Greetings everyone!

In this newsletter, we are very fortunate to have many excellent contributions. I hope you take the time to read the informative articles. In particular, Gerry Gray (FDA) provides an update on CDRH guidances of interest to medical device statisticians. Zhen Jiang and Estelle Russek-Cohen (FDA) provide an overview of medical devices reviewed in the Center for Biologics Evaluation and Research (CBER). Abha Sharma (Roche) shares her experiences with companion diagnostic devices. And our newsletter editor, Alvin Van Orden (FDA), provides a biography of the new Director of the Division of Biostatistics, Ram Tiwari. I am sure you will enjoy these articles. Please thank the authors the next time you happen to see them.

If you are attending JSM in Chicago, Jul 30-Aug 4, please come to the general MDD business meeting, Monday Aug 1, 6-7pm, Hilton-Boulevard A. For the first time, we’ll be offering food and beverages, so don’t miss out! As our Program Chair Scott Evans points out in his message below, we have an exciting JSM program in store for MDD members, including our first ever CE course, to be given by Don Rubin and Lilly Yue.

I would like to point out that the winner of our inaugural JSM student paper competition (Alex Kaizer, U Minnesota) will be presenting his paper in Thursday’s topic contributed session 646, Multiplicity in Diagnostic Device Development and Validation. I would encourage you to attend that session. Thanks go to Cindy Yang and the Student Paper Committee for putting on the competition and the students for submitting their papers.

Don’t forget about the annual ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop, Sept 16-18, Washington DC. A number of the sessions this year will be devoted to medical devices, more so than in previous years. Please check out the program at the Amstat website.

The 9th Annual FDA/AdvaMed Medical Devices and Diagnostics Statistical Issues Conference was held May 3-4 2016, Arlington VA. It was another great success, with “Day 0” preceding it on May 2. Past MDD Chair Peter Lam (Boston Scientific) and Vicki Petrides (Abbott) review the activities of the conference in their message below. In addition to Peter and Vicki, I want to especially thank Roseann White (DCRI), Richard Kotz (NAMSA), and Ted Lystig (Medtronic) for helping to shape the Day 0 program and Ted for leading the first ever poster competition at the conference.

Elections results are in for the 2017 MDD section officers. The new officers will be Chair Elect Xiting (Cindy) Yang (FDA), Program Chair Elect Alicia Toledano (Biostatistics Consulting, LLC), and Council of Sections representative Greg Maislin (U Penn). We are excited to have our new officers on board. Congratulations to them!
At this year’s JSM, we will once again have a competition for best contributed or topic contributed paper presentation based on audience use of the ASA JSM app. The winning presenter will receive a cash award and recognition. For further information, please see future MDD website announcements and message posts.

I would like to announce the new Division Director for the Division of Biostatistics, CDRH, Dr. Ram Tiwari. Ram assumes the position vacated by Dr. Greg Campbell last year. Ram had been Associate Director for Statistical Science and Policy in the Office of Biostatistics (OB). He joined CDER in 2008 from the National Cancer Institute and has over 25 years of experience in academia, including serving as chair of a large mathematics department. He has provided leadership in developing new and innovative Bayesian methods for meta-analysis, non-inferiority trial designs, and drug safety analysis. He has directed a very successful OB ORISE Summer Intern Program from universities across the US. We are excited to have Ram lead the division in the era after Greg.

In case you missed them, we offered two webinars the latter half of last year, Overview of Agreement Statistics for Continuous, Binary, and Ordinal Data, by Lawrence Lin (JBS Consulting, U Illinois at Chicago), Sep 24, 2015, and Clinical Trial Designs for Validating Prognostic and Predictive Markers in Oncology, by Daniel Sargent (Mayo Clinic), December 8, 2015 (offered jointly by the MDD and Biopharm sections). Thanks go to Hope Knuckles (Abbott) for organizing Dr. Lin’s webinar, Norbert Pantoja-Galicia (FDA) for moderating it, and Biopharm program chair Satrajit Roychoudhury (Novartis) for co-organizing Dr. Sargent’s webinar. More excellent webinars are on their way. Stay tuned!

In case you missed it, we enlisted Greg Pappas (Associate Director for National Devices Surveillance, FDA) to write an article for the December 2015 issue of *Amstat News*, entitled “FDA Moves Toward Establishing a National Medical Device Evaluation Plan”. If you haven’t already done so, I hope you’ll get a chance to read this vision for the future of real-world evidence generation for medical devices.

