MRCT ANNUAL MEETING

November 28, 2012, Harvard Faculty Club

HARVARD Global Health Institute

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Welcome and Introduction to MRCT: Goals and Progress

Rebecca Li, PhD, Executive Director	MRCT

HARVARD Global Health Institute

Agenda and Expectations

Barbara Bierer, MD, Senior Vice President of Research, Brigham & Women's Hospital; Professor of Medicine, Harvard Medical School	MRCT

Annual Meeting Objectives

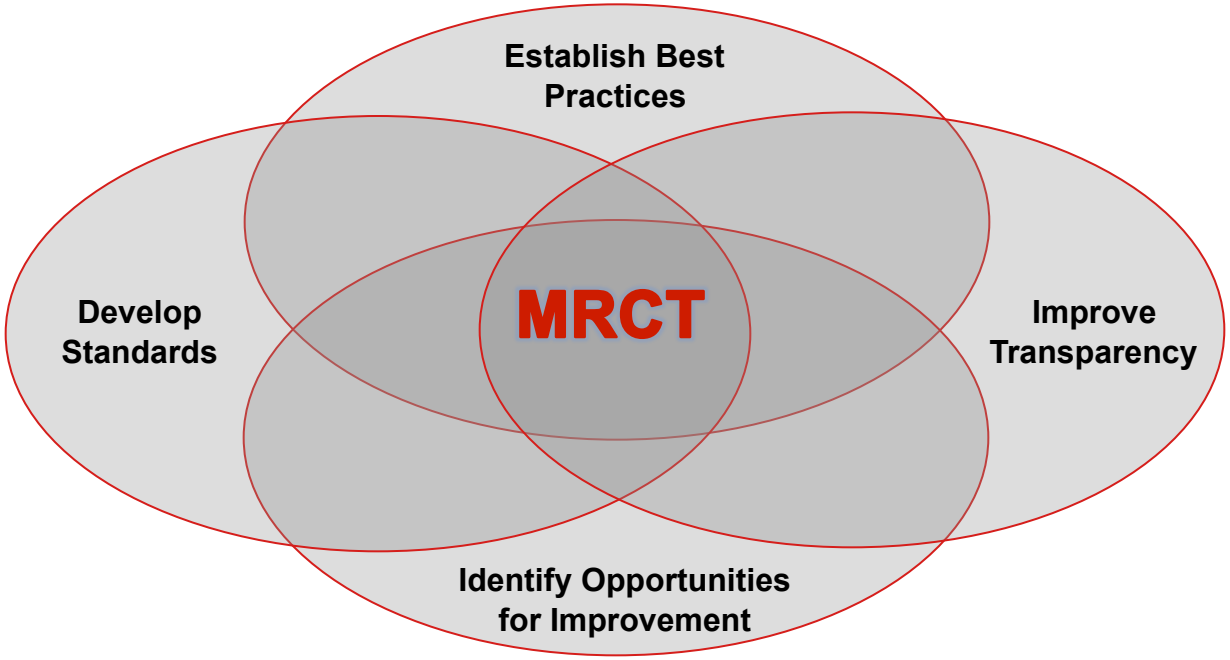
- Provide an update to all stakeholders regarding current initiatives and progress
- Engage regulators in the MRCT initiatives and mission
- Obtain feedback from regulators and stakeholders on MRCT ongoing and planned initiatives
- Collect survey data on potential new initiatives (please complete)
- 2013 Budget and Proposed New Initiatives (EC/SC meeting)

Collaborating to Improve Multi Regional Clinical Trials

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

The MRCT Center's Purpose is… *To improve the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world; to simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research.*

Objectives



HARVARD Global Health Institute

Agenda

Topics	Timing	Presenters / Moderators
Breakfast, Welcome & Overview of Agenda	8:30 – 9:15 am	Barbara Bierer Rebecca Li
Keynote: Regulatory Perspective on MRCT Issues	9:15-10:00am	Robert O'Neill
Roadmap Project of Ongoing Clinical Initiatives	10:00– 10:30 am	Rohin Rajan, Pete Lyons
MRCT Protocol Ethics Initiative / Panel discussion	10:30-11:00 am	David Forster, Susan D'Amico
Global Regulatory Authority and Regional Stakeholder Presentations (Working lunch)	11:30-2:00 pm	Agnes Klein, Sonali Kochhar, Vijai Kumar, Ock Joo Kim, Evgeny Rogoff, Sabine Haubenreisser, Ann Meeker O'Connell
Break	2:00 – 2:15 pm	
MRCT DMC / DSMB Initiative / Panel discussion	2:15 – 2:45 pm	Charles Knirsch
MRCT TRAINING Initiative / Panel discussion	3:35 – 3:45 pm	Natalie Rossignol
Wrap-up / Steps for moving forward	3:45 – 4:30 pm	Mark Barnes Rebecca Li

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Keynote Speaker – Dr. Robert O'Neill

HARVARD Global Health Institute

A Regulatory Perspective on MRCT's and Potential Strategies to Synergize Initiatives

Robert T. O'Neill Ph.D.

Senior Statistical Advisor to CDER

OTS, CDER, FDA

For presentation at the MRCT Center at Harvard meeting, November 28, 2012

Outline of my talk

- Background on FDA's acceptance of foreign clinical data and MRCT's
- The regulatory interest in evidence from MRCT's
- Share some other work streams that are relevant
- Ideas for alignment with Harvard's MRCT center and other initiatives
- Contribute to the ongoing dialogue for moving these initiatives forward

FINDINGS

In FY 2008, sponsors relied heavily on data from foreign clinical trials to support their marketing applications for drugs and biologics. Eighty percent of approved marketing applications for drugs and biologics contained data from foreign clinical trials. Over half of clinical trial subjects and sites were located outside the United States. Western Europe accounted for most foreign clinical trial subjects and sites; however, Central and South America had the highest average number of subjects per site. Based on the increase in foreign clinical investigators conducting clinical trials under INDs over the last10 years and the observations of FDA reviewers, sponsors' reliance on foreign clinical trials for FDA-regulated drugs and biologics appears likely to grow.

FDA inspected clinical investigators at less than 1 percent of foreign sites. FDA inspected clinical investigators at only 1.2 percent of clinical trial sites for applications approved in FY 2008. FDA inspected 1.9 percent of domestic clinical trial sites and 0.7 percent of foreign clinical trial sites. The agency targeted domestic sites and original applications, although inspection files and interviews with medical reviewers indicated the main reason for inspecting a specific site was a large number of enrolled subjects.

Challenges to conducting foreign inspections and data limitations inhibit FDA's ability to monitor foreign clinical trials. FDA may be unaware of some ongoing, early-phase clinical trials because sponsors are increasingly conducting early-phase clinical trials outside the United States without INDs. Logistical challenges and sponsors' submission of clinical trial data in a nonstandard format also hinder FDA's ability to monitor foreign clinical trials. FDA was also unable to account for all clinical trial information because application files were missing or the sponsors failed to provide site locations and subject enrollment in the clinical study reports.

The report did not address the planning, analysis, or interpretation of a study

RECOMMENDATIONS

FDA should take steps to improve its system for overseeing foreign clinical trial data. Toward that end, we recommend that:

FDA should require standardized electronic clinical trial data and create an internal database. Requiring sponsors to submit their clinical trial data in a standardized electronic format would help ensure that reviewers had all necessary information from sponsors to effectively analyze the data, enable FDA to create an internal database to systematically cull clinical trial information, and enable FDA to more effectively select sites for inspection and meet its review timelines.

FDA should monitor trends in foreign clinical trials not conducted under INDs and, if necessary, take steps to encourage sponsors to file INDs. As sponsors submit future marketing applications with the results of foreign clinical trials that were not conducted under INDs, FDA should assess whether enrolled subjects were at additional risk and whether clinical trial data collected were both accurate and reliable. Should FDA determine that clinical trials not conducted under INDs compromised the rights, safety, and well-being of subjects or the integrity of the data submitted by sponsors, it should consider taking steps to encourage sponsors to voluntarily consult with FDA on their clinical trial protocols or submit INDs to the agency. FDA could also explore providing incentives to promote these, if it deems them appropriate.

FDA should continue to explore ways to expand its oversight of foreign clinical trials. To improve its oversight of foreign clinical trials, FDA could take the following additional actions:

Continue to develop inspectional agreements with foreign regulatory bodies. By sharing past inspection details as well as future plans, FDA would be better able to maximize its resources allocated to inspections of foreign clinical trial sites. FDA's recent agreement with the European Medicines Agency is a positive step for the agency to extend its oversight capability outside the United States.

Inspect clinical trials in more countries. FDA could target clinical trials in more countries, such as those in countries that the agency has not previously inspected or where Good Clinical Practice standards have only recently been adopted.

Look to new models of oversight. FDA could explore other oversight models, such as a quality risk management approach, to oversee clinical trials.

A key guidance known as ICH E5

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97D–0299]

International Conference on Harmonisation; Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data; Availability

Federal Register / Vol. 63, No. 111 / Wednesday, June 10, 1998 / Notices

Key Features of E5

- Established a framework
- Bridging concept
- Classification of intrinsic and extrinsic factors as ethnic factors to consider
- Provided a cap on how much additional data could be asked for by a regulator in a region
  - Allowed another clinical study to be requested if needed

The Q & A addendum was very helpful and stimulated new thinking, especially Q11

Guidance for Industry

E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

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Questions and Answers

Key Features of the Q & A's

- Clarified some points of ambiguity in the initial guidance - indicated more experience needed and we would learn more
- Introduced the multi-regional trial concept for bridging - actually that design is very prevalent today - but also potentially problematic to interpret if not planned or conducted well

Q11: ***There seems to be an impression that the E5 bridging study would always be conducted after data in the original region is complete. Is this correct?***

It may be desirable in certain situations to achieve the goal of bridging by conducting a multi-regional trial under a common protocol that includes sufficient numbers of patients from each of multiple regions to reach a conclusion about the effect of the drug in all regions. Please provide points to consider in designing, analyzing and evaluating such a multi-regional trial.

A11: Bridging data should allow for extrapolation of data from one region to another. Although E5 speaks generally to extrapolation of data to a new region, E5 was not intended to suggest that the bridging study should necessarily follow development in another region. In the answer to Q1, it is made clear that it is also possible to include earlier studies conducted in several regions in a global drug development program so that bridging data might become available sooner. This can expedite completion of a global clinical development program and facilitate registration in all regions. A bridging study therefore can be done at the beginning, during or at the end of a global development program. For a multi-regional trial to serve as a bridging study for a particular region, it would need to have persuasive results in that region, because it is these regional results that can convince the regulators in that region that the drug is effective, and can "bridge" the results of trials in other regions in the registration application.

Guidance for Industry

E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

Questions and Answers

A multi-regional trial for the purpose of bridging could be conducted in the context of a global development program designed for near simultaneous world-wide registration. 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. The primary endpoint(s) of the study should be defined and acceptable to the individual regions and data on all primary endpoints should be collected in all regions under a common protocol. In instances where the primary endpoints to be used by the regions are different, data for comparison purposes on all primary endpoints should be collected in all regions.

3.2.4 Bridging Studies for Safety

Even though the foreign clinical data demonstrate efficacy and safety in the foreign region, there may occasionally remain a safety concern in the new region. Safety concerns could include the accurate determination of the rates of relatively common adverse events in the new region and the detection of serious adverse events (in the 1 percent range and generally needing about 300 patients to assess). Depending upon the nature of the safety concern, safety data could be obtained in the following situations:

- A bridging study to assess efficacy, such as a dose-response study, could be powered to address the rates of common adverse events and could also allow identification of serious adverse events that occur more commonly in the new region. Close

Guidance for Industry

E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

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Questions and Answers

For a study intended to serve as a bridging study, the following points should be considered:

Planning

The multi-regional trial would have to satisfy requirements of the region where the application is to be filed with respect to design and analysis (see answer to Q1). In general, a multi-regional study should be designed with sufficient numbers of subjects so that there is adequate power to have a reasonable likelihood of showing an effect in each region of interest. Minor differences in design (e.g., age inclusion criteria, concomitant medication, etc.) may be acceptable and prior discussion with regulatory agencies is encouraged. For safety evaluation, it is important to make as uniform as possible the method for collection and assessment of safety information among regions.

Analysis

Given the goal of the multi-regional bridging study, it is critical to provide efficacy and safety results by region, with attention given to the usual analyses (e.g., demographic and baseline variables, patient disposition). It will be of interest also to examine consistency of effects across regions. In a dose response study, it will be especially important to analyze dose response relationships for efficacy and safety both within the regions and across the regions.

Evaluation

It is difficult to generalize about what study results would be judged persuasive, as this is clearly a regional determination, but a "hierarchy of persuasiveness" can be described.

1. Stand Alone Regional Result

The most persuasive would be demonstration of the effect in the entire study, with the results of each region of interest also demonstrating a statistically significant result. It will also be important to compare results across regions.

2. No Significant Regional Result But Similar Results Across Regions

With an effect demonstrated in the entire study, an analysis of results by region might not show a significant result in a region of interest but the data might nonetheless be persuasive to regulators in that region. Consistent trends in endpoint(s) intended for comparison across the regions or, in the case of a dose-response study, similar dose-response relationships across regions, might support an argument that the drug is not sensitive to intrinsic or extrinsic ethnic factors. Other data, for example, from approved drugs in the same class within region(s) could support such a bridging conclusion.

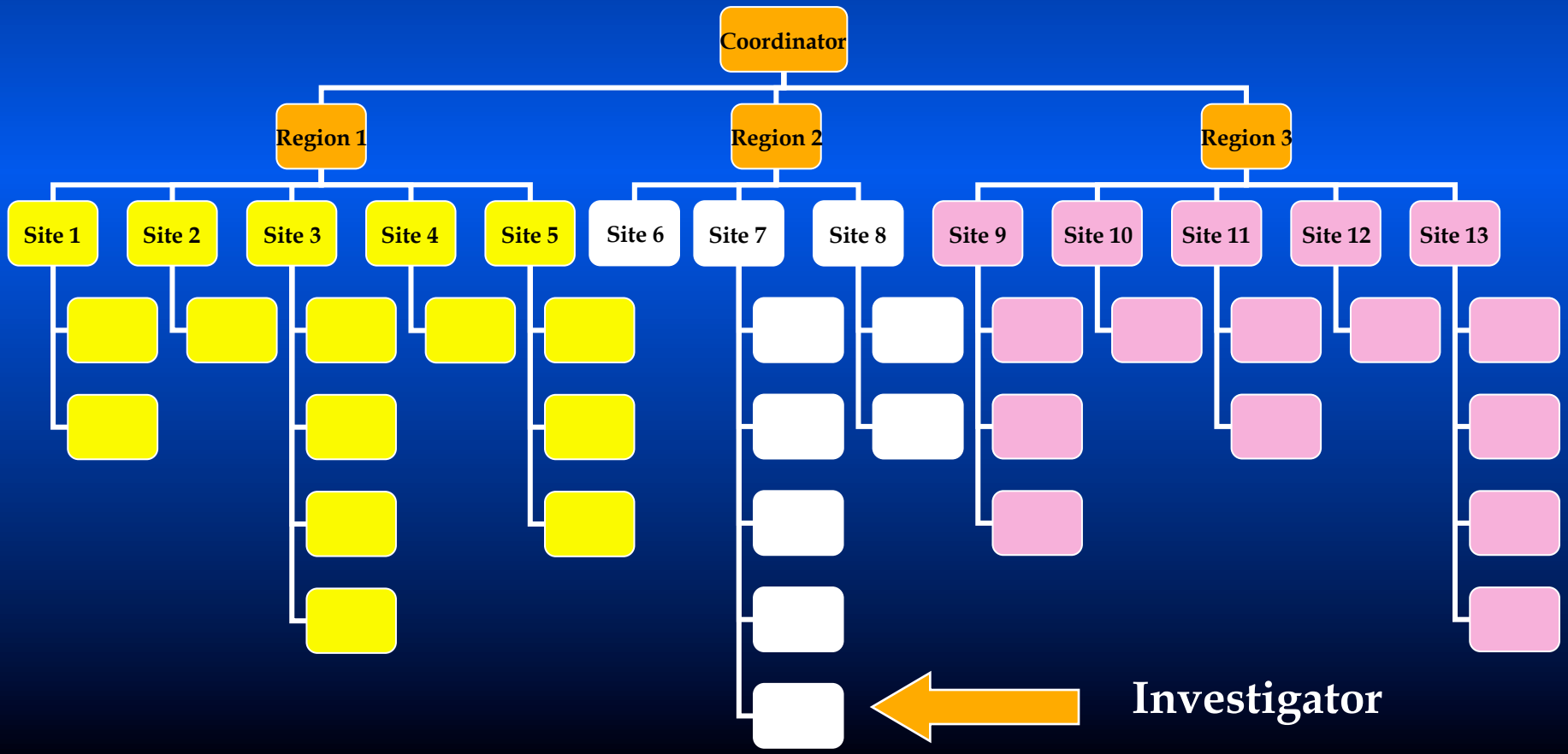
Generally, at FDA, clinical trial data is evaluated with respect to results inside and outside the United States

or

inside and outside North America

Conceptual view of a multi-regional clinical trial;

Sources of variability in estimates of treatment effect / response and other factors



FDA's review of RCT's generally involves evaluation of study results (statistical analyses) according to region, and maybe country - often difficult to interpret

- Evaluate the study data and the conduct and key metrics of quality (will refer later to DSI site selection auditing program)
- Evaluate statistical displays of key sources of variation, bias and uncertainty
- Regional and site outcomes evaluated:
  - Dropouts, differences in response rates, outcomes, covariates, exposures, follow-up, concomitant drugs
- Individual patient profiles nested within sites - which sites and which patient records to evaluate in more detail - possible auditing strategies (usually relies on electronic records)
- Possibly intrinsic factors (markers, gender, ethnicity) or possibly extrinsic factors)recruitment patterns, medical support system, standards of care
- Align inspection with review of data and insights for audits

Interpretation of the global estimate and region specific estimates is challenging

and the causes for heterogeneity are usually unknown

Intrinsic or Extrinsic factors and their evaluation

Differences in treatment effects are expected

Too much heterogeneity is problematic

Issue - What to make of it ?

