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BIOPHARMACEUTICAL REPORT

Chair: B. Christine Clark **Editors:** Junyuan Wang, Paul Gallo, Amy Xia

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Note from the Editors

Welcome to the first issue of the Biopharmaceutical (BIOP) Report for 2016! We are excited to unveil a "new look" for the Report, including a new masthead, featuring the new section logo, and a new format. This is the first major change to the Report format since its first issue in 1992. These changes occurred thanks to the efforts of many people, but in particular **Paul Gallo**, who slides to the role of "Past Editor" for 2016, last year's section chair **Dionne Price**, and the wonderful staff at ASA including, but not limited to, Graphic Designers **Sara Davidson** and **Meg Ruyle**, Meeting Planner **Christina Link**, and Communications Manager **Megan Murphy**. We welcome feedback on the design changes, and any other suggestions to help improve the Report further. Other changes to the Report staff and responsibilities for this year are that **Junyuan Wang** takes over as Editor, and we welcome **Amy Xia** as the incoming Associate Editor. We thank outgoing editor **Ugochi Emeribe** for her great service during the past years.

In this issue's transition report from Section chairs **Dionne Price** (2015) and **B. Christine Clark** (2016), they highlight a number of recent accomplishments and current initiatives of the section. For our feature article in this issue, we're happy to present an introduction and overview of graphical multiplicity methods that have been developed in recent years and are quickly gaining in popularity and usage. Finally, another highlight of this issue is the thorough and interesting report from the Membership Committee describing the results of last summer's membership survey.

TRANSITION REPORT FROM THE BIOPHARM SECTION CHAIRS

B. Christine Clark and Dionne Price

As we enter into a US Presidential Election year, many will find themselves reflecting on the State of the Union in the USA. We will review the accomplishments of the nation and consider our future. As such, it seems quite appropriate that we pause and