
Germany	19	31
Netherlands	14	25
Belgium	3	13
Czech Republic	9	17
Sweden	2	9
Norway	6	11
UK	4	9
Finland	0	2
Switzerland	0	1
Iceland	2	2
Poland	8	8
Denmark	11	11
USA	51	49

Why concentrate Interaction test on USA?

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Break out deaths by country and treatment

country	metoprolol	placebo
Hungary	16	29
Germany	19	31
Netherlands	14	25
Belgium	3	13
Czech Republic	9	17
Sweden	2	9
Norway	6	11
UK	4	9
Finland	0	2
Switzerland	0	1
Iceland	2	2
Poland	8	8
Denmark	11	11
USA	51	49

Why focus on USA?

Unlike the PLATO Trial, there seem no reason to believe Interaction is real

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Are the other/better methods to test for consistency?

- Quan et al. (2010b) proposed 5 alternative methods.
- These are of two types:
  - Methods that tend to conclude consistency until there is sufficient evidence to the contrary, e.g., interaction tests
  - Methods requiring a certain strength of signal of similarity in order to conclude consistency, e.g., Japanese MHLW proposals
- Which type is appropriate for a given situation?
- Where should the *burden of evidence* lie?

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Five methods to test for consistency

Quan et al. (2005)

1. Each region should achieve a proportion, π, of the observed overall effect.
2. Each region should achieve a common pre-specified constant value ($b \geq 0$).
3. Demonstrate through hypothesis testing that each region achieves a proportion, π, of the overall effect.
4. A test for treatment-by-region interaction must not yield a significant result.
5. Tests for individual regions having effects lower than the overall effect must all not yield significant results.

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Difficulties in implementation of methods: Method 1

Quan et al. (2010a)

- Trial planned to have 90% power, to detect a one-sided difference between two treatments with significance level 0.025.
- Consider a single region (e.g., Japan) out of the set of regions.
- Let D_J be the estimated treatment effect in Japan and D_{All} be the estimated effect over all regions
- Require $\Pr(\frac{D_J}{D_{All}} > 0.5) \geq 0.8$
- If all treatment effects truly equal in all regions
  - Sample size fraction for Japan = 22.4%
  - Too high for a country with only 2% of the world population

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Conclusions

- Statistical methodology for MRCTs is still evolving
- Experience over time will determine acceptable methods
- Issues relate to conflict in the desire to estimate a global effect versus a local (single region) effect.
- Regulatory agency involvement can focus attention on a single region with unwanted consequences (e.g., for Type I error rate control, effect reversal, etc.) familiar to users of subgroup analysis.
- Definition of “a region” needs to be clarified

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END OF PRESENTATION

ANY QUESTIONS?

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