Are these treatment differences real and are they systematic in the sense that treatment effects are consistently better or worse in the U.S. and what are the reasons for it

Study undertaken by FDA statisticians to evaluate possibility of systematic regional differences

- Major cardiovascular outcome studies evaluated over the last 10 years
- Overall study result statistically positive, ie. demonstrated overall effect
- Region never pre-specified as a factor to be evaluated statistically
- 24 independent studies

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 60, No. 12, 21
ISSN 0735-1097/$36.00

CORRESPONDENCE

Research Correspondence

Regional Treatment Effects in Studies of Cardiorenal Drugs

A Summary of Recent Clinical Trials

*John Lawrence, PhD
Steve Bai, PhD
H. M. James Hung, PhD
Robert O'Neill, PhD

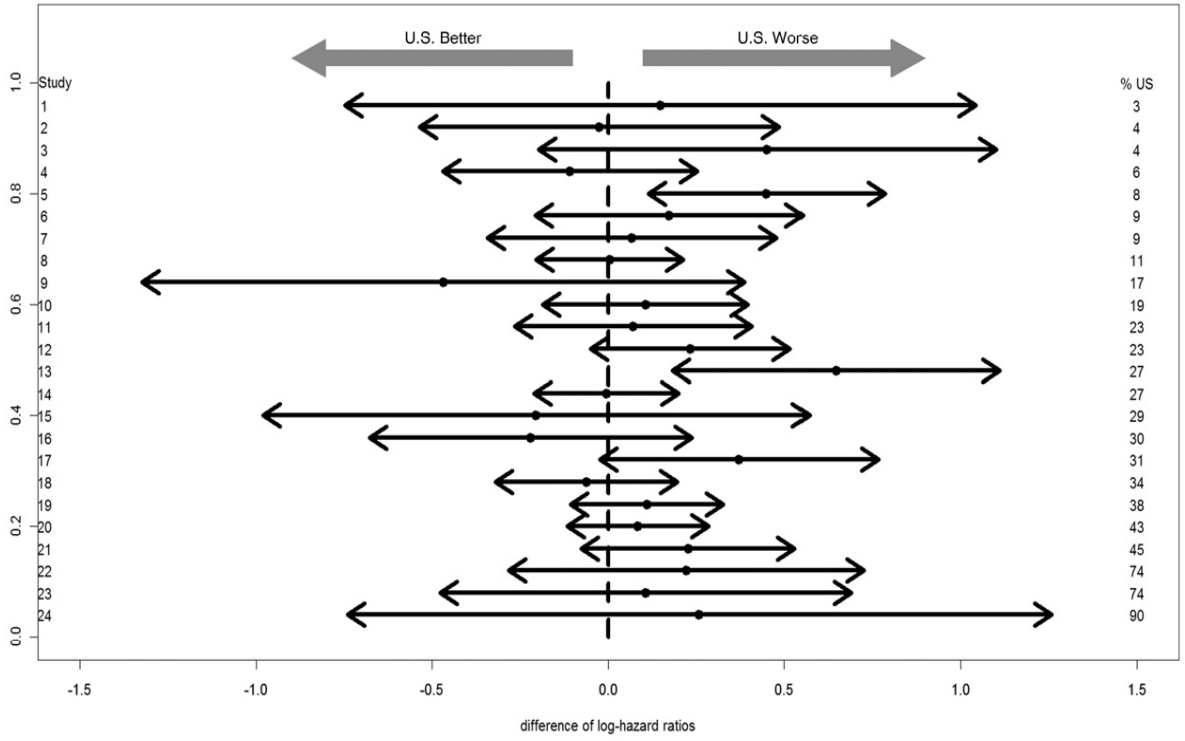


Figure 1 Estimates and Confidence Intervals for Difference in Log-Hazard Ratio Between U.S. and Non-U.S. Treatment Effects for Each Study

Studies are listed in order from top to bottom by percent of U.S. enrollment (shown in the column on right). **Circles** indicate the point estimate of the difference between log-hazard ratios (U.S. compared with non-U.S.), and **arrows** represent the 95% confidence interval for this difference.

In 16/24 studies, the effect was less in US

P = 0.023

P = 0.007

An Example:

Toprol –XL; the Current Drug Label ; "Clinical Trials" section

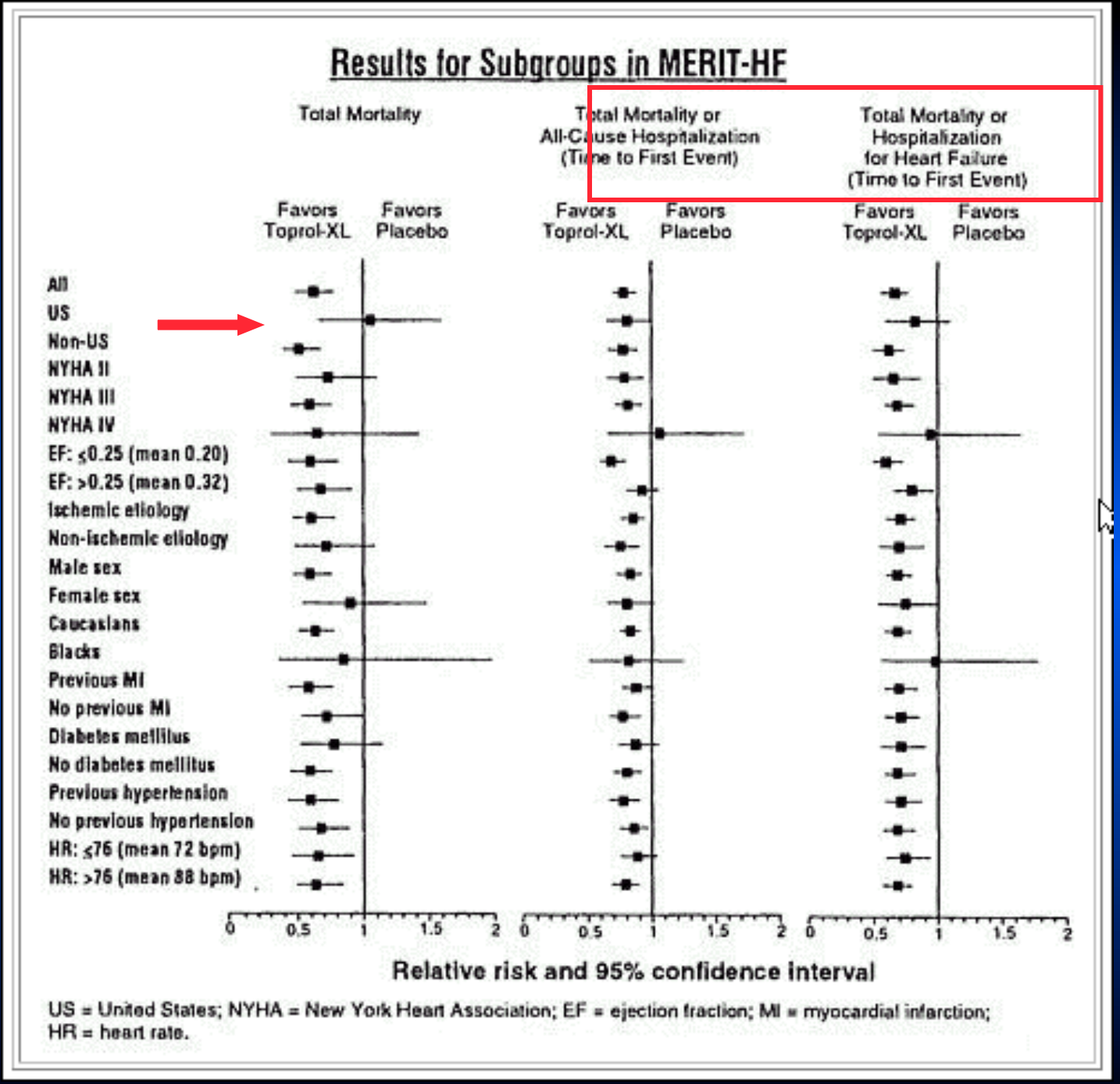
MERIT-HF was a double-blind, placebo-controlled study of Toprol-XL conducted in 14 countries including the US. It randomized 3991 patients (1990 to Toprol-XL) with ejection fraction </= 0.40 and NYHA Class II-IV heart failure attributable to ischemia, hypertension, or cardiomyopathy. The protocol excluded patients with contraindications to beta-blocker use, those expected to undergo heart surgery, and those within 28 days of myocardial infarction or unstable angina. The primary endpoints of the trial were (1) all-cause mortality plus all-cause hospitalization (time to first event), and (2) all-cause mortality.

The *trial was terminated early* for a statistically significant reduction in all-cause mortality (34%, nominal p=0.00009). The risk of all-cause mortality plus all-cause hospitalization was reduced by 19% (p=0.00012). The trial also showed improvements in heart failure-related mortality and heart failure-related hospitalizations, and NYHA functional class.

The table below shows the principal results for the overall study population. The figure below illustrates principal results for a wide variety of subgroup comparisons, including US vs. non-US populations (the latter of which was not pre-specified). The combined endpoints of all-cause mortality plus all-cause hospitalization and of mortality plus heart failure hospitalization showed consistent effects in the overall study population and the subgroups, including women and the US population. *However, in the US subgroup and women, overall mortality and cardiovascular mortality appeared less affected. Analyses of female and US patients were carried out because they each represented about 25% of the overall population*. Nonetheless, subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

A figure

From the label



A Recent Example of differential treatment effects - what to make of it -In a multi-regional study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Questions

Ticagrelor

July 28, 2010

Department Of Health And Human Services
Public Health Service
Food and Drug Administration

The Advisory Committee is asked to opine on the approvability of ticagrelor to reduce thrombotic events in patients with acute coronary syndromes or myocardial infarction, whether treatment is intended to be medical management or percutaneous coronary intervention (PCI).

The support for this claim comes primarily from PLATO, a randomized, event-driven double-blind comparison of ticagrelor (180 mg loading dose plus 90 mg twice daily) and clopidogrel (300 or 600 mg loading dose plus 75 mg daily), on a background of aspirin (anywhere from 160 to 500 mg loading plus 75 to 325 mg daily). The primary end point was time to first event of cardiovascular mortality, myocardial infarction, or stroke, tested with α=0.05 (adjusted for one interim analysis). Overall results were as follows:

	Clopidogrel n=9291	**Ticagrelor n=9333**	**HR**
CV death, MI, stroke	10.9%	9.3%	0.84 (0.77-0.92)
MI	6.4%	5.4%	0.84 (0.75-0.95)
CV death	4.8%	3.8%	0.79 (0.69-0.91)
Stroke	1.1%	1.3%	1.17 (0.91-1.52)

4. Do you believe the difference in clinical outcomes between the US and the rest of the world was attributable …

    4.1. … the play of chance? There is only one country out of 43 whose results fall outside the 95% confidence limits for a region having the observed number of events. If you think that chance is the most likely explanation, are you sufficiently sure of that to take the overall results to be applicable to the US?

    4.2. … a difference in dosing of aspirin, which was generally higher in the US? If so…

        4.2.1. Aspirin dose was one factor among dozens explored. How do you adjust for such multiplicity?

        4.2.2. How compelling are the external data that the dose of aspirin makes any difference in prevention of thrombotic events?

        4.2.3. How do you explain the apparently different effect of aspirin dose on ticagrelor and clopidogrel?

        4.2.4. If you think that aspirin dose is the most likely explanation for the discouraging results in the U.S., do you feel sufficiently sure that when administered with a low dose of aspirin, Brilinta will provide a clinical advantage over clopidogrel in the U.S. population?

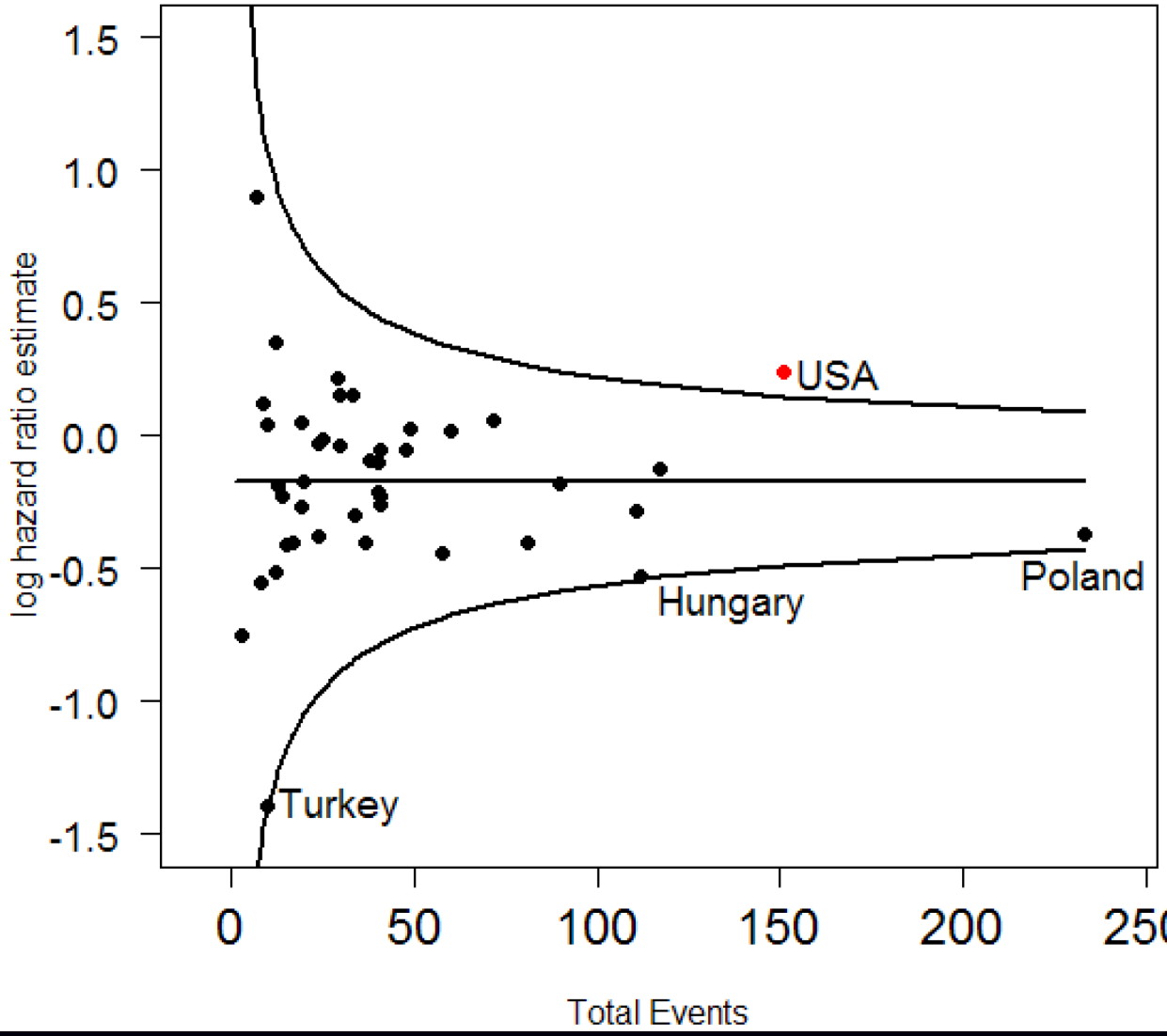
    4.3. … some other identifiable factor?

    4.4. … some unidentified set of population and care factors?

	Ticagrelor (n/N)	Clopidogrel (n/N)	HR (95% CI)
PLATO Overall N=18,624	9.8% (864/9333)	11.7% (1014/9291)	**0.84** (0.77, 0.93)
Non-US n=17,211	9.6% (780/8626)	11.8% (947/8585)	**0.81** (0.74, **0.90**)
US n=1,413	12.6% (84/707)	10.1% (67/706)	**1.27** (**0.92**, 1.75)

- 95% CIs of the US and non-US subgroups do not overlap
- In the US, clopidogrel did 'better' and ticagrelor did 'worse'

Funnel Plot: US is an outlier



Possible Explanations for US versus Non-US Difference

- Play of chance
- Concurrent ASA
- Other factors

PHARMACEUTICAL STATISTICS
Pharmaceut. Statist. **9**: 217–229 (2010)
Published online 28 June 2010 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/pst.439

Trial design issues and treatment effect modeling in multi-regional schizophrenia trials[‡,§,‖]

MAIN PAPER

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[2]*Office of Biostatistics, Office of Translational Sciences, CDER, US Food and Drug Administration, MD, USA*
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In recent years, we have seen an increasing trend of foreign data as part of clinical trial data submitted in new drug applications (NDA) to US Food and Drug Administration (FDA). To understand the design and analysis characteristics, we studied schizophrenia multi-regional clinical trials (MRCTs). The schizophrenia data set consisted of a total of 12585 patients collected from 33 clinical trials with 63.8% patients from North America, the largest region. The data set constituted 10 schizophrenia drug programs in support of NDAs submitted to FDA from December 1993 to December 2005.

Two main objectives were pursued. First, we investigated some study design issues including potential heterogeneity of treatment effect via meta analysis and placebo response pattern over time. Second, we performed empirical modeling in two ways, supervised and unsupervised, to explain potential impact of baseline covariates on treatment effect in MRCTs.

Based on our analysis results, placebo response appeared to increase over time and primarily attributed to US region. On average, the observed treatment effect in the US was generally smaller than non-US region. Both supervised and unsupervised empirical modeling selected baseline Positive and Negative Syndrome Scale total score as one of the most important covariates explaining a treatment effect. Region

Table I. Summary of baseline characteristics by region.

Region	Baseline PANSS*	Baseline weight*	Baseline height*	Baseline BMI	Age*	% of male
Asia ($N = 1156$)	93.9 (13.8)	58.1 (14.7)	162.5 (9.9)	21.9 (4.8)	33.5 (9.7)	68
Eastern Europe ($N = 2628$)	93.1 (12.0)	70.6 (14.9)	169.8 (9.4)	24.5 (4.6)	37.7 (11.2)	53
North America (N = 8033)	92.2 (14.8)	86.3 (21.1)	172.9 (10.0)	28.9 (7.03)	40.3 (10.3)	75
South Africa ($N = 145$)	92.3 (14.1)	67.0 (14.5)	169.7 (9.5)	23.4 (5.5)	33.9 (10.8)	74
Latin America ($N = 178$)	97.0 (15.7)	65.6 (12.8)	164.8 (9.7)	24.1 (4.0)	34.5 (11.6)	67
Western Europe ($N = 445$)	97.4 (14.0)	75.4 (16.9)	171.4 (9.6)	25.7 (5.4)	37.0 (10.4)	65

Note that for age summary, four adolescent trials are excluded.
*Weight in kg and height in cm, BMI kg/m^2; reported values are mean (standard deviations).

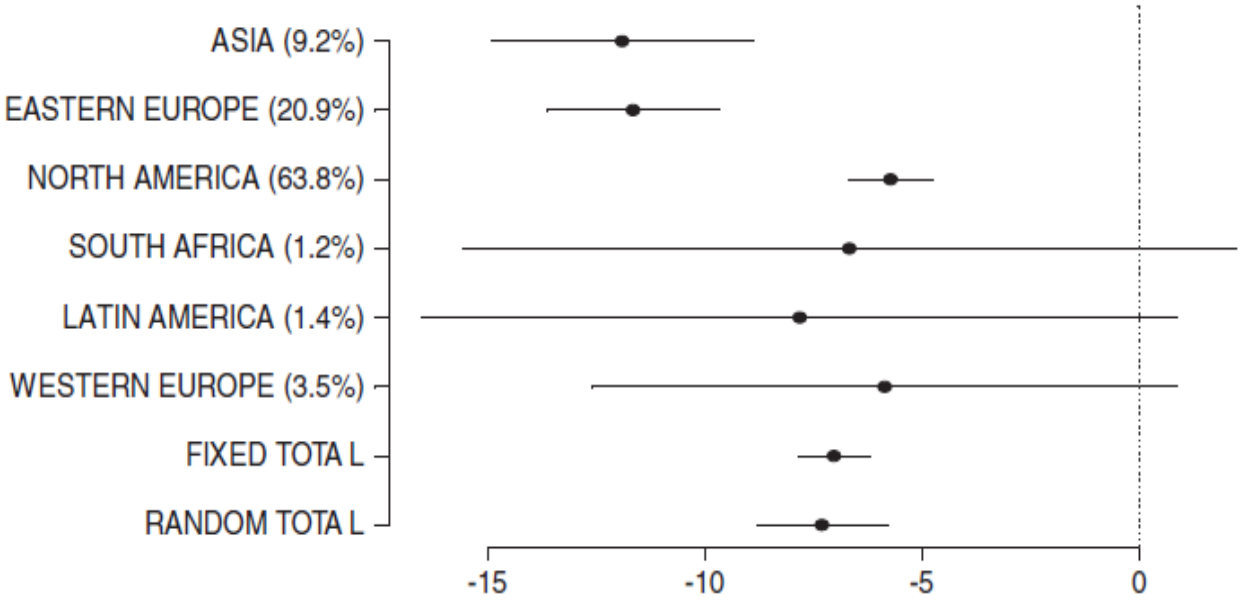

Figure 2. Region data percentage and average treatment effect. Both fixed effect and random effect models were considered.