Please see the listing below of our current officers. I want to thank the current and past officers for all their efforts to keep our section flourishing. I especially want to thank our new communications officer, Zhiheng Xu (FDA) for taking over the reins from communications guru Jeng Mah (Beckman Coulter), keeping our members alerted to the latest news with MDD community posts, and setting up our Twitter account Follow@ASA_MDD.

Finally, I hope we can all seek to be mentors and mentees with each other and to those outside our section. I believe mentoring is especially helpful to statisticians working in the medical device area. The panoply of therapeutic and diagnostic medical device technologies, pre-clinical and clinical study designs, and attending statistical challenges suggests to me that anyone can benefit from mentoring and sharing of information in this area. The ASA encourages mentoring and supports it with material such as “Mentoring in a Bag” and “Mentoring in a Box” written by the Committee on Applied Statisticians (CAS). If you would like to be set up with a mentor or would like to mentor someone, please let one of the section officers know and we’ll try to identify some potentially good matches.

Best wishes,
Gene Pennello

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<th>MDD Section Officers</th>
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<td><strong>Position</strong></td>
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A Message from the Program Chair, Gene Pennello

Greetings everyone. Here is an update on upcoming educational opportunities.

For those of you who aren’t immersed in the regulatory process, a “guidance” is a document that describes FDA’s interpretation of or policy on a regulatory issue, including the evaluation or approval of submissions to the Agency. Although they are not legally binding, guidances are seen as the most complete description of FDA’s thinking or policy in a given area. Guidances are issued by each FDA Center (Drugs, Biologics, Devices) separately, although some guidances are co-signed by multiple Centers. Guidances are often published twice, first as a “draft” guidance that is put out for public comment (usually for a 3-month period), and next as a “final” guidance that is ready for implementation. Comments on draft guidances can be submitted electronically to http://www.regulations.gov.

The FDA Center for Devices and Radiological Health (CDRH) annually posts on the FDA website an outline of guidance development for the upcoming year, which includes an “A list” of guidances that the Agency intends to publish, and a “B-list” of guidances that will be published as resources permit. Along with the listing of guidances under development, CDRH also retrospectively reviews guidances as they reach each 10-year birthday to determine whether they are still relevant and sufficiently up to date. The CDRH outline of guidance development can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm467223.htm.

Of note, the CDRH final guidances on adaptive study designs and benefit-risk determinations for medical device Investigational Device Exemptions (IDEs) should be out very soon. A draft guidance on the use of real-world data is also on the A list for publication this year.

Since the Center for Biologics Evaluation and Research (CBER) also regulates medical devices, you may note that many of the guidances issued by CDRH are also co-sponsored by CBER as well. These include many of the guidances that are of interest to statisticians. The cover page of the guidance indicates which centers are the sponsors. Guidances that are of interest to the statistical community include those in the table on the right:

Gerry Gray, Associate Director, Div. of Biostatistics, CDRH

<table>
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<th>Guidance</th>
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<tr>
<td>Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices</td>
<td>Final issued 6/21/2016</td>
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<td>Radiation Biodosimetry Medical Countermeasure Devices</td>
<td>Final issued 4/18/2016</td>
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<td>Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval</td>
<td>Final issued 4/13/2015</td>
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<td>Expedited Access for Premarket Approval of Medical Devices Intended for Unmet Need for Life Threatening of Irreversibly Debilitating Diseases or Conditions</td>
<td>Final issued 4/13/2015</td>
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<td>Evaluation and Reporting of Age, Race, and Ethnicity Data in MedicalDevice Clinical Studies</td>
<td>Draft issued 6/20/2016</td>
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<tr>
<td>Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions</td>
<td>Draft issued 6/17/2016</td>
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<td>Adaptive Design for Medical Device Clinical Studies</td>
<td>Draft issued 5/18/2015</td>
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<td>Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (IDEs)</td>
<td>Final on the “A” list</td>
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<td>Patient Preference Information – Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Device Labeling</td>
<td>Final on the “A” list</td>
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<tr>
<td>Use of Real-World Observational Patient Data to Support Decision Making for Medical Devices</td>
<td>Final on the “A” list</td>
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<tr>
<td>Reporting of Computational Modeling Studies in Medical Device Submissions</td>
<td>Draft on the “A” list</td>
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<tr>
<td>Evaluation of Sex-Specific Data in Medical Device Clinical Studies</td>
<td>Final issued 8/22/2014</td>
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<tr>
<td>Defining the Unique Device Identifier (UDI)</td>
<td>Draft on the “B” list</td>
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Greetings to all. I hope that you are enjoying the summer.