Also a concern with evaluation of Safety

Rates are higher in non - North America sites

Suicide Rates in Short-term Randomized Controlled Trials of Newer Antidepressants

Tarek A. Hammad, MD, PhD, MSc, MS, Thomas P. Laughren, MD, and Judith A. Racoosin, MD, MPH

(*J Clin Psychopharmacol* 2006;26:203–207)

TABLE 3. Rates of Suicide per 100,000 Person-years and Poisson-based 95% CIs for Active-controlled Depression Trials by Drug Group and Location (11,883 Patients, 94 Trials, 16 Cases)

Drug Group	Location	No. Patients	No. Person-years	No. Suicides	Rates/100,000 Person-years	Poisson-based 95% CIs
AAs	Non–NA	2702	319	6	1881	690–4094
	NA	1451	176	1	568	14.4–3166
SSRIs	Non–NA	3497	432	5	1157	376–2701
	NA	1694	200	1	500	12.3–2786
TCAs	Non–NA	2347	245	3	1225	253–3579
	NA	740	71	0	0	0–5196

NA indicates North America.

Some (a priori) Planning Concepts that are important for sponsors and regulators (and perhaps DMC members) to be aware of

- Sample size overall and per region
- Expected variation in treatment effects
- Sources of variability and/or systematic differences
  - Investigator
  - Patients
  - Study conduct
  - Medical/clinical environment
  - Quality of the data

CLINICAL TRIALS ARTICLE

Clinical Trials 2010; **7**: 147–156

Regional differences in multinational clinical trials: anticipating chance variation

Ian C Marschner

Investigates the expected chance variation in regional treatment effects from multinational studies. Advocates studying this expected variation during the design stage, hence limiting the potential for surprises and misinterpretations at the end of the study – Probably not sufficient without understanding design changes

Use of order statistics

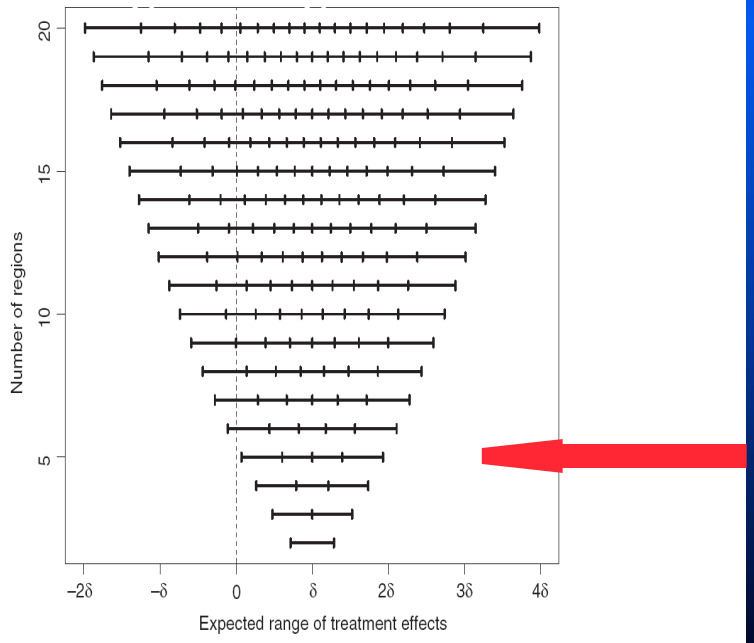

Figure 1 Expected range of regional treatment effects in a study with 80% power for a treatment difference of δ and $\alpha = 0.05$. For each range, the j-th tick mark from the left denotes the expected value of the j-th largest regional treatment effect

Difficulties in interpreting chance results – even when there is a treatment effect

PHARMACEUTICAL STATISTICS
Pharmaceut. Statist. **9**: 173–178 (2010)
Published online 28 June 2010 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/pst.440

Consideration of regional difference in design and analysis of multi-regional trials[‡,§]

H. M. James Hung[1,*,†], Sue-Jane Wang[2], and Robert T. O'Neill[2]

Assume 4 regions but of different proportional allocation of subjects

Table I. Probability of reversal (assuming the true global effect size is very close to the estimated effect size).

p	Probability that one region shows a reversal	Probability that two regions show reversals
$(r_1, r_2, r_3, r_4) = (0.25, 0.25, 0.25, 0.25)$		
0.001	0.17	0.01
0.01	0.29	0.05
0.05	0.38	0.11
$(r_1, r_2, r_3, r_4) = (0.20, 0.10, 0.30, 0.40)$		
0.001	0.23	0.02
0.01	0.33	0.06
0.05	0.40	0.13
$(r_1, r_2, r_3, r_4) = (0.10, 0.10, 0.10, 0.70)$		
0.001	0.32	0.06
0.01	0.39	0.11
0.05	0.43	0.17

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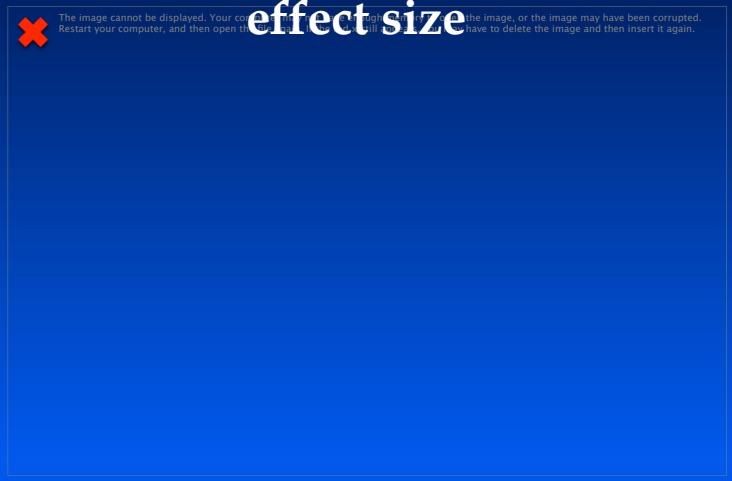
Consideration of regional difference in design and analysis of multi-regional trials[‡,§]

MAIN PAPER

H. M. James Hung[1,*,†], Sue-Jane Wang[2], and Robert T. O'Neill[2]

Between region variability relative to effect size

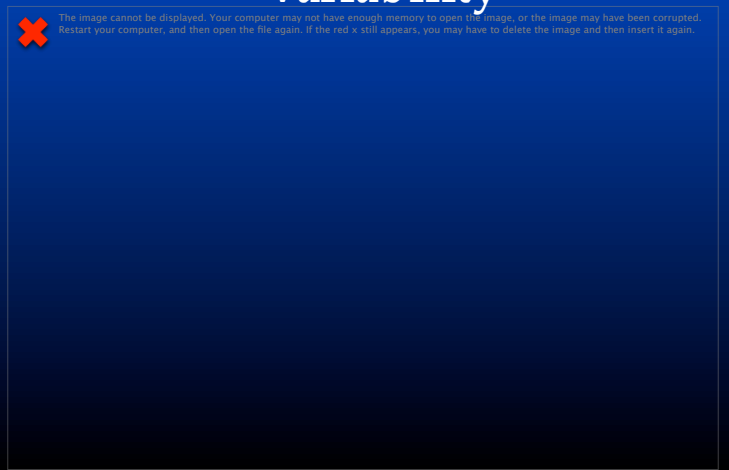


Study Design Planning

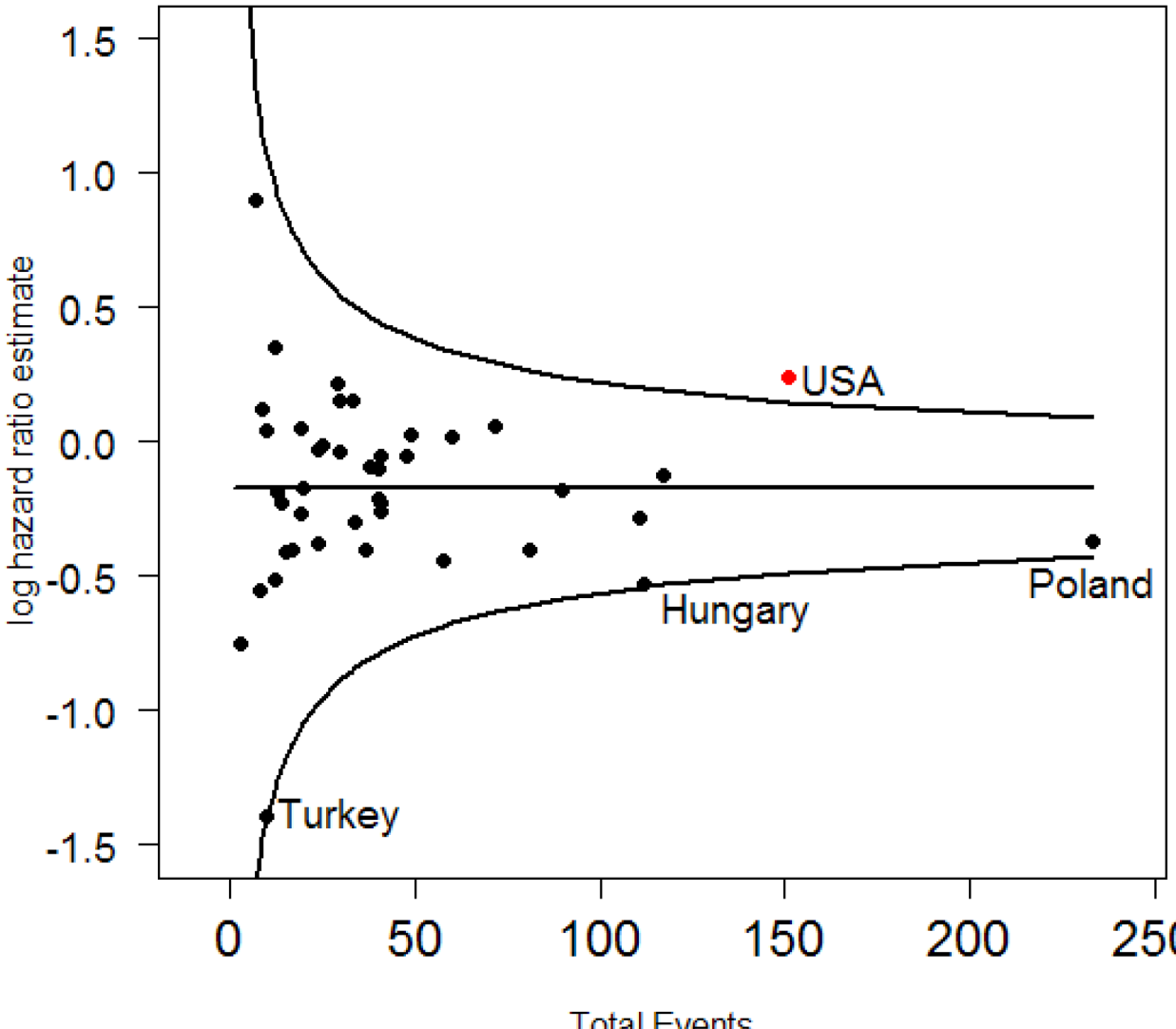
IMPACT ON SAMPLE SIZE

Multi-regional trial according to sources of variability

Between-region variability relative to within-region variability



Funnel Plot: US is an outlier



Some thoughts on what can be done about regional effects as a design or analysis feature in multi-regional trials

- At protocol planning stage
  - Be aware of expected heterogeneity/ variation
  - Have an analysis plan that expects some heterogeneity
  - Decide in advance how much is too much
  - Sample size the trial according to expected heterogeneity
  - Choose sites (and investigators) with some prior information on performance if possible
    - Completion rate, dropouts, voluntary withdrawal background rate of outcomes (disease), quality of ascertainment, audit/ inspection history
  - Plan endpoints (eg. Composites) with knowledge of sensitivity to medical culture and health care environment

Some thoughts on what can be done

- At analysis stage
  - Analyze and display results using models that account for site, country and region
  - Evaluate statistical interactions and use other tools to explore chance variation
  - Evaluate intrinsic / extrinsic factor contributions and imbalances
    - Intrinsic factor identification and possibly prior or external genomic studies to elucidate PK/PD or responsiveness/ sensitivity may be conducted prior to later phase studies
    - The emphasis should be at the study design and analysis stage: Recognizing that extrinsic factors will contribute a source of variability and there should be planning for heterogeneity of treatment effects

Planning for heterogeneity and analysis plans to deal with it

- How and why are sites selected - What is known about investigator training (relevant the Harvard MRCT initiative)
- Use of central statistical monitoring to identify outliers
- Rationale for number of sites per country/region
- Sample size per site
- What might the stratification be:
  - Not obvious – country, region, size
- When only a single large study may be conducted – raise the bar

CLINICAL TRIALS ARTICLE Clinical Trials 2012; 0: 1–9

A statistical approach to central monitoring of data quality in clinical trials

David Venet[a,b], Erik Doffagne[a], Tomasz Burzykowski[a,c], François Beckers[d], Yves Tellier[d], Eric Genevois-Marlin[e], Ursula Becker[f], Valerie Bee[g], Veronique Wilson[g], Catherine Legrand[h] and Marc Buyse[c,i]

CLINICAL TRIALS DATA MANAGEMENT AND TRIAL CONDUCT Clinical Trials 2012; 9: 257–264

The potential for central monitoring techniques to replace on-site monitoring: findings from an international multi-centre clinical trial

Julie M Bakobaki, Mary Rauchenberger, Nicola Joffe, Sheena McCormack, Sally Stenning and Sarah Meredith

CLINICAL TRIALS ARTICLE Clinical Trials 2012; 9: 330–339

An adaptive strategy for assessing regional consistency in multiregional clinical trials

Joshua Chen[a], Hui Quan[b], Paul Gallo[c], Soo P Ouyang[d] and Bruce Binkowitz[a]

What to monitor

- Primary and secondary endpoints
- Baseline values
- Rates of dropouts prior to study completion
- Randomization codes
- Blinding
- Adverse event rates
- Consider inspection/audit strategies – cannot inspect quality into the trial (next slides courtesy of CDER' DSI)

GCP Site Selection Tool

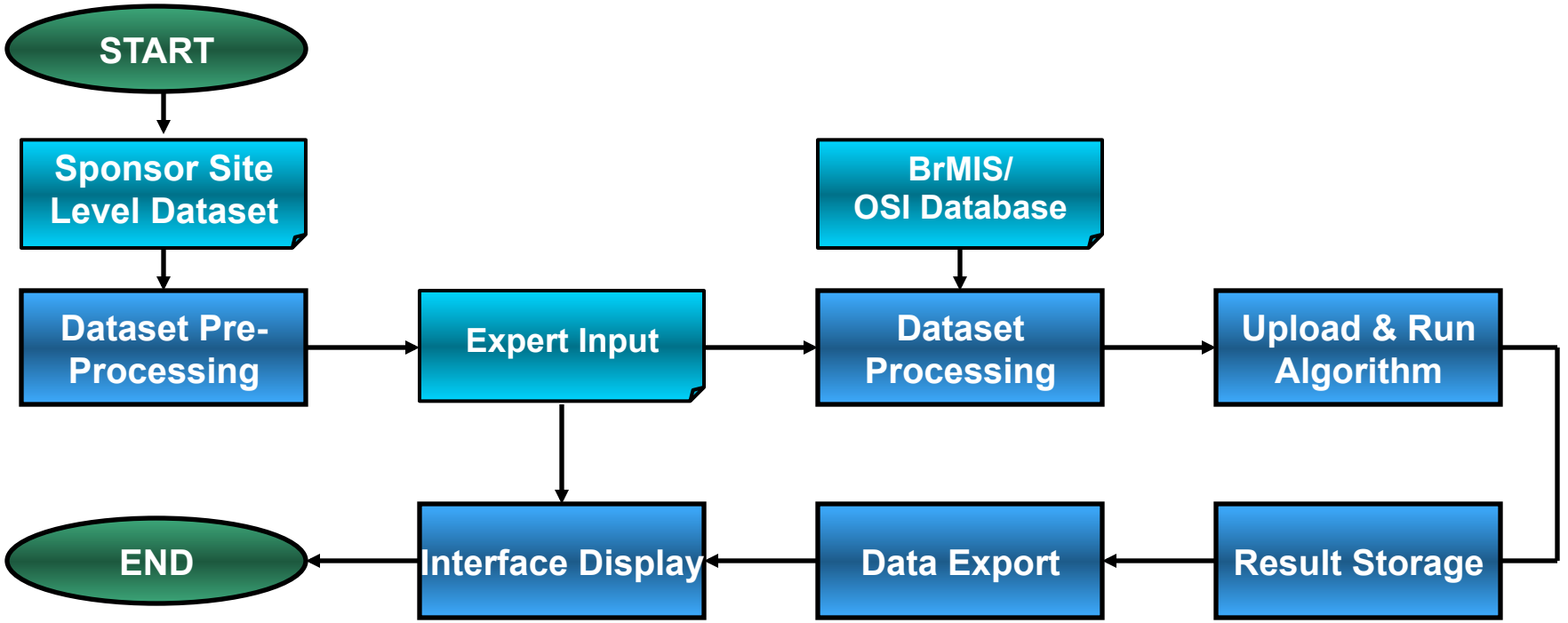
Objectives:

- Develop a tool to support prioritization of clinical trial sites for inspection.
- Define a multi-decision approach to score clinical site/ investigator based on risk-based multi-attribute algorithm.

Goals:

- Develop a more consistent, science-based approach to selection of clinical sites for inspection.
- Enable deployment of limited resources towards sites that pose the potentially greatest risk to public health
- Significantly reduce time and effort required to select sites

Site-Level Dataset Review & Integration Process



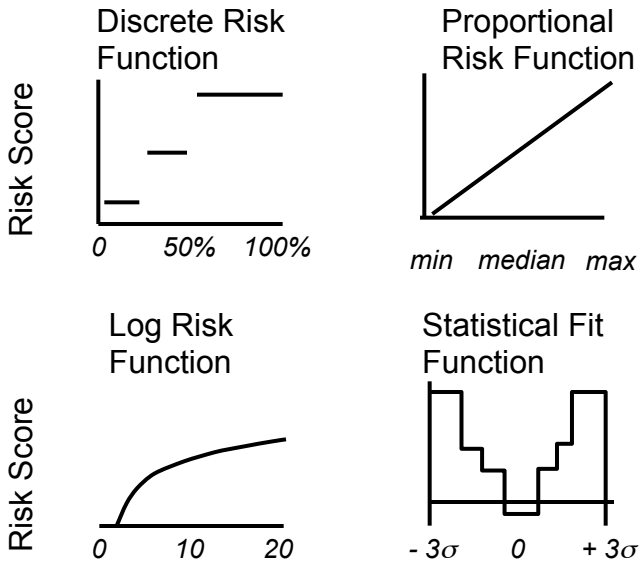
FDA data review and integration process consist of:

- Automated process to ensure appropriate structure and quality of the data.
  - Data Processing Step
- Manual review to evaluate other data quality concerns.
  - Data Pre-Processing and Interface Display Steps

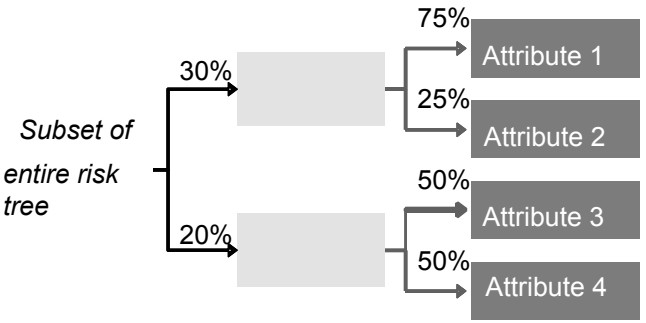
Example of the Decision Analysis Algorithm

1 Attribute Raw Values

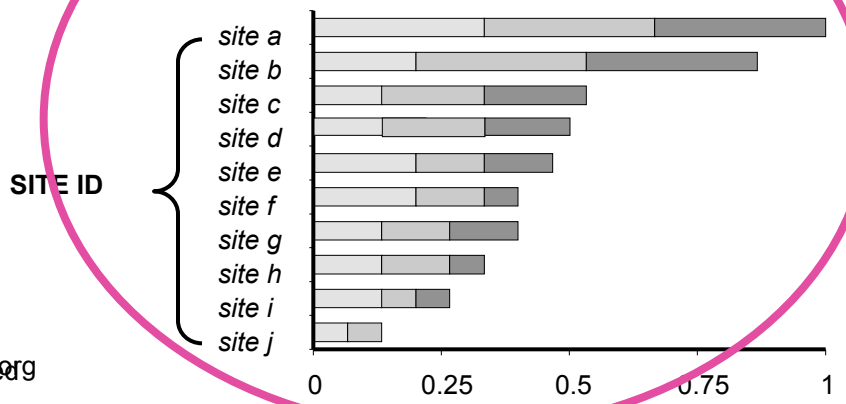
2 Risk Functions applied to Attribute Values



3 Hierarchical Weighting Schema applied



4 Final Risk Score for each site



* Information shown on this slide are example of the risk function methodologies utilized but does not represent the actual algorithm values

Some related work and initiatives that are relevant to today's meeting

- PhRMA Working Groups on the Multi-regional Clinical Trial (MRCT)
- *Pharmaceutical Statistics* : Special Issue on

  Multi-regional clinical trials –What are the challenges ; July/September 2010; Volume 9, Issue 3 ; pages 171-253
- *J. Biopharmaceutical Statistics*: Special Issue on

  Statistical Considerations for the Design and Analysis of Bridging and Multiregional Clinical Trials (2012), 22:5,875

Some other initiatives that are linked to MRCT's mission

- Several DIA meetings on the topic
- APEC regulators steering committee
  - Their identified needs and future plans
  - European initiatives
- PhRMA's methodological teams, reports and findings
- Regulatory statistics – programs to train next generation – how to interact in multidisciplinary team approach – for advice and review (my interest)

DIA meeting

9:00-9:45 AM SESSION 1: PLENARY KEYNOTE ADDRESS

Keynote Speaker

Towards the Definition of Appropriate Globalization in Clinical Trials: the Case for Transparent Coopetition

Robert M. Califf, MD
Vice Chancellor for Clinical Research
Duke University Medical Center
Director, Duke Translational Medicine Institute

9:45-10:45 AM SESSION 2 – PART 1

Perspectives on Multiregional Clinical Trials (MRCTs): FDA, EMA, Health Canada, and Industry

Session Chairperson

Mike Ward
Manager, International Programs Division
Therapeutic Products Division
Health Canada

This keynote panel discussion will address broad questions that cover multiregional clinical trial (MRCT) conduct including the current state; data monitoring committees, data quality, integrity and human subject protection; potential barriers to MRCT data acceptability and address heterogeneity of results with ability to verify source data; perspective on CROs and other service provides involved in MRCTs and last, regulatory harmonization to facilitate efficient conduct of MRCT.

Panelists

Leslie Ball, MD, CAPT, USPHS
Director, Division of Scientific Investigations
Office of Compliance, CDER, FDA

Fergus Sweeney, PhD
Head of Sector, Compliance and Inspections
European Medicines Agency, European Union

Agnes V. Klein, MD, DrPH
Director, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutic Products
Health Canada

Panelists

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Robert M. Califf, MD
Vice Chancellor for Clinical Research
Duke University Medical Center
Director, Duke Translational Medicine Institute

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Office of Translational Sciences
CDER, FDA

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Director, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutic Products
Health Canada

Mark Paxton, PhD
Associate Vice President, International Regulatory Affairs, Pharmaceutical Research and Manufacturers of America (PhRMA)

Ian Marschner, PhD
Professor, Statistics
Department of Statistics
Macquarie University, Australia

Diana Zuckerman, PhD
President, National Research Center for Women & Families

12:00-1:00 PM NETWORKING OPPORTUNITY AND LUNCHEC

4 PhRMA MRCT KIT Workstreams

- PhRMA MRCT KIT chairs: B. Binkowitz, E. Ibia
- Workstreams:
  - Issues when endpoints/timepoints/etc. differ between health authorities (C. Girman)
  - Considerations when defining "region" (Y. Tanaka, C. Mak)
  - Consistency (H. Quan, J. Chen)
  - Survey of PhRMA companies MRCT practices (N. Scott)

PhRMA Survey of MRCT Practices

- Greater, region independent, standards to guide the conduct of **all** trials
- Greater cross-regulatory collaboration to align:
  - Therapeutic area specific requirements
  - Safety data requirements
  - Logistics of drug import / export

Consistency Team

- Ideally, all regions should be treated identically in the consistency definition
- Overall sample size plays a key role in examining consistency, and in fact it may not be possible to partition the regions to achieve desired power depending on the number of regions and the definition of consistency. Keep # of regions small.
- Don't conclude inconsistency without attempting to understand why
  - Multiplicity issues
  - Further exploratory analyses :Baseline characteristics, medical practice, and other intrinsic/extrinsic factors that may confound the results
  - Totality of the data/evidence
    - Overwhelming vs marginal overall effect
    - Consistency in other important endpoints and subgroups
    - External data (e.g., same class, same patient population, etc.)
  - Hill's criteria

Issues when endpts/timepts/etc. differ between health authorities: Summary Recommendations

Different Regional requirements	Potential handling in MRCT
Different clinical endpoints as primary/co-primary	**Pre-specify different primary or co-primary hypotheses in protocol, and describe separately in study report**
Different timepoints for primary endpoint	**Pre-specify different timepoints in primary hypothesis for different regions as long as blinded trial duration extends to longer duration** **If analysis done at earlier timepoint, need to consider later timepoint as supplemental information, or account for interim look** **Need to ensure trial integrity because of earlier unblinding.**
Different non-inferiority margins	**If trial size is sufficient for both margins, pre-specify different margins for different regions in protocol; describe separately in report**
Different analytic populations or methods	**Pre-specify differences in protocol and describe separately for different regions in report**
Different study designs	**Depending on magnitude of differences, can handle minor differences in MRCT by pre-specifying in protocol**

Considerations when defining "region"

Factors	Rationale
Race and ethnicity	Surrogates for genomic issues and therefore a supposedly homogeneous, w.r.t. drug effects, group
Medical practice	Encompasses practices of treating a patient including local medicines, hospital treatment
Human Development Index	Surrogate for ability to provide and have access to the "latest" developments in health care (Adult literacy, GDP, Education, life expectancy)
Disease Epidemiology	Goes to the differing characteristics of the disease (including genomics/biomarkers) which are reflected by many of the issues on this list. Provides the background information that can indicate where disparate characteristics occur that will affect the planning, analysis and execution of the clinical trial.
Geographic proximity	The traditional idea of a region, yet still very fluid
Geopolitical / Institutional	Health Authority driven
Culture	Broad term to encompass common health practices, ethics, and behaviors that impact on a clinical trial that arise from within a common culture.

Considerations when defining "region"

- **Region does not necessarily have to be geographical or political.**
- **Different factors should be considered depending on therapeutic area / disease state.**
- "Region" should be pre-defined (with justifications)
  - How these definitions are accounted for in the study design should be noted with the pre-definition
  - how region will be analyzed should be pre-specified in the planning stage (stratification, consistency method should be integral in the design).

PhRMA Survey of MRCT Practices

- Processes and enforcement to achieve standardization:
  - Centralized quality management plans
  - Global monitoring guidelines (consider PhRMA white paper on acceptable approaches for risk-based clinical trial monitoring: "PhRMA BioResearch Monitoring Committee: Perspective on Acceptable Approaches for Clinical Trial Monitoring", Drug Information Journal, Vol. 44, No.4, July 2010)
  - Guidelines to restrict and manage when protocol amendments may be utilized

Alignment with Harvard's MRCT initiatives

The story behind the MRCT Center?

- Most life science companies have increased the their reliance on emerging markets to meet their recruitment goals for their development programs. Typically, industry relies on global standards for how they design, conduct and oversee these trials. At the same time, sponsors are "outsourcing" many of these functions to CROs and other third parties.

- Academic medical centers, medical and public health schools and not-for-profit humanitarian organizations increasingly are seeking t o address health issues in, and conduct clinical trials in, developing regions of the world.

- Policymakers, regulators, and citizens believe/suspect that standards for the design, conduct, and oversight clinical trials are lower in emerging markets than in the West.

- In collaboration with life sciences companies, clinical research organizations, non-profit organizations, industry associations and academic institutions, the MRCT Center explores opportunities for industry and academic leadership to improve the design, conduct, and oversight of multiple-regional clinical trials.

- We are broadening our coalition of MRCT stakeholders to shape the future of multi regional clinical trials and public confidence in the standards for the design, conduct, and oversight of such trials.

MRCT's Core Values

The MRCT Center Applies Its Core Values to All Projects

Respect and Professionalism

- Respect people, efficacy, safety and fairness
- Professional conduct of all those engaged in human research studies
- Leadership and management of the initiative by a qualified party that has no conflicting financial or clinical research interests

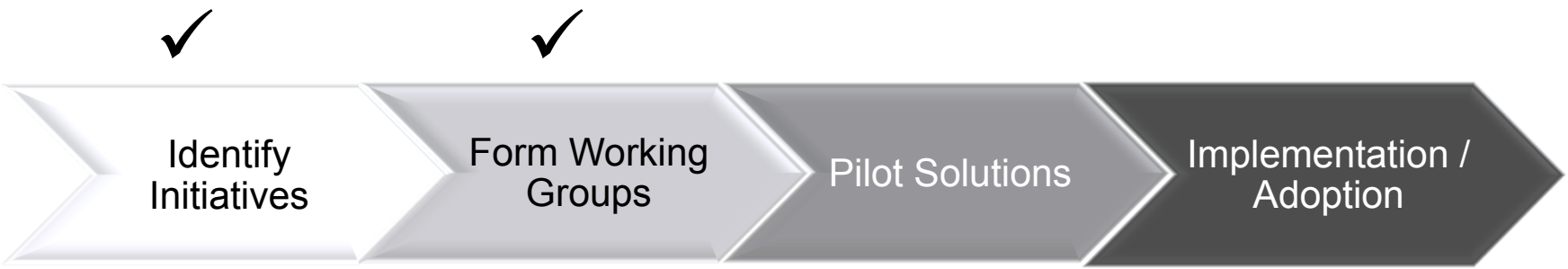
Collaboration & Transparency

- Authentic, substantive partnership with individual leaders, non-governmental organizations, researchers and industry employees who live and work in the developing world
- Sharing best practice ideas and learning across private sponsors of clinical research, where such sharing is legal and appropriate
- Transparent disclosure to the public of our work

Quality & Continuous Improvement

- A broad and representative process for identifying best practices and studies/assessments/ evaluations to investigate the worth of those practices
- Peer review of proposals submitted both by work groups from within this initiative and by others
- Sufficient technical assistance for piloting and evaluating innovations

MRCT Implementation Strategy



- Impact
- Significance
- Expertise
- Actionable

- Global Diversity
- World-class experts
- Enthusiastic leaders
- Deliverables / timeline

- Real world testing
- Pre-determined metrics for success

- Dissemination
- Publication strategy
- Roll out at partner organizations

The MRCT Center Initiatives Update

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Focus Areas	Update
Investigator Training	**Symposia on September 18th 2012 with Key Experts to:** • Provide a forum for those working in this area to collaborate with others • Derive a consensus list of "key selection standards or criteria for sites and Pis" **Working Group Established (Co-chairs Natalie Rossignol, Program Officer, Gates Foundation; Sarah Carter, Executive Director, Amgen)**
Data and Safety Monitoring	**Working Group Established (Co-Chairs Janet Wittes, President, Stat Collaborative; Charles Knirsch, VP of Global Medical Research, Pfizer)** • Mark Barnes, Barbara Bierer, Martha Brumfield, Jeff Cooper, Dennis Dixon, Alan Eggleston, Susan Ellenberg, Joan Herbert, Sonali Kocchar, John Orloff, Jerry Sadoff, Steve Snapinn, Yoko Tanaka
Regional Ethics Committee Support	**Panel on September 18th with Key Experts (Lead by Debasish Roychowdhury, Head of Oncology, Sanofi) :** • Discuss issues and guidance for Regional Ethics Committees • Discuss approaches to move forward on this initiative
Protocol Ethics Guidance	**Working Group Launched, August 22, 2012 (Co-chairs Susan D' Amico, AVP Compliance, Reata Pharma; David Forster, Chief Compliance Officer, Western IRB)** • Mark Barnes, Barbara Bierer, Francois Bompart, Christine Grady, Kate Heffernan, John Isidor, Holly Lynch, Natalie Rossigno,l Marjorie Speers, Luann Van Campen, Mary Wacholtz, Delia Wolf

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How might we align all these initiatives

- Training is a huge issue – both Harvard MRCT and APEC recognize this – currently little ownership or coordination
  - Needs a sustained, resourced home that reaches regulators, sponsors, investigators, and maybe patients participating in trials
- Recognize what regulators control vs. what the sponsor controls
  - CRO's , investigators, choices of sites,
- The protocol , design, site selection, analysis plan
- The oversight / monitoring plan and conduct
- Evaluation of the data and study quality
- The auditing / inspection strategies

Concluding Remarks

- A lot of interest in MRCT's from different sources , organizations, and perspectives
- Already some material to build upon
- Partnering, sharing and collaborating seems the way to go
- Hope this talk provides some regulatory perspective – it is a personal perspective and others at FDA could supplement this

Roadmap Project of Ongoing Clinical Initiatives	10:00– 10:30 am

Multi-Regional Clinical Trials Center

Roadmap and Opportunity Analysis for Clinical Development Improvement Initiatives

Deloitte Consulting LLP

Executive Summary of Results

- At the initiative level, MRCT is clearly differentiated from other efforts across consortia
  - MRCT's unique initiatives enable high-impact solutions for various clinical trial stakeholders and opportunities for collaboration with regional and global consortia
- MRCT initiatives are focused in highly concentrated high-level categories such as Trial Operations, Standards and Regulatory Guidance, suggesting that there is a strong demand for solutions in these areas
- At a sub-category level, MRCT initiatives are aligned to Standards Guidance, Trial Operations Training and Regulatory Policy Guidance, suggesting that these efforts are complex and multi-faceted, requiring distinct and collaborative approaches
- Although a global focus does not completely differentiate MRCT from other consortia with similar missions, it does provide a broader aperture of impact for MRCT's initiatives
- The path forward for MRCT will represent a continued effort to differentiate and collaborate to develop holistic approaches

In the immediate term, MRCT should focus on differentiating itself from other consortia through global application of our initiatives

MRCT: Mission and Initiatives

The mission of MRCT Center at Harvard is to:

- Improve the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in or involving the developing world
- Simplify research through the use of best practices; and to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subject research

Current MRCT Initiatives

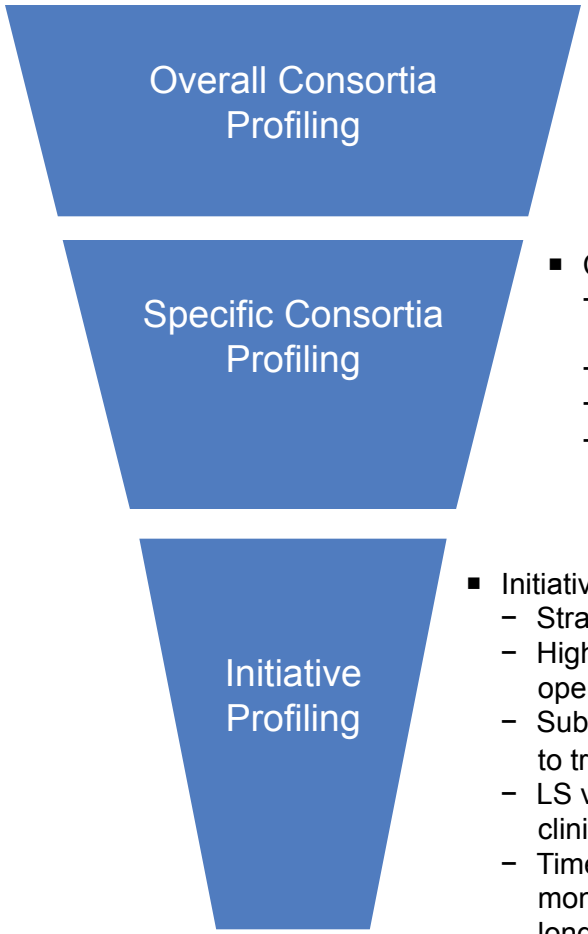
PI and Site Training	▪ Develop a standardized training and certification program for investigators and other study staff ▪ Broaden the traditional concept of study site feasibility to include a site ethical assessment
Data and Safety Monitoring	▪ Develop best practices for data and safety monitoring boards (DSMBs) ▪ Train and qualify DSMB members for trials in the developing world / from emerging markets
Regulatory Authority Engagement	▪ Support assistance, training and guidance for research ethics committees in emerging countries ▪ Ensure the REC infrastructure for trialists promotes human subjects protection
Protocol Ethics Guidance	▪ Develop a standardized protocol/ICF ethics section ▪ Derive an “ethics” checklist to guide the team at the study design stage ▪ Develop a system for evaluation of ethical issues at the program level ▪ Ensure that there are global perspective, regional-specific sections

Study Objectives and Analysis Methodology

Study Objectives

- Evaluate consortia initiatives to determine potential opportunity areas for MRCT that are consistent with its unique organizational focus, mission and initiatives portfolio
- Highlight MRCT's differentiated position amongst other consortia active in clinical development
- Recommend MRCT's forward path as comprised of specific, targeted collaboration opportunities with other consortia and other stakeholders in the clinical trial enterprise

Methodology

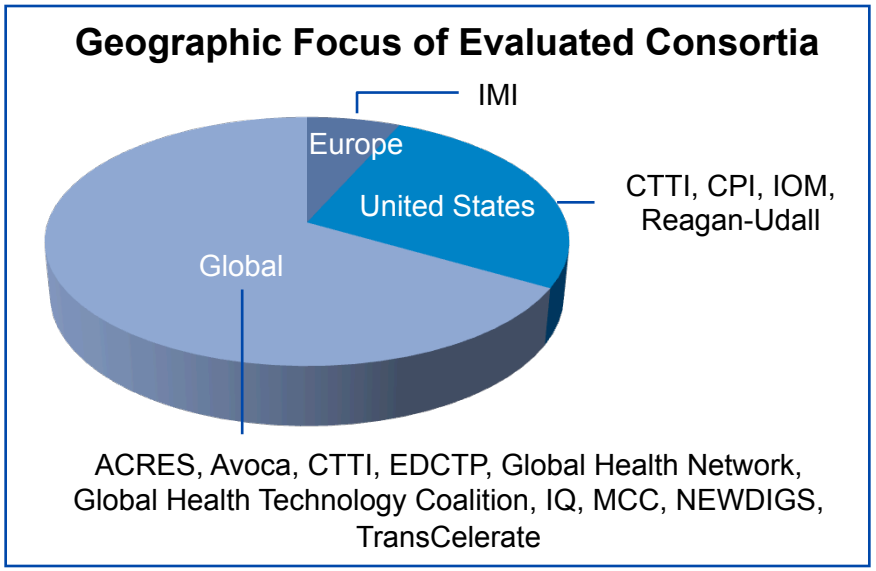


- Started with ~25 consortia
- Used criterion based on core area of consortium focus (i.e., discovery vs. clinical development) to reduce count to 15