JSM is not too far away and I would like to inform you of the MDD-sponsored events at the meeting. A summary of a short course, invited sessions, contributed sessions, contributed poster sessions and topic contributed sessions is below.

MDD is sponsoring an excellent short course, Designing Observational Comparative Studies Using Propensity Score Methodology in Regulatory Settings taught by Don Rubin (Harvard University) and Lilly Yu (CDRH/FDA). This will be a popular course, so sign up soon.

There are two invited sessions. The first focuses on benefit:risk evaluation in medicine. Speakers include Qi Jiang (Amgen) and Weili He (Merck) who have recently published a book on the topic, Telba Irony (CDRH/FDA), and Gene Pennello (CDRH/FDA and MDD Chair) with Norberto Pantoja-Galicia (FDA/CDRH and MDD Program-Chair Elect). The second invited session is focused on enrichment strategies. Speakers include Vlad Dragalin (Janssen), Cyrus Mehta (Cytel), and Richard Simon (NCI/NIH).

There are 3 contributed sessions. Themes include: (1) trial design and analysis issues in medical devices, (2) diagnostics, classification, and prediction, and (3) statistical methods in medical devices and diagnostics. We also have a contributed poster session.

Finally there are two topic contributed sessions focused on statistical methodology to address challenges in medical diagnostic devices, and multiplicity in diagnostic device development and validation.

We are planning to schedule webinars in the fall. Speakers will include Dr. Greg Campbell.

I look forward to seeing you at JSM.

Scott

ANNUAL FDA/ADVAMED WORKSHOP

The 9th Annual FDA/AdvaMed Statistics Workshop was held in Arlington, VA on May 3 and 4 and it went extremely well according to the positive feedback received after the event. There were 165 attendees and speakers, including 10 international participants from Spain, Canada, Germany, Finland, Israel, and England. There was also a Day 0 ASA/AdvaMed statistical short course titled “Statistical Methods in Health Economic Evaluations” presented by Shelby Reed, Brad Hammill and Roseann White from Duke University and Jim Lee from Altarum Institute, with 38 participants registered. Thanks to all volunteer organizers, chairs, and speakers for the informative presentations sharing their knowledge, insight, and best practices dealing with the statistical challenges in medical devices and diagnostics.

Among the four entries for the inaugural poster competition in the statistical workshop, the poster titled “A Quantitative Method for Assessing the Association between Patient Reported Outcome Measures and an Objective Endpoint” coauthored by Chul Ahn, Bo Zhang, Phyllis Silverman, Zhiwei Zhang, and Xin Fang from CDRH/FDA was the winning poster. A big thank-you to Estelle Russek-Cohen (CBER), Vicki Petrides (Abbott), and Ted Lystig (Medtronic) for their time commitment serving on the poster committee.

The 10th Annual FDA/AdvaMed Statistics Workshop will be held at the Marriott Metro Center in Washington, DC on April 26-27, 2017. Please submit ideas for topics to Ruey Dempsey at AdvaMed (rdempsey@advamed.org), ideally by the end of August. There will be several planning conference calls in September after the session topics of interest are received and consolidated. The expectation is to have the topics finalized by end of October so that the volunteer organizers and speakers can be identified. There will be another poster competition, so please also consider submitting a poster. We also encourage you to submit topic suggestions for the Day 0 ASA/AdvaMed short course to be held at the Marriott Metro Center in Washington, DC on April 25, 2017. If there is sufficient demand, we may be able to have 2 short courses, one each for diagnostics and therapeutics. Please email your suggestions to the 2017 MDD program chair, Norberto.Pantoja-Galicia@fda.hhs.gov.

Peter Lam (Boston Scientific) and Vicki Petrides (Abbott Diagnostics)
Center for Biologics Evaluation and Research (CBER): The Other Center that Regulates Medical Devices
By Zhen Jiang and Estelle Russek-Cohen
CBER’s Division of Biostatistics

CBER regulates a diverse portfolio of medical products including vaccines, gene and cell therapies, products to treat inherited coagulation and anti-coagulation disorders like hemophilia, and products associated with maintaining a safe blood supply. Many statisticians who work with CDRH are surprised to find that CBER, in spite of its name, also regulates medical devices.