- Consortia were profiled based on:
  - Type (e.g., public-private, industry)
  - Longevity (e.g., date founded)
  - Sponsors
  - Geographic emphasis

- Initiatives were profiled based on:
  - Strategic / operational alignment
  - High-level focus area (e.g., trial operations)
  - Sub-focus area (e.g., training related to trial operations)
  - LS value chain focus area (e.g., clinical development)
  - Timeframe (e.g., near-term is < 6 months, mid-term is 6-12 months, and long-term is > 12 months to fruition)

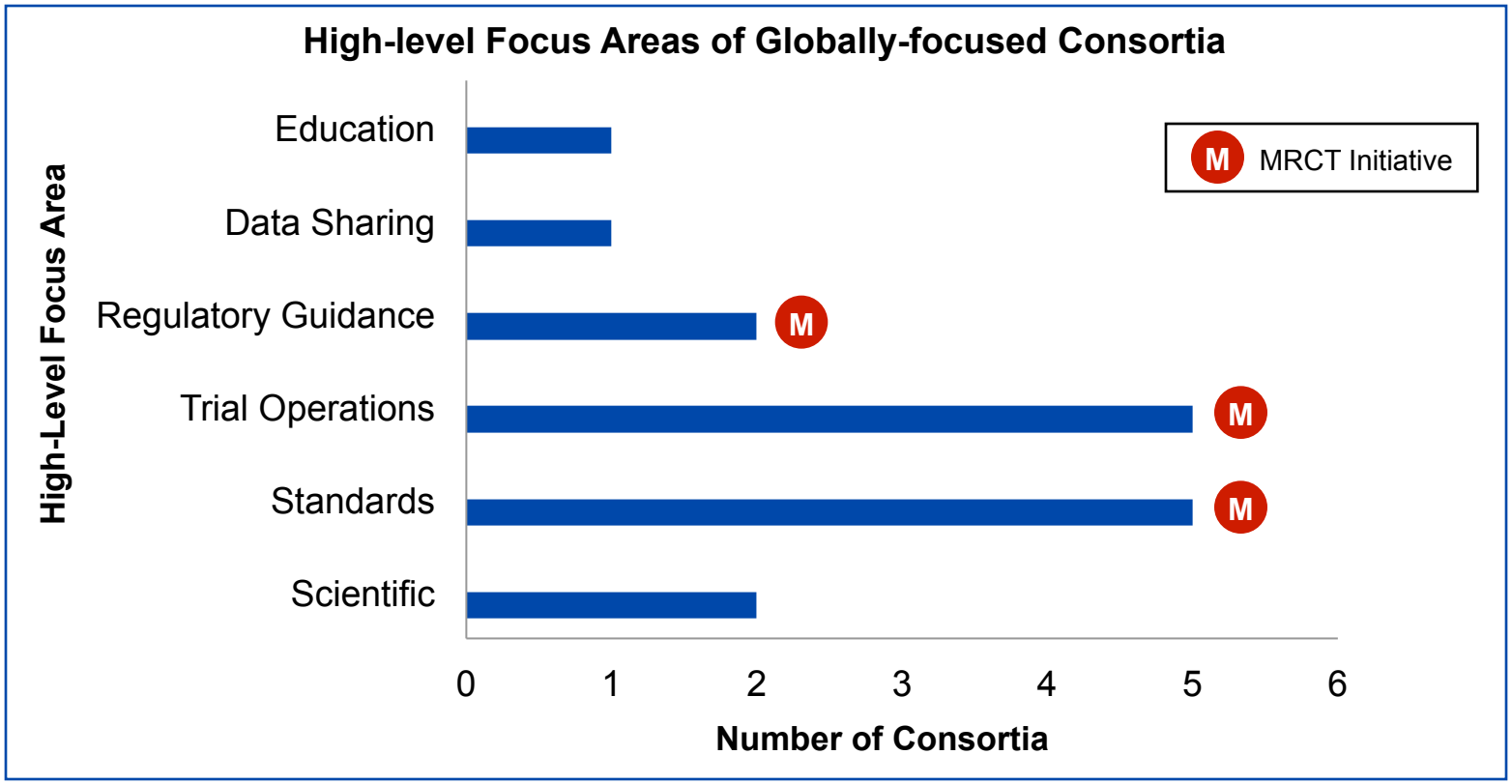
MRCT is one of nine consortia profiled in this study with a specific focus on global application of initiatives



- 7% of all consortia evaluated focus on Europe
- 27% exhibit an explicit focus on the U.S. via collaborations with government agencies and national academic and research centers
- 67%, the overwhelming majority of consortia reviewed, have a global emphasis for their initiatives

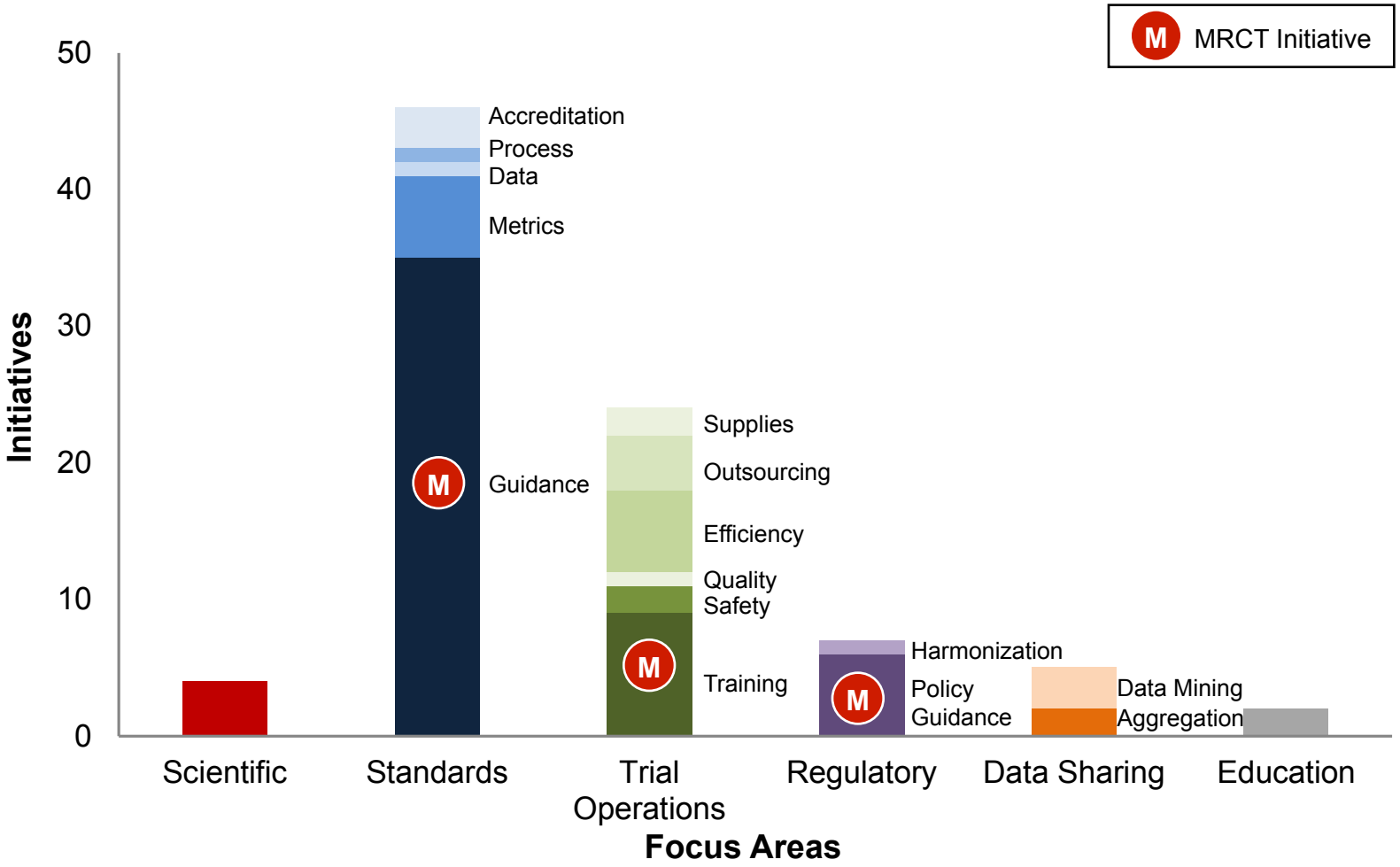
Although a global focus does not completely differentiate MRCT from other consortia with similar missions, it does provide a broader aperture of impact for MRCT's initiatives

MRCT is one of eight consortia profiled in this study with a focus on Regulatory Guidance, Trial Operations and Standards Development



MRCT initiatives are focused in highly concentrated high-level categories suggesting that there is a strong demand for solutions in these areas

MRCT initiatives fit into three specific sub-categories: Standards Guidance, Trial Operations Training and Regulatory Policy Guidance



MRCT initiatives are aligned to three of the major sub-categories focus areas suggesting that these efforts are complex and multi-faceted, requiring distinct and collaborative approaches

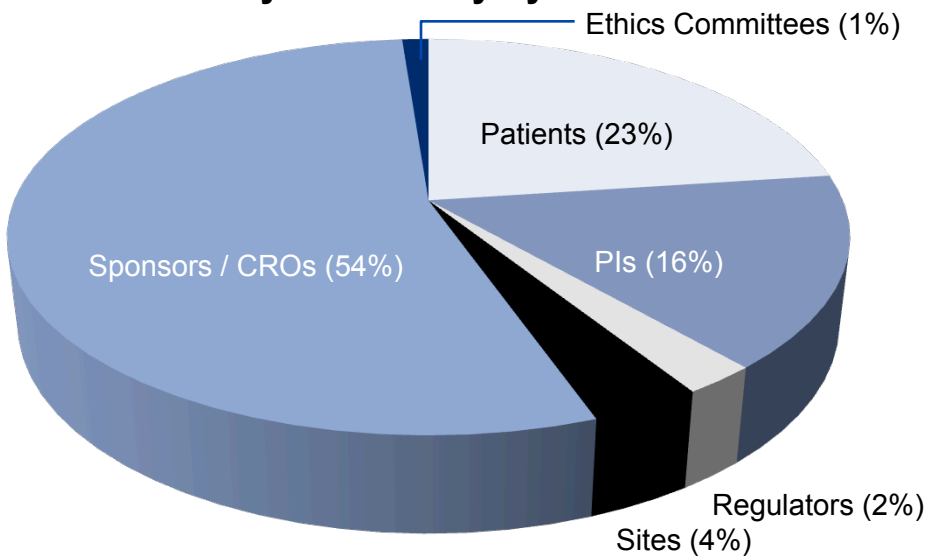
At the initiative level, MRCT is clearly differentiated from efforts of other globally-focused consortia

Trial Operations	**Training (6)**	**MRCT (2): DMC / DSMB; PI & Site Training** TransCelerate (1): Mutual recognition site qualification IMI (3): EMTRAIN, Eu2P, SafeSCIMet
Standards	**Guidance (8)**	**MRCT (1): Protocol Ethics** IQ (4): Leadership groups, Biology, CMC, Cross Disciplinary CPI (2): Data Submission, Polycystic Kidney Disease IOM (1): Clinical research transformation
Regulatory Guidance	**Policy Guidance (6)**	**MRCT (1): Regulatory Authority Engagement Initiative** NEWDIGS (1): Adaptive Licensing CPI (3): TB drug regimens, PK disease, AZ Biosignatures Reagan-Udall (1): TB drug regimens

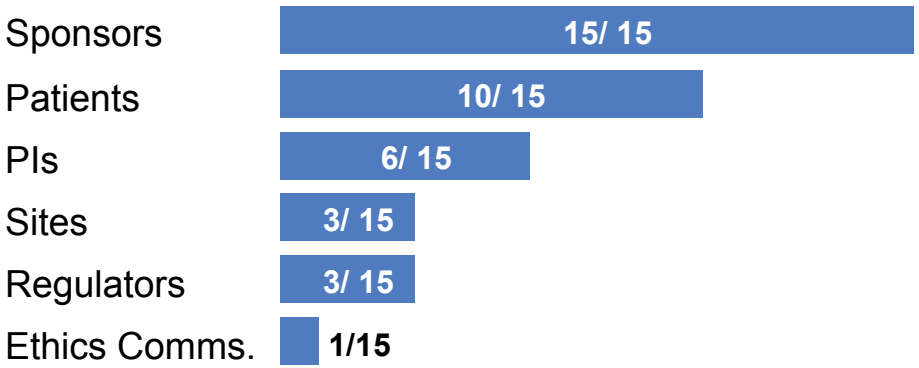
MRCT's unique initiatives enable high-impact solutions and opportunities for collaboration with regional and global consortia

In addition to a unique initiative focus, MRCT efforts seek to benefit many stakeholders across the clinical trial enterprise

Primary Beneficiary by Initiative



Primary Beneficiaries by Consortia



The path forward for MRCT will represent a continued effort to differentiate and collaborate to develop holistic approaches

Maintain a Differentiated Focus

- For strategic initiatives such as Protocol Ethics, translate these recommendations into tactical steps as a means to facilitate sponsor uptake via pilot programs
- Build and expand on the Regulatory Authority Engagement Initiative for faster / deeper insights into policy changes at a regional level
- Evaluate and expand into opportunity areas aligned with MRCT's mission and focus, including:
  - Operationally-focused regulatory guidance initiatives
  - Data-sharing initiatives
  - Education-focused initiatives

Collaborate to Create a Comprehensive Solution

- For MRCT's training efforts, evaluate partnership opportunities with TransCelerate (mutual recognition for site qualification) to expand training impact
- For PI and Site Training, develop and incorporate output and lessons from Site Metrics efforts (CTTI) and Site Quality Informatics (ACRES) as needed
- For DMC and DSMB Training, engage in discussions with:
  - Critical Path Institute on Predictive Safety Testing, e-Patient Reported Outcomes, and Data Submission Guidance
  - CTTI for Expedited Safety Reporting

MRCT Ethics Working Group Update	10:00– 10:30 am

Protocol Ethics Working Group

David Forster, WIRB Susan D'Amico, Reata

Protocol Ethics Team

Co-chairs: DAVID FORSTER (WIRB), SUSAN D'AMICO (Reata Pharma)

Christine Grady NIH

Delia Wolf HSPH

Francois Bompart Sanofi France

Holly Lynch HLS - Petrie Flom

Jennifer Miller - Bioethics International

John Isidor – Human Subject Protection Consulting

Kate Heffernan - KGH Advisors

Lindsay McNair - Equipoise Consulting

Luann Van Campen - Lilly

Marjorie Speers - AAHRPP

Mary Wacholtz - Janssen (J & J)

Natalie Rossignol – Gates

Marc Wilenzick - MRCT

Mark Barnes, Barbara Bierer (ad-hoc) MRCT

Protocol Ethics Issues Identified in Phase 1 Report

1. Limitations on current systems for reviewing trials regarding:
   - Effectiveness - quality of the review and ability to detect ethical problems
   - Efficiency – time for protocol review
   - Expertise - in some regions, local ECs lack the level of expertise or sufficient resources required to review complex protocols

2. Study teams developing protocols may not have a rigorous methodology to ensure that all ethical issues have been considered and addressed

Protocol Ethics Working Group Deliverables

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Impact: Improved investigator/monitor quality and regulatory compliance with a focus in emerging countries

Deliverable	Issue addressed	Timeline
Protocol ethics template section	2	• Draft completed 11/27/12 • Final version 1/16/13
Develop points-to-consider document that guides the user towards drafting a standardized protocol and ICF ethics section	2	• Draft completed December 2012 • Final version 1/16/13
Develop an on-line decision tree and checklist that provides guidance at the main decision points during the design phase and allows users to populate sections within a prescribed template format	2	• Draft ready for programming Mar ’13 • Final available June 2013
Develop companion checklist for ECs to ensure that key ethics issues have been addressed	1	June 2013

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Areas Covered by Ethics Workgroup

1. Equipoise, choice of controls or alternative justification
2. Population selection
3. Eligibility criteria – justifying certain inclusion criteria (i.e. inclusion/exclusion of pregnant and nursing women, other vulnerable populations) this includes gender / capacity etc but not disease-specific inclusion criteria
4. Justification of the country / regions and proportions of recruitment
5. Study related injury –adhering to local and regional laws
6. Privacy and Confidentiality – identifiers, local laws
7. Adequacy of safety monitoring plan – is an appropriate plan in place?
8. Degree of Collaborative Partnership / Community Engagement
9. Risks and Benefits
    - To participant
    - To community, (i.e. capacity building)
10. Payments to subjects –undue influence
11. Informed consent process
12. Results return – incidental findings – respecting participants, return of general results, address if the subjects will be unblinded to study arm at end of study
13. Post trial access

Progress to Date

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

- Submission to FDA Public hearing: recommended Ethics section in non-labeled drugs– May 2012

- Teleconferences twice a month starting August 2012

- 12 members convened in-person 11/27/2012 and completed Draft of Protocol template section and Points to Consider document

- Evaluated technology for web tool

Questions for Panel Discussion

1. Are there additional areas that we should address?

2. Any suggested refinement?

3. Suggestions on pilots, focus groups?

4. How to implement ?

Global Regulatory Authority and Regional Stakeholder Presentations (Working lunch)	11:30-2:00 pm	Agnes Klein - Health Canada Vijai Kumar – Excel Lifesciences (India) Ock Joo Kim – Korea Evgeny Rogoff- Russia Sabine Haubenreisser – EMA Ann Meeker O'Connell – FDA

Helping the people of Canada maintain and improve their health

Aider les Canadiens et les Canadiennes à maintenir et à améliorer leur santé

Challenges in multiregional clinical trials

Harvard University

Boston, Massachussets

Agnes V. Klein, MD

Health Canada

November, 2012



Multiple challenges

- **Differing legislation and regulatory requirements**
  - Intent is the same in all (OECD Recommendation)
  - Legal interpretation: what is the flexibility for each situation?
- Differing philosophical approaches to market authorizations
- Differences in standards of clinical/medical practice
  - Influence of medical practice on the decisions about drugs
  - Influence of new therapies on the practice of medicine
  - How do the two forces interact/mesh?
- Integration of the two: (ex: mBC and targeted therapies)

Issues encountered during GCP inspections

- Training of investigators and all personnel involved in CTs
  - PI may not be an academician: a CRO set up privately with minimal, or no training of personnel, poor understanding of GCPs and the need to follow rigorous process
  - Poorly kept source records
  - Challenges/concerns in electronic data capture systems
- Issue: variable enforcement authority in jurisdictions
- International linkages shed additional light on deficiencies
  - Including clinical trials
  - Collaboration needed between regulators to align/synchronize requirements

What are the challenges that can be identified in MRCTs?

- Broad range of challenges
- Entire gamut from legislation, to regulation, to state of the art and the science of clinical trials, to clinical outcomes, to ethics, populations/sub-populations, statistical considerations and changing approaches to trial design and analysis…
- We have learned to work with challenges so that these challenges can be leveraged into successes: often creative solutions are needed (PERs)
- Can the model be extended to the international arena?
- Further work and education are needed in a multiplicity of areas
- Better communications on the intrinsic and societal value of research are needed

Investigator training

Issue

- Regulations require that all those participating in the conduct of trials be adequately trained
- Lays the onus on the sponsor: no direct regulatory authority or obligation to train: however we do
- Regulator speaks in many venues in order to train
- (Relatively new) GCP Inspection Programme helps with education
- International exchanges are of most value:
  - Improve local practices
  - Help to export practices (Ex: PAHO and PANHDRA)
- Through the exchanges with Latin America there has been opportunity to influence new processes in development in those countries

Ethical considerations

- Declaration of Helsinki, WHO Guidelines, Tri-Council Policy, Belmont, etc.
- The degree to which, and the form in which ethics processes are used in other countries is not always clear
- In Canada, there is a trend to develop “centralized” Research Ethics Boards (REBs)
- There is no direct regulatory authority to require a certain type of REB structure: the regulations, however, do require them
- In general, the process is slow and is viewed as an impediment to MRCTs

Ethical considerations

Special ethical considerations in:

- Subpopulations: Women, Pediatrics, Elderly, Very elderly…
- **Best practices in pediatrics:** What is it?

  A voluntary guidance for researches, REBs and institutions on ethical considerations addressing health research with children
- Updating the Guidance for the conduct of clinical trials in women
  - Includes comments on Pregnancy and Lactation
  - Considers other factors in determining whether clinical trials need to be conducted in women
  - A guidance and hence provides a framework mostly

There are also special considerations in analysis of the studies and clinical applicability

Overview : “Best Practices for Health Research Involving Children and Adolescents”

WHY?

- Special ethical challenges in health research involving children
- Significant gaps in the relevant Canadian policy framework
- Impedes health research involving children

What?

- Describes and discusses the relevant policy landscape in Canada
- Identifies ethical issues in health research involving children
- Provides voluntary guidance for researchers, REBs and instions
- Foundational document –options for further guidance/resources
- Harmonizes and contributes to ethical norms

Who?

- Collaborative Initiative: NCEHR, Centre for Genomics Policy (McGill), Maternal, Infant, Child and Youth Research Network (MICRYN), Health Canada, Others

Created: 2008-2012

Controls and Trial Designs

Controls

- Issues with Placebo: Separate statement that is based on appropriate design of trials with controlled trials as the “gold standard”: years until fruition
- Analysis in preparation and considerations to legislate the registration and disclosure of trials
- In the interim, an administrative listing is being created

Continuous improvement of the CT process is needed

- The time is now: novel designs, novel endpoints, novel analyses and novel statistical methods that will likely allow a better balance between the clinic and trial outcomes

Challenges for regulators

- Differing flexibilities in regulations and their interpretation
- Issues for education
- Trial design, endpoints and analysis
- Security of data in an age of electronic data capture
  - Are the data credible?

Thank you

Transition from an Excellent Clinician to a Competent Investigator

The Indian Challenge

MRCT
Annual Meeting
Cambridge, MA
November 28, 2012

Vijai Kumar, MD
Excel Life Sciences, Inc.

EXCEL LIFE SCIENCES

Background

- India a market of branded generics until 2005
- Clinical trials not mandatory for product approval until 1987
- GCP guidelines implemented in 2005
- Simultaneous phase global clinical trials on since 2005
- Competent in medical research; naïve in pharmaceutical industry sponsored research

Indian data and US FDA NDAs

- Retisert
- Tigecycline
- Telbivudine
- Aliskerin
- Januvia

FDA Inspections in India – 2005-2011

- US FDA inspections started in India in **2005**
- **30 site inspections in 10 therapeutic areas**
- Maximum inspections in **Psychiatry**
  - 10 (33%)
- Maximum inspections conducted in **Bangalore**
  - 7 (23%)

EXCEL LIFE SCIENCES

Data Quality & Data Integrity

- All 30 inspections have been **DA i.e Data Audit**.
- Observations
  - 53% had NAI (No Action Initiated)
  - 47% had VAI (Voluntary Action Initiated)
  - **Not a single OAI** (Official Action Initiated) till date
- Common deficiencies included:
  - 04: Inadequate drug accountability
  - 05: Failure to follow investigational plan
  - 06: Inadequate and inaccurate records
  - 15: Failure to notify IRB of changes, failure to submit progress reports
  - 18: Others

Background on Competence & Training

Competence, Experience & Training (CET):

- Clinicians very well trained and experienced in patient care.
- However the CET in the field of clinical research is basic and not consistent
- Investigator growth not kept pace with increased trials

Criteria	Clinical	Clinical Trial
Competence	++++	++
Experience	++++	++
Training	++++	++

EXCEL LIFE SCIENCES

Status in India

- Training strictly limited to the few hours during the SIV
- Dedicated efforts for nation-wide effective training program taking shape
- Creation of islands of experience resulting in more trials
- Leading to increased work load impacting Quality

Next Steps

- Capacity building
- Enhance competence level
- Target tier II and III cities
- Continuous training at multiple levels
  - Investigators
  - Site team members
  - Coordinators
  - Other support staff
  - EC members
  - Community out reach programs
- Training to focus on the 3 sections of each trial

Pre Trial Stage

Focus on:

- Developing a reliable patient data base
- Projections for enrollment
- Ethics Committee submission and approval process
- Site set up
- Workload & manpower estimate
- Recruitment & retention strategies
- Contractual and commercial obligations

Trial Stage

Focus on:

- Patient identification
- Consenting process
- Screening and randomization
- Active follow up
- Quality and timely documentation
- Manage unscheduled visits
- Manage safety events
- Monitoring process

Post Trial Stage

Focus on:

- Study close out process
- Archival

Training Outline

- Active interaction between:
  - Regulatory
  - Industry
  - Academia; specialty associations/professional bodies
- Identify team of trainers & mentors
- Education on drug development
- Industry internship
- Therapeutic area specific modules
- Certification mandatory for participation

DCGI Initiatives

- GCP Inspection. Trained by US FDA field staff
- Registration of Ethics Committees
- Guidelines for compensation of trial related injury
- New Drug Approval Committees (NDAC) for IND & NDA approval

Immediate Regulatory Issues

- Training of DSMB members
  - Observers for global studies
  - Train the trainer program
- Convert more clinicians to competent investigators
- Assistance in causality analysis to determine compensation

Thank You

Vijai Kumar, MD
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EXCEL LIFE SCIENCES

Needs and Priorities in MRCT in Korea

Ock-Joo Kim
Professor of Medical Humanities
Director, Human Research Protection Program
Seoul National University Hospital

MRCT Annual Meeting
28th November, 2012
Harvard Faculty Club Theatre Room

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

DISTRIBUTION OF CLINICAL TRIALS I N ASIA-PACIFIC COUNTRIES

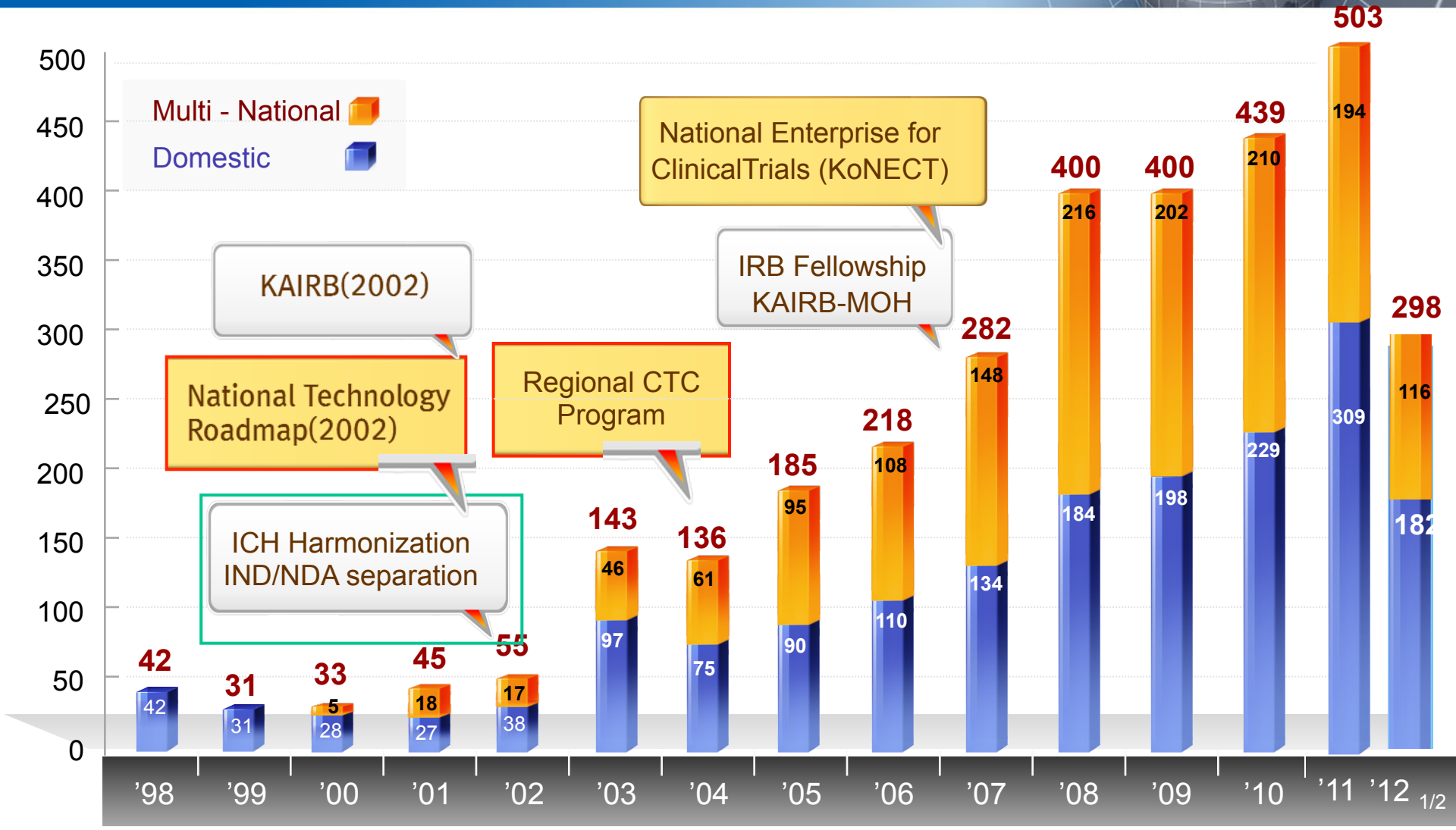
Region-wise distribution of clinical trials

Country	Phase I	Phase II	Phase III	Phase IV	Total
Australia	318	810	1354	236	2718
Korea	224	601	792	499	2116
China	192	445	709	392	1738
India	145	369	792	162	1468
Taiwan	112	361	666	269	1408
Thailand	43	178	417	141	779
Singapore	147	207	310	58	722
New Zealand	61	165	384	44	654
Philippines	8	77	287	62	434
Malaysia	8	60	261	39	368
Indonesia	2	18	66	23	109
Total	1260	3291	6038	1925	12514

Source: ClinicalTrials.gov (as on August 22, 2011)

: cumulated

Clinical Trials Approved by KFDA



Source: KFDA 2012

KOREAN ASSOCIATION OF IRBs (2002-)/MOHW , INTERNATIONAL ACCREDITATION

- 2002. 3. **Initially established as a non-governmental organization**
- Since 2007, MOHW supports **KAIRB activities**
  - **Government grants for IRB fellowship** training (2 or 6 months., 10/yr) at Western IRB
  - **Joint IRBs, Mutual Recognition, National IRBs Evaluation since 2010**
  - **Nation-wide education with FDA, MOHW (IRB members, staffs, investigators, community members, etc)** ; currently ongoing

❖ **International Accreditation (24 as 2010)**

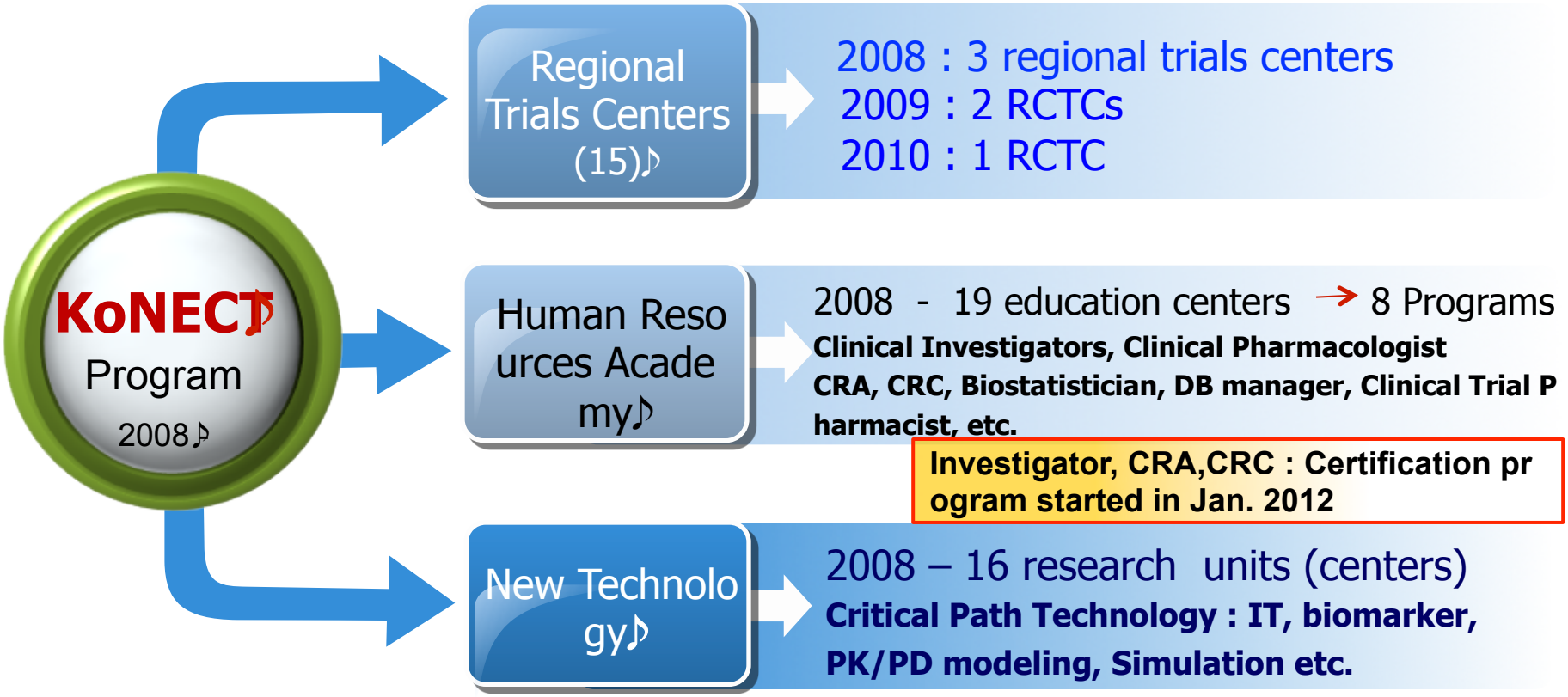
Table 1. Accredited institutions and recognized IRBs in Korea[12, 13]

AAHRPP accredited	FERCAP/SIDCER recognized
Samsung Medical Center [2006]	Seoul National University Hospital (SNUH) Institutional Review Board[2006, 2009]
Severance Hospital, Yonsei University College of Medicine [2010]	Asan Medical Centre Institutional Review Board[2006, 2009]
The Catholic University of Korea Catholic Medical Center [2010]	Kangnam St. Mary's Hospital (KSMH) Institutional Review Board[2007]
	Chonnam National University Hospital Institutional Review Board[2007]
	Inje University Busan Paik Hospital (IJUBPH) Institutional Review Board[2007]
	Hallym University Sacred Heart Hospital Institutional Review Board[2008]
	Daegu Cathulic University Medical Center (DCUMC) Institutional Review Board[2008]
	Kyung Hee University Hospital (KHUH) Institutional Review Board[2008]
	Ajou University Hospital Institutional Review Board[2008]
	Inha University Hospital Institutional Review Board[2009]
	Kangbuk Samsung Hospital Institutional Review Board[2009]
	Chungnam National University Hospital Institutional Review Board (CNUH-IRB)[2009]
	International Vaccine Institute (IVI) Institutional Review Board[2009]

Seoul National Univ. Hospital(2012)
Bundang SNUH
Borame SNUH

❖ Office of Human Research Subject Protection (in Major Hospitals)

KoNECT supports programs for clinical trial s infrastructure, 2007. 12



KoNECT (Korea National Enterprise for Clinical Trials) established in December 2007 with support from the Korean government, academics and related business industries in order to meet the increasing demands for clinical trials and to raise national competitiveness by fostering necessary human resources, developing core technology, and building a solid infrastructure to become a global clinical trial hub.

KONECT – HUMAN RESOURCES ACADEMY

- [‘08] 9 Institution – 18 Education Program
- [’09] 1st Evaluation of educational programs (CRA Program - resuffling)
- [’10] Remodeling of Education/Training Programs (17 to 8 categories)
- - Clinical Investigator, Clinical Pharmacologist, Pharmaceutical Medicine, CRC, CRA, DB Manager/ Pharmacoepidemiology/Biostatistics, Trial Pharmacist
- [’11] Standardization of Educational Program, Upgrade of Quality

PROGRAMS & TRAINEES

(source: Korea National Enterprise for Clinical Trials)

FIELDS	2008		2009		2010	
	Number of programs	Number of trainees	Number of programs	Number of trainees	Number of programs	Number of trainees
Clinical investigator training programs	4	1741	5	910	6	2124
CRC training programs	6	2390	7	2577	6	1870
CRA training programs	4	409	5	1303	6	1087
Clinical pharmacologist training programs	5	56	4	118	5	364
Pharmaceutical medicine training programs	2	35	2	48	3	46
Pharmacoepidemiologist/ biostatistician/ data manager training programs	4	474	5	661	3	595
Trial pharmacist training programs	3	166	3	211	3	164
TOTAL	28	5271	29	5828	32	6250

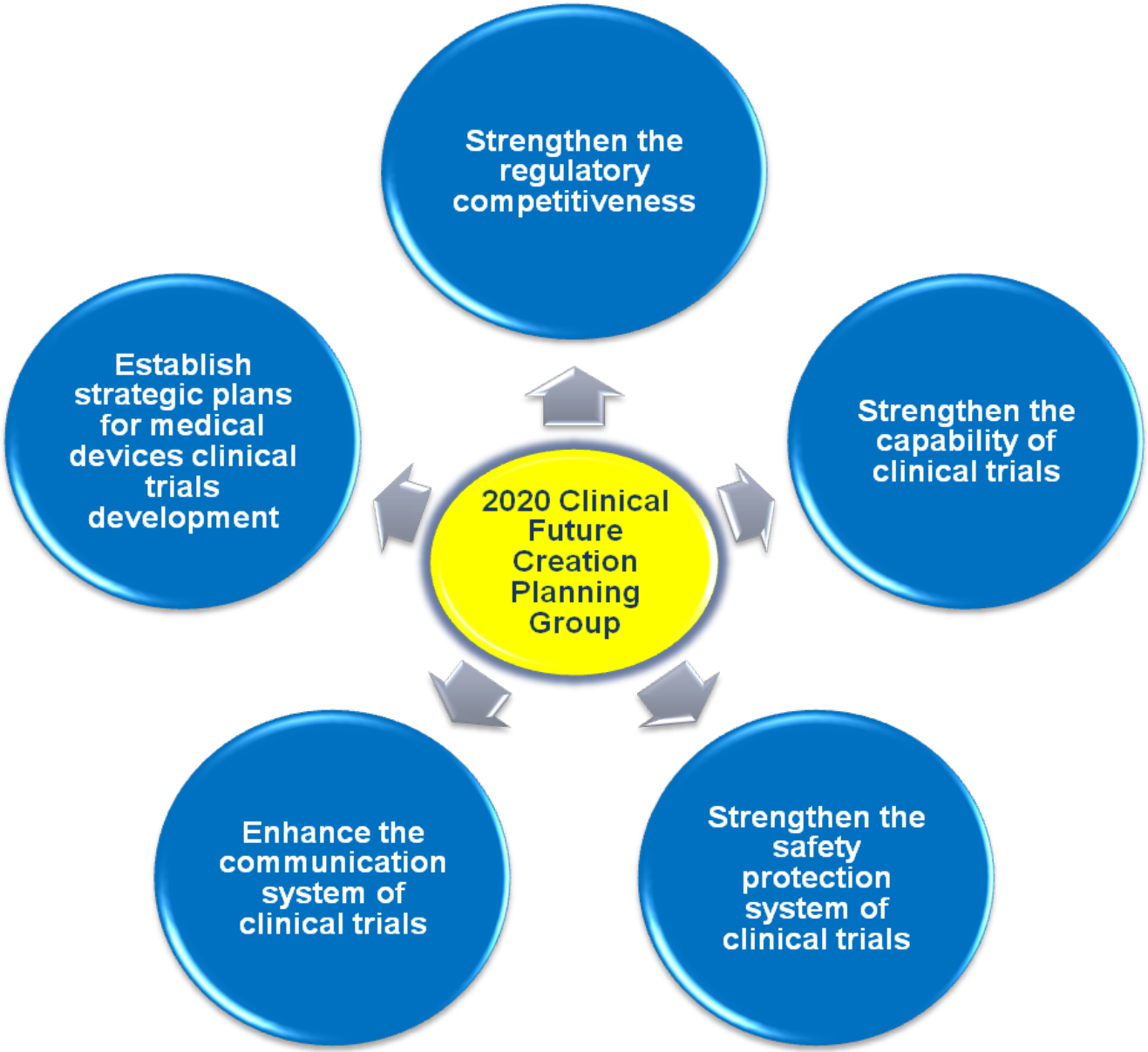
CERTIFICATION SYSTEM FOR CLINICAL TRIALS PROFESSIONALS, KoNECT ATTA

- **Target Professionals**
  - Physician Investigators, CRC's, and CRA's Methods for certification
- **Methods for certification**
  - Completion of training + (job experience) + written exams♪
- **Duration of certification -** Two years
- **Maintenance of certification**
  - Continuing education needed♪
- **Levels -** Two levels:
  - Level 1: Qualified (competency)
  - Level 2: Certified (expertise)
- **1st Examinations:**
  - Date: Feb 4, 2012 10:00~11:00
  - Level: Qualified
  - Questions: 50 MCQ (Type A)
  - Pass Criteria: 70% and higher
  - Examinees: 50 PI, 100 CRC, 100 CRA

Requests, Suggestions on Certification System

- **Suggestions and Opinions**
  - Contribute to quality improvement
  - Hope for well-established system
  - Need for resources to prepare for exams
  - Request for online testing service
  - Quality assurance of system for international recognition
  - Expand to other professionals and increase number of slots for exams
- **Certification exams mainly test knowledge and awareness of skill sets**
  - interpersonal skills may be different by culture
- **No controlled studies to confirm the effectiveness of certification system**
  - no direct correlation between certification and performance, career development, salaries, etc.
- **Need for follow-up**
  - keep updated databases on job positions, salaries, and satisfaction indices
  - conduct survey on performance put through companies and institutions where certified persons work
  - performance evaluation report from designated supervisors

Five 'issues and tasks' of '2020 clinical trial future creation planning gro up' adopted by Korea FDA "Comprehensive Plan for Clinical Trial Devel opment"



KOREA Comprehensive Plan for CT (2012 – 2020) – strengthening CT safety protection system

Support for Center for HRP

- Korean FDA began to support and promote establishment of Center (Office) for Human Research Protection in each clinical trial center
- Currently around 10 big hospitals have OHRP/CHRP
- Establishing a CHRP has an advantage when CT center applies for governmen tal grants

Clinical Trial Compensation Guidelines

- To develop a standard guildelines for clinical trial compensation guidelines initiated by Korean FDA
- A draft prepared by the Clinical Trial Compensation Guidelines Korea Pharmaceutical Manufactures Association (KPMA) & Korean Research Based Pharmaceutical Indust ry Association(KRPIA) [2008]
- Reviewed by the Korean Association of IRBS [2012 – undergoing; aiming at 2013]

IRB accreditation and IRB member Training

- Bioethics and Safety Act (2013.2. Total revision) mandates govenmental ev aluation and accreditation of IRBs
- Ministry of Health, KFDA, KAIRBs work together to improve IRBs and IRB members
- Education management for IRB memebrs and staffs.

Promotion of Internal audit

- Korean FDA promote internal audits for ongoing study protocols by Quality Ass urance unit since Feb. 2012.
- Currently around 5-7 hospitals have QA units at OHRP/CHRP
- Routine audit; For-cause audit ; Spot Audit

Korean FDA's New Inspection Initiative

- **New model of oversight**
  - Launched in 2007
  - Based on thinking : Quality is a System Property
  - Every 3 years to oversee whole Accredited Clinical Institutes to ensure the system is working
- **Surveillance inspections -** Real-time, Risk-based approach
  - Selection of trial protocols based on quality risk management process
    - Development phase/ Therapeutic area
    - Study population (pediatric, other vulnerable)
    - Number of serious unexpected adverse drug reaction at trial site
  - Inspection team – more than 2 inspectors
  - scheduled inspections to review overall operations and procedures of the institution(IRB, Investigator, etc)
  - Examine to determine whether they conform to current KFDA regulations and IRB/institution's own written procedures
- **Directed inspections**
  - Unscheduled, focused on the specific clinical trial or trials.
  - result from a complaint, clinical investigator misconduct, or safety issues pertaining to a trial or site.

Recent Initiatives for Clinical Trial In Korea – government, academia, industry

- **KoNECT/MOHW - Global Leading CT Center Consortium ($ 2 million each for 2 centers, 2012 Dec)**
  - Global Unmet Needs Area · Early Phase center of Excellence, · Global/Asia Network
- **KFDA, KAIRB – participants outreach program**
  - Clinical trial information center · education program for potential participants · pu blication of pamplet, brochures, online for adults; cartoons & short movies for chi ldren
- **KFDA Guidelines**
  - for DSMB (2008); for evaluating clinical trials with children (2007); for evaluating clinical trials with women (forthcoming)
- **KFDA funds for clinical trials for children (5.5 million for 2012)**
- **Promoting GCP, research ethics education at various levels**
  - medical schools, graduate schools, GCP, CITI Korea, KAIRB –KFDA joint symp osium (2012)

CONTRIBUTORS

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- **Howard Lee, MD PhD, Professor of Clinical Pharmacology, Clinical Trial Center, Seoul National University Hospital, Korea**

Clinical Trials in the Russian Federation

What are the features ?

Scope

- Basic facts
- Legal framework
- Site selection
- Specifics
- Insurance
- Submission of the dossier
- Expert bodies
- Pharmacovigilance

Basic facts

- Country population - 143 million
  (73% -urban habitants)

- Highly urbanized healthcare system
- High recruitment & low drop-out rate
- Experienced, GCP trained investigators (all – MD)
- Monitors with healthcare background - up to 90%
- High quality data

Legal Framework for Clinical Trials

- Federal Law from 12.04.2010 №61-FZ “On circulation of medicines”
- Order of the Ministry of Healthcare of the Russian Federation from 19.06.2003 №266 “On the approval of Clinical Practice in the Russian Federation”
- National standard “Good clinical practice” GOST P 52379-2005 (Non-binding guidance)

Federal Law from Apr 12, 2010 №61-FZ “On circulation of medicines”

Article 3

The results of the clinical trials conducted outside of Russia are accepted only if a mutual recognition agreement exists between Russia and a respective country (countries)

Article 40

Special permission is required for border crossing of biological material (e.g. test samples of urine, blood, serum)

Article 41

Special requirements for clinical trial contracts

Article 43

Special requirements for patient’s inform consent form

Article 44

Requirement for life and health insurance of tiral participants

Important legal provisions

- Clinical trials can be performed only by the research sites registered in the official database of MoH (accreditation)

- Only a qualified person (MD) with at least 5 years of professional experience in clinical trials area can serve as Principal Investigator

Clinical Trial Sites in Russia

TOTAL: 844

Official Databases of MoH

- **Clinical trials sites** (in Russian) http://grls.rosminzdrav.ru/Ree_orgCI.aspx

- **Clinical trials permissions** (in Russian) http://grls.rosminzdrav.ru/CIPermitionReg.aspx

Insurance

- **Mandatory insurance** (trial participants)
- **Insurance should be issued by the Russian companies**
- **Legal framework –** Government Decree from Sept 13, 2010 №714 “The typical rules for compulsory insurance of the life and health of a patient involved in clinical trials of a medicinal product”
- **Insurance fee:** 1445 - 9811 rub (~46- 316$) per patient
- **Coverage**: max (in case of death) - 2 000 000 rub (~64 500$) per person
- **Insurance should cover an entire period of the study**

Initial Dossier for Submission of Clinical Trial

- **Application letter** (if not provided by the manufacturing company)
- **Application fee payment order** (original)
- **Clinical trial protocol** (in English & Russian)
- **Investigator Brochure** (in English & Russian)
- **Informed Consent Form** (in English & Russian)
- **Case Report Form**
- **Insurance certificate** (in Russian insurance company)
- **List of participating clinical sites**
- **CVs of PIs**
- **Patient-related documents** (if any)

Clinical trials fee

- **Legal base -** Tax Code of the Russian Federation (chapter 2, art. 333.32.1)
- For International Multicenter Clinical trials – 200 000 rub (~6300$)
- Should be transferred to the MoH
- Cover scientific and ethical assessment of the application

Official Expert Insitutions

- Federal State Institution Scientific Center for Expertise of Medical Products of the Ministry of Health (scientific review - 1 month)

- Ethical Council of the Ministry of Health (ethics review - 1 month)

Grounds for denial

No approval can be granted for:

- clinical trials of medical devices and equipment
- clinical trials without the definite goals to evaluate a medicine
- clinical trials involving vulnerable patient groups, including:

- Under-aged patients
- Military and law-enforcement personnel
- Convicted individuals
- Pregnant women

Final MoH approval is granted after:

- Positive response from the Federal State Institution Scientific Center
- Approval of the Ethical Council at the Ministry of Health

Following study start?

SAE & SUSAR can be submitted to Roszdravnadzor in 2 ways:

A) by CIOMS form via e-mail to: clinic@roszdravnadzor.ru

http://www.syncitium.easy-site-build.com/f/CIOMS-I_FORM.pdf

B) in database of Roszdravnadzor directly

(only for authorized users)

Thank you!

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA needs and priorities relating to Multi-regional Clinical trials

MRCT Annual Meeting
28 November 2012
Harvard Faculty Club, Cambridge

Sabine Haubenreisser, MSc, PhD
European Medicines Agency Liaison Official at the U.S. FDA

Disclaimer

The views presented in this presentation/ these slides are those of the author and should not be understood or quoted as being made on behalf of the European Medicines Agency and/or its scientific committees

The facts……

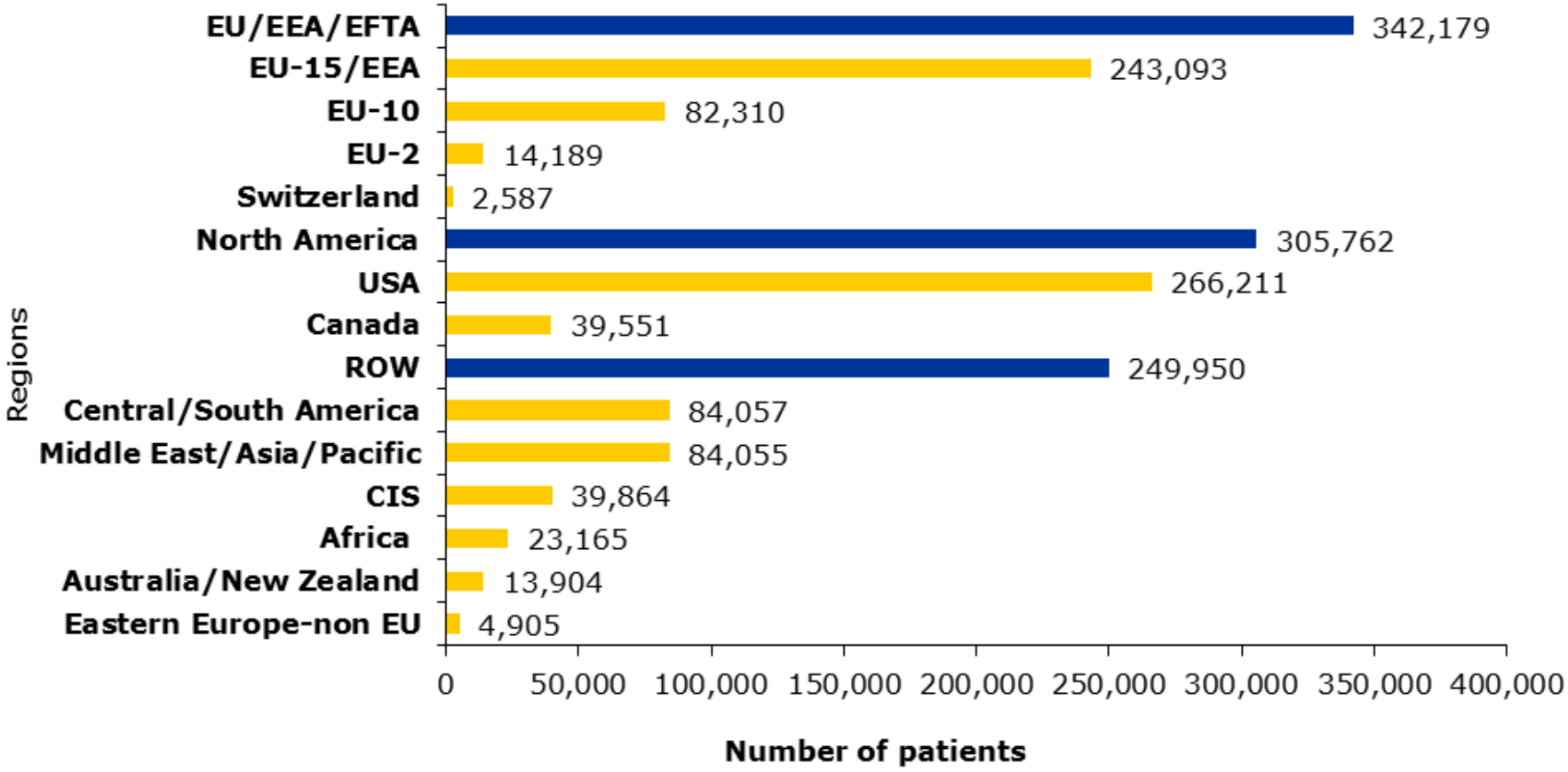
Between 2005 and 2011

897,891 Patients in pivotal trials

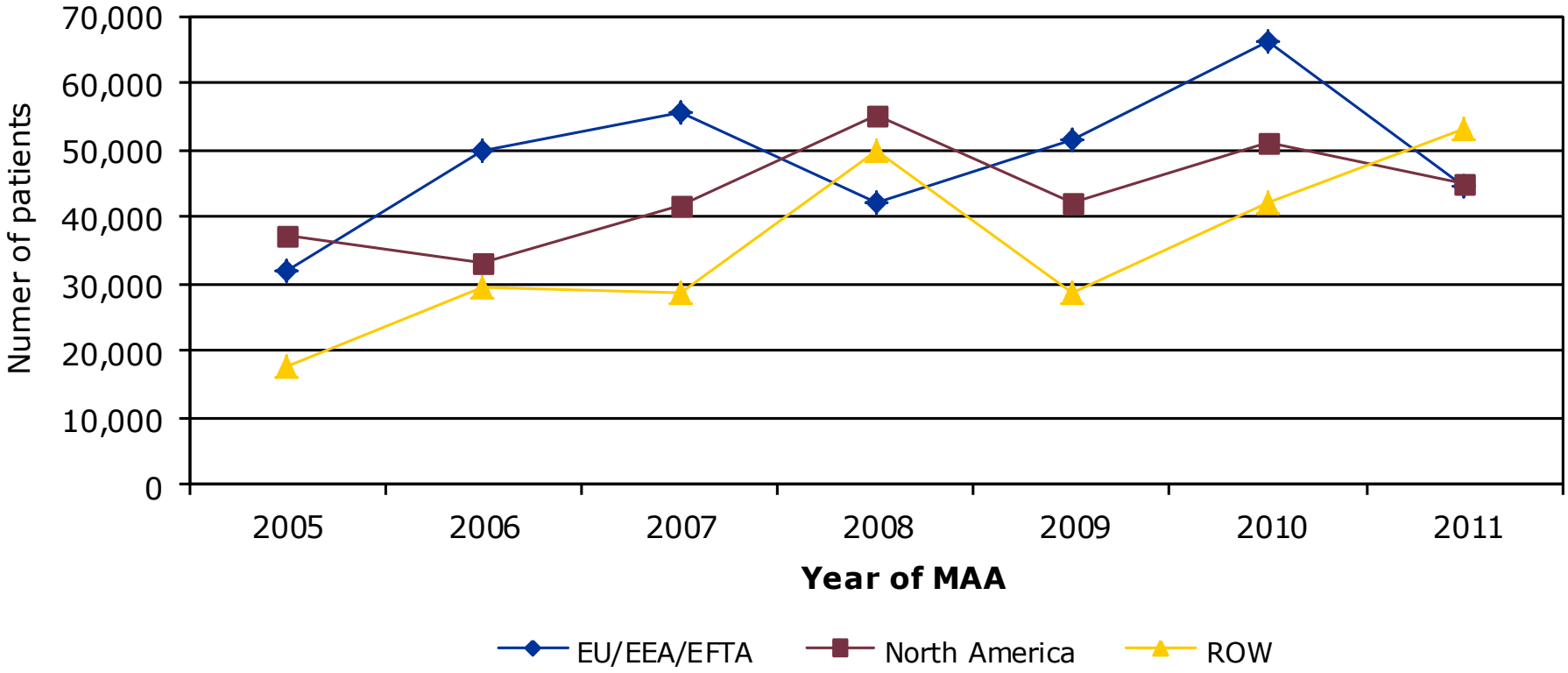
(38.11% in Europe, 34.05% in North America, 2.58% Africa, 9.36% Middle East/Asia Pacific, 4.44% CIS, 9.36 % Latin America, 2.1% other)