Among the diagnostic devices regulated by CBER, a highly multiplexed assay to characterize antigens on red blood cells has recently been approved via a pre-market application (PMA). This device can be used to better match donor and recipients for blood transfusions compared with traditional means. Patients that require repeat transfusions (e.g. sickle cell anemia patients) may build up antibodies. A device that does a better job with matching may reduce the risk of antibody buildup due to mismatches.

CBER has cleared multiple devices for human leukocyte antigen (HLA) genotyping, which is important for blood and organ donor matching. CBER also clears and/or approves devices used in blood establishments including centrifuges, devices that capture platelet donations, blood bags, and devices that reduce pathogens in blood or its components. We also review and approve diagnostic assays for retroviruses like human immunodeficiency virus (HIV). We have also approved an HDE for separating and isolating specific cells for use in cancer patients.

One of the unique regulatory pathways at CBER is a Biologic Licensing Application (BLA) for a blood donor screening assay. In some ways, this could be considered as a super-PMA, but the regulations are a hybrid of that for a device and for a biologic. Many in vitro diagnostic (IVD) companies come to CBER with their blood donor screening assays for infectious diseases. These assays are designed to work in a donor population that is largely asymptomatic and at very low risk for the diseases in question. An introduction to these kinds of assays is in a Joint Statistical Meetings (JSM) proceedings paper [1]. The assays can be more complex, especially when pools of blood are combined from multiple donors in an effort to cut cost. This can lead to complicated algorithms and some interesting statistical challenges. In contrast to a traditional IVD, subjects that test positive via the new investigational assay will be told to consider additional follow-up. Fortunately, transfusion-transmitted disease is exceedingly rare in the United States with the implementation of donor screening assays and donor selection.

The Therapeutics Evaluation Branch (TEB) at CBER is unique in that statisticians review New Drug Applications (NDAs), BLAs, PMAs, 510(k)s and rarely, an Humanitarian Device Exemption (HDE). The statistical challenges are varied as well. Our therapeutic devices include a device that reduces pathogens in blood; the end-product of the device is evaluated in a therapeutic randomized clinical trial.

The clinical validation study for an in vitro companion diagnostic test can have an ‘All-comers Randomized design’ or an ‘Enrichment design’. In the ‘All-comers Randomized design’ patients are randomized to receive the Drug or the Control treatment. Patient randomization may be stratified on the binary IVD test result (negative or positive, where positive could mean response to the drug is likely, for example), if available at time of randomization. In an ‘Enrichment design’, enrollment is limited to the subset patients who have a companion diagnostic test result (e.g., positive result) that predicts that the benefits of being treated with Drug will outweigh its risks. Both of these study types can be conducted prospectively or by planning a prospective analysis of a retrospectively conducted study [1, 2].

The cobas® EGFR mutation test detects defined mutations of the epidermal growth factor receptor (EGFR) gene in NSCLC patients. The test was previously approved for use in tumor samples from NSCLC patients. Recently, the indications for use of the test have been extended to blood samples from NSCLC patients [3]. Blood samples from NSCLC patients are also referred to as ‘liquid biopsy’ samples as opposed to the tumor samples which are obtained by ‘surgical biopsy’. This is the first ‘liquid biopsy test’ approved for use by FDA. This new test may benefit patients who may be too ill or are otherwise unable to provide a tumor sample for EGFR testing.

The performance characterization of the cobas® EGFR mutation test in blood samples included an analytical accuracy study using samples from NSCLC patients, an LoD study using cell line DNA and using blood samples from NSCLC patients, and a study of commutability of sample types (comparison of contrived samples with intact cell line DNA and mechanically sheared cell line DNA), endogenous and exogenous interference studies, precision and reproducibility studies, etc. Additional studies to evaluate the robustness and stability of the test were also performed.

To demonstrate the clinical utility of the cobas® EGFR mutation test for selecting patients for treatment with Tarceva® in blood samples, a prospectively planned, retrospective bridging analysis was conducted on the ENSURE study, a multicenter, open label, randomized Phase III study to evaluate the efficacy of Tarceva® versus chemotherapy as the first-line treatment for stage IIIIB/IV NSCLC patients. The results demonstrated a significant benefit in progression free survival in patients with a positive result in both blood and tissue specimens. The hazard ratio for progression free survival (PFS) in patients with positive results in both blood and tissue samples was 0.29 with a 95% CI of (0.19, 0.45). The hazard ratio was similar to the PFS benefit observed in the overall population (HR = 0.33; 95% CI: 0.23, 0.47).

References:
How do you replace a Legend?

By Alvin Van Orden

As you know, the beloved leader of the medical devices statistics community, Dr. Greg Campbell retired last year. How do replace someone like Greg? Short answer: You don’t. But even the biggest shoes have to be filled eventually, and you search, as you might for any open job position, for three qualities.

1. Diligence, to work hard enough to get the job done.
2. Skills, the technical ability to do the job.
3. Agreeableness, someone with whom you want to work

The position requires intense statistical training, management experience, and the communication skills to be an ambassador of statistics and medical devices.

Where do you find such a person? Well, you might try looking in a remote village in India with only 400 people. That’s where Dr. Ram Tiwari comes from. Now let me tell you why this humble man from a humble background is imminently qualified for the job.

Diligence

Ram grew up in a household of about 40 people, including grandparents, aunts, uncles, cousins, etc. His family didn’t particularly value education, but they did value hard work. He grew up helping on a farm growing corn, sugar cane, rice or whatever else would help provide for the family. He excelled in the classroom, so, recognizing his aptitude, they sent him off to the city after the 10th grade to pursue a better education.

This was not the only time he’d have to leave family to pursue education. After finishing Bachelors and Masters (Statistics) degrees at Allahabad University, he was given the opportunity to teach at Allahabad because he had finished at the top of his class. But as becomes a pattern in his life, after a few years Ram felt the need to progress and move on. He applied for a scholarship from the Indian government to study in the US, with the requirement that he returns to India after he finished his studies. By this time, he was married and had a young daughter, who he had to leave behind to pursue his education. He worked tirelessly at Florida State University (FSU), both as a teaching assistant and working some extra hours in the FSU library on a job that required him to cut and paste the serial numbers on books for $2 an hour, to pay for his ticket back to India to see his family in the summer.

In job after job (and we’ll get to those in a second), you see how his willingness to work hard helped him succeed. He’s not afraid of challenges. He welcomes them. When he eventually moved his family to the United States, his parents tried to convince him he’d be better off in India. He didn’t have a driver’s license, and when they made a trip to the grocery store, each of his three girls (they would later add a son and now have 4 kids) would have to carry something as they walked home. It was tough at first, but he worked hard and got ahead.

If you ask him about his hobbies, they mostly revolve around work. He just loves statistics and finding new challenges. He took this job at an age that some start considering retirement, and it’s not because he was aspiring to this prominent position. He was just looking for a new challenge.

Skills

It’s a given that a candidate will need a PhD, and Dr. Tiwari got his at Florida State University a few years after Dr. Campbell. It was a powerhouse statistical program for a stretch before many of the brightest minds fled for other opportunities. Thirty-five years later, he can still discuss with conviction his dissertation: A Mathematical Study of the Dirichlet process.

Of course, that was just the beginning of a long career in statistical research. His CV lists 180 published papers. If you published a paper every other month, it would take you 30 years to publish that many papers. The topics of these papers show a broad range of expertise and interest.
For evidence of his administrative experience, I’ll point you to his time as Chair of the Dept. of Mathematics at the University of North Carolina at Charlotte. He took over a program that was just starting a PhD program. He had to recruit new PhD students and qualified teachers. (He says this was just after the break-up of the Soviet Union and they were able to bring in qualified mathematicians from Russia.) Then he had to find resources to pay these teachers and deal with the inevitable politics or academia.

For evidence of his ability to be an ambassador of statistics, take a look at his service at NCI where he helped distribute the majority of NIH’s statistical grants. He was not stingily deciding which grants to approve or disapprove. Ram went to schools, research institutions, and professional meetings, helping statisticians learn about funding opportunities and mechanisms, growing the number of statistical grants given out by the NIH by helping to create more qualified applicants.

From NCI, he came to FDA to work in CDER (drugs) where he tried to promote their use of Bayesian statistics and innovative methods. He showed comfort with the FDA/government working environment, and he is keenly aware of the statistical methods that, as much as he tried to promote them in CDER, are still more commonly used in CDRH.

**Agreeableness**

Whether or not a person is someone you’d like to work with, is a personal question, and I don’t have any data to back up the assertions that I’m about to make. But let me assure you that Dr. Ram Tiwari is very agreeable. He is very calm, pleasant, easy to talk to, open to new ideas and sincerely wants to improve things around him. We are very excited that he is part of our team.

The community of medical device statisticians is full of hard working, talented, and friendly people, so Dr. Tiwari will fit right in.

**Hope to see you soon!**