70,291 clinical trial sites in **106** countries

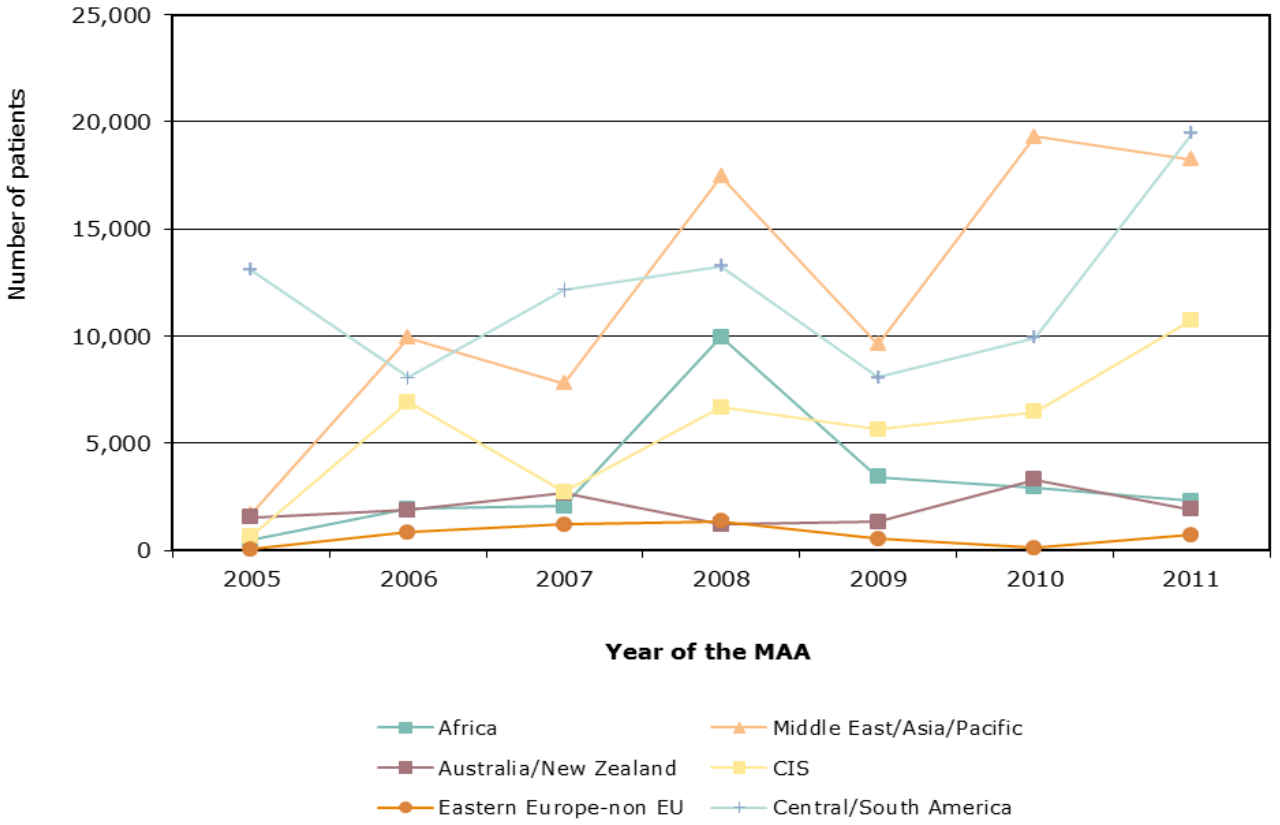
485 new centralised MAA applications plus line extensions, **265** GCP inspections



Number of patients in pivotal trials submitted in MAAs to the EMA per region/sub-region during the period 2005-2011. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World) and then split into its component sub-regions.



Number of patients in pivotal trials submitted in MAAs to the EMA per region and year. The data are shown as three "global regions" – EU/EEA/EFTA, North America and ROW (Rest of the World).



Number of patients in pivotal trials submitted in MAAs to the EMA in the sub-regions of ROW region per year.

What are the challenges?

Acceptability

- Ethical requirements
- Data quality

Applicability

- to EU population
- to EU medical practice

- Pivotal data?
- Need for bridging studies?

Acceptability

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012
EMA/121340/2011
The European Medicines Agency Working Group on Clinical Trials conducted outside of the EU/EEA

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

Released for Consultation	26 May 2010
End of consultation	30 September 2010
Agreed and Endorsement by CMD	14 June 2011
Agreed by EMA Working Group on Clinical Trials conducted outside of the EU/EEA	05 July 2011
Endorsement by CHMP	19 October 2011
Endorsement by EMA Management Board	15 December 2011
Endorsement by Heads of Medicines Agencies	24 February 2012
Date coming into effect	1 May 2012

Keywords	***Clinical trials, GCP, Marketing Authorisation Applications, EMA, EU, Ethics, conducted outside of the EU***

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An agency of the European Union

"Reflection paper on ethical and GCP aspects of clinical trials conducted in third countries for evaluation in marketing authorisation applications for medicines for human use, submitted to the EMA" published April 2012

Four areas are addressed:

1. Undertake international cooperation in the regulation of clinical trials, their review and inspection and capacity building in this area
2. Clarify the **practical** application of ethical standards for clinical trials, in the context of EMA activities
3. Determine the **practical** steps undertaken during the provision of guidance and advice in the drug development phase
4. Determine the **practical** steps to be undertaken during the Marketing Authorisation phase

Key points of reflection paper

- No new legal requirements – practical steps based on existing EU legal framework
- Clear message that ethical standards are supported at the MAA step
- Reinforcement of proactive steps (advice to sponsors/applicants, capacity building)
- Triage at MAA step to focus on specific trials – questions to applicant/ triggering of GCP inspection
- Option for CHMP to seek expert advice in difficult situations
- Clear and consistent information in EPAR

Next steps

Continue implementation of the practical actions set out, and further development of policy and processes where needed.

- Update of assessment report and EPAR
- Review assessment of dossiers and inspection with focus on key trials
- Access to ethical expertise for CHMP
- International cooperation
  - Training, capacity building
  - Opportunity for joint or observed inspections
  - Identify funding and opportunities for synergy
  - Information sharing with international partners on planned and conducted inspections (based on confidentiality arrangements)

Applicability

ICH E5 (Ethnic Factors in the Acceptability of Foreign Clinical Data)

- Focused on bridging studies
- Medicine´s sensitivity to ethnic factors

ICH Topic E5(R1) Questions and Answers

- Focused on the use of multi-regional studies as bridging studies
- Identifies basic issues
  - Definition of disease and patient
  - Control group
  - Efficacy variables
  - Safety assessment
  - Medical practice, concomitant medications
  - Duration of the trial
  - Severity distribution
  - Dose and dose regimens

Relevance of submitted clinical data from emerging regions is not always clear and extrapolation to a European population may sometimes be difficult due to several factors.

INTRINSIC			EXTRINSIC
Genetic		Physiological and pathological conditions	Environmental
Gender		Age (children - elderly)	Climate Sunlight Pollution
	Height Bodyweight		
		Liver Kidney Cardiovascular functions	**Culture** Socio-economic factors Educational status Language
	ADME Receptor sensitivity		
Race			Medical practice Disease definition/Diagnostic Therapeutic approach Drug compliance
Genetic polymorphism of the drug metabolism			
		Smoking Alcohol	
		Food habits Stress	
Genetic disease		Diseases	Regulatory practice/GCP Methodology/Endpoints

Source: ICH 1998 E5(R1): Ethnic Factors in the Acceptability of Foreign clinical Data

Reflection Paper on Extrapolation of Results in Clinical Studies conducted outside EU to the EU-Population

Study of a number of files for which the interpretation of the data for EU had been found to be difficult

Emphasizing ICH E5 where relevant

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/11/WC500013468.pdf

Findings

Medical practice

- Differences in co-medications and invasive procedures (antithrombotic agents, cardiovascular field)

Disease definition

- Heterogeneous medical conditions (fibromyalgia)
- Medicalization of some conditions
- Insufficient standardization and validation of scores and scales (psychiatric diseases)

Study population

- Different inclusion criteria
- Life style, medical and social environment

Conclusions of Study

Propose prospective analysis of potential extrinsic/ intrinsic factors when conducting a clinical trial in a certain region.

This may facilitate regulator's decision whether certain clinical trials conducted outside EU are relevant to EU setting or whether additional trials required.

Recommended to address identified factors in planning stage and in a more structured fashion during Scientific Advice.

EMA approach to non-EU trial data

Two principles:

- Acceptability – ethics, subject protection and data quality
- Applicability – intrinsic and extrinsic factors

Two sets of process:

- Prospective – guidance, scientific advice, PIP….
- Confirmatory – assessment, inspection….

Global approach:

- Network of regulators
- International ethical and data quality standards in place and reinforced globally
- International clinical development plan addressing common standards and needs

Goal

- Subjects/patients participating in trials are fully protected – wherever the trial takes places

- Availability of safe and effective new medicines, as early as possible, with data relevant to all regions

Acknowledgements

Fergus Sweeny, PhD

Head of Sector Inspections and Compliance Sector, European Medicines Agency

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CDER Perspective: Enhancing Trial Quality and Efficiency

November 28, 2012

Ann Meeker-O'Connell
Director ,Division of Good Clinical Practice Compliance (Acting)
OSI, OC, CDER, FDA

Disclaimer

- This communication constitutes an informal communication that represents the best judgment of the speaker at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

Desired State for Clinical Development

"Maximally efficient, agile clinical development programs that reliably produce high quality data and protect trial participants without extensive regulatory oversight"

- Janet Woodcock, MD
  CTTI Monitoring Workstream #3 Workshop

Are we there yet?

What Is Quality?

Quality in clinical trials = the absence of errors that matter

Example: Errors that Mattered

- eCRF screen design confused site personnel
  - Collected signs/symptoms for secondary endpoint
    - **(5) Resolved**
    - **(4) Worse**
    - **(3) Improved**
    - **(2) Same**
    - **(1) New**
- Widespread discrepancies in data entry
- System audit trails incomplete

Building Quality into Clinical Trials

- Traditional monitoring and auditing approaches
  - Aren't suited to *preventing* errors that matter and may not readily detect systemic errors
- "The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol."

  FDA Draft Clinical Monitoring Guidance (published 29 August 2011)
- For a trial, the protocol – or more appropriately the investigational plan – is a blueprint for quality

Planning for Quality Supports Consistent Conduct of Global Trials

- Prospectively identify the aspects of the trial that are "critical to quality"
- Identify important and likely risks to "critical to quality" aspects
- Tailor the investigational plan and its implementation to eliminate -- or reduce the impact of --"errors that matter"

CTTI Quality-by-Design Project

- General principles about what really matters in clinical trials can and should be developed—i.e., what do we really need to get right to ensure reliability of results and patient protection?

https://www.ctti-clinicaltrials.org/website-administration/documents/QbD%20workshop_exec%20summary_1_30_12_FINAL_v3.pdf

Project Goal

- Produce a draft document outlining:
  - High-level principles for building quality into trials
  - One potential approach to prospective quality planning
- Test the document through a series of workshops with hands-on exercises involving:
  - Different therapeutic areas
  - Different product types
  - Various stakeholders
  - Different functional lines
- Refine and publish document and case-studies

FDA Requirements: Clinical Trial Quality

- Broad sponsor responsibilities for clinical trials under 21 CFR 312, including:
  - selecting qualified investigators
  - monitoring trial progress
  - ensuring trial is conducted per investigational plan
  - reviewing and analyzing accumulating evidence relating to the safety and effectiveness of drug

Where do Quality by Design and Quality Risk Management fit?

Key Concepts

- There is not one “right way” to implement QbD and QRM in clinical trials

- Approaches must be
  - sufficiently flexible and
  - not unduly burdensome

- Should not be “another layer” added to existing practices

How do we get there?

- Success rests on:
  - Focus on first principles: obtaining reliable evidence for decision-making
  - Broad engagement of stakeholders, including *Clinical investigators, Patients, and Regulators*
  - Early identification and discussion of barriers to implementation
  - Willingness to pilot and refine QbD and QRM

Thank you!

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MRCT DMC/DSMB Initiative	2:15-2:45 PM

DSMB Working Group Update

Charles Knirsch, Pfizer

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Co-Chairs: Charles Knirsch (Pfizer), Joe Massaro (BU)

- Alan Eggleston (CMed)
- Martha Brumfield (CPI)
- Jeff Cooper (Huron)
- Dennis Dixon (NIH)
- Susan Ellenberg (Penn)
- Joan Herbert (MMV)
- Sonali Kocchar (Path)
- Joe Massaro (BU_
- John Orloff (Novartis)
- Jerry Sadoff (J & J)
- Steve Snapinn (Amgen)
- Yoko Tanaka (Lilly)
- Janet Wittes (Stat Collaborative)

- Mark Barnes, Barbara Bierer (MRCT, ad hoc)

Data Safety Monitoring Issue and Goal

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Impact: Increased engagement of experts from emerging world on Data Monitoring Committees for multi-regional trials.

Goal – to identify, train, recruit experts from emerging regions who have expertise in medicine or statistics, experience in clinical trials, and who would like to serve on Data Monitoring Committees.

HARVARD Global Health Institute

1. Identify qualified DSMB members from the developing world

2. Educate and train DSMB members for trials in the developing world

3. Apprentice DSMB members from emerging markets to serve on boards

Data Safety Monitoring Project Progress

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

1. Identify qualified DSMB members from the developing world

   Progress – Met with Fogarty Institute; agreement they would solicit qualified Fogarty International Clinical Research Scholars & Fellows for the program once regions are determined

2. Educate and train DSMB members for trials in the developing world

   Progress – Proposal to partner with Society of Clinical Trials and co-sponsor a training workshop at the SCT meeting (May 17, 2013, Boston)

3. Apprentice DSMB members from emerging markets to serve on boards

   Progress – Pharma members of workgroup are reviewing trials:

   - to be conducted in emerging countries
   - in the pipeline to start in Summer/Fall of 2013
   - would be appropriate to allow fellows to participate

Timeline – 6-12 fellows to be trained in May and start participation in Spring/Fall of 2013

DSMB Training Curriculum (Proposed)

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Target Audience - Investigators, ethicists and statisticians who have never served on a DSMB or need a refresher

SESSION A (1/2 DAY) – Lead by SCT

- What is the role of the DSMB, composition
- Charter – role, what is it, how used
- Cover the various roles (chair, presenters, etc)
- DSMB review process of protocol and ICF prior to study start
- How to present to the DSMB
- Role-playing based on real trials
- Stopping rules

SESSION B (1/2 DAY) – Lead by MRCT

- Provides further depth on issues that arise from global trials
- Ethics issues
- Case studies (country-specific)

Issues for Panel Discussion

- Suggestions on the draft training curriculum?
- Suggestions on how to incorporate regional / country-specific case studies into the training?
- Number of active DMC's in your country?
- Suggestions on how to move into wider implementation if the pilot program is successful?
- Other thoughts on approach?

MRCT PI Competence and Training Initiative	**3:15-3:45 PM**

PI Competence and Training Working Group Update

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

Co-chairs: NATALIE ROSSIGNOL (Gates) , SARAH CARTER (Amgen)

- Mohanish Anand (Pfizer)
- Tracy Blumenthal (Rapidtrials)
- Ann Claiborne (IOM)
- Sheila Clapp (fhi360)
- Amy Davis (PRMR)
- Kim Havens (PPD)
- Anna Ravdel (Synergy)
- Jim Thomasell (ACRP)
- Jennifer Webb (DIA)
- Helmut Wolf (Novartis)
- Investigators from emerging countries (TBD)

- Mark Barnes (MRCT) – ad hoc
- Barbara Bierer (MRCT) – ad hoc
- Marc Wilenzick (MRCT) – ad hoc

PI Competence Issues Identified in Phase 1 Report

1. Tremendous variation in skills and experience of PIs and coordinators worldwide; lack of adequate training and support can threaten research and data integrity; first time PIs and coordinators may have little background in research design or ethics

2. Training programs are not typically modified or tailored to suit specific regional (geographic) or cultural requirements.

3. Lack of metrics to establish correlation between PI certification or training and improvements in the quality and efficiency of clinical research

4. Lack of guidelines for core competencies that must be obtained by investigators prior to conducting clinical research

Attachment 4
Suggested Core Competencies for Investigators

• Fundamentals of Clinical Research (General)
o Purpose and Objectives
o Study designs
o Randomization
o Analytical approaches
o Elements of a protocol (study design)
o Differences in the objectives of clinical research and medical practice
• Responsibilities of an investigator
o What is a 1572
o What it means to be solely responsible for all aspects of a clinical trial
o Delegation of Authority
• Ethical principles in Clinical Research
o Applicability of the research to the potential study population.
o Differences between clinical research and medical practice; conflicts of interest within physician-researchers
o Difference between a patient and a clinical research volunteer
o Need for ensuring fair benefits to subjects
o Nature of the comparison group (worldwide best standards or local ones? Placebo?)
• IRBs/ Ethics Committee:
o Role
o Identifying an appropriate IRB/EC
o Potential responses and site level actions
o Ongoing review
o Reporting requirements
• Informed Consent
o Process to educate patients and to obtain informed consent
o Assuring informed and voluntary consent

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The MRCT Center at Harvard

Impact: Improved investigator/monitor quality and regulatory compliance with a focus in emerging countries

Deliverable	Issues addressed	Timeline
Develop minimum training standards (list of core competencies) for PIs and clinical staff	1, 4	JUNE 2013 Draft for discussion at DIA roundtable forum in June 2013
Review currently available GCP training materials, assess against proposed standards and identify the gaps	1,2	December 2013
Develop a web-repository of training materials that meet minimum standards to be open-access	1, 4	December 2013
Determine measurements of impact for training initiative outputs.	3	June 2013 Draft for discussion at DIA roundtable forum in June 2013

Questions for the Panel Discussion

- What is perceived by the regulatory agencies as high priorities in the area of investigator and site staff competence?
- Should MRCT efforts be limited to GCP training or expand to areas listed on the PI competency list?
- What are the gaps in investigator and site staff training in your country that could be addressed by MRCT?
- What are potential metrics or measurements to evaluate success of the training standards (e.g., decreased # of audit findings)?
- How should training be modified or tailored to suit specific regional (geographic) or cultural requirements?
- Workgroup Membership suggestions?
- Partner suggestions? How and where?
- What could be an initial focus for the group (country, city, project)?

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Wrap Up and Closing Remarks

Rebecca Li, PHD	MRCT
Mark Barnes, JD	MRCT

HARVARD Global Health Institute

MRCT Website Launching Soon!

MRCT Multi-Regional Clinical Trials
The MRCT Center at Harvard

HARVARD Global Health Institute

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Building a Learning Community Among Key Stakeholders

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QUICK LINKS

- Understand our Mission
- Register for an Event
- Become a Partner
- Get Involved with MRCT

FEATURED PROJECTS

Protocol Ethics Project
Impact: Increased transparency regarding ethics in the protocol, ICF and study design

Investigator Competence Project
Impact: Improved investigator/monitor quality and regulatory compliance with a focus in... more

Data Safety Monitoring Committee Project
Impact: Increased protection of participants through increased engagement from individuals in... more

PARTNERSHIPS SPOTLIGHT

DIA www.diahome.org
The global forum for therapeutic innovation & regulatory science

ACRP Association of Clinical Research Professionals
The Association of Clinical Research Professionals (ACRP) is the primary resource for clinical... more

PhRMA
Represents leading research-based pharmaceutical and biotechnology companies in the US.

NEW & NEWSWORTHY

MRCT Annual Meeting
MRCT Annual meeting on November 28, 2012 with the Regulators. Click here to download the agenda

NEW PARTNERS HIGHLIGHT
Welcome to our four new 2012 MRCT partners, DIA, ACRP, Synergy, PhRMA

Harvard MRCT September 18, 2012 Symposia
"Standardizing and Measuring PI and Site Qualifications for Conducting Clinical Trials" Proceedings from Harvard MRCT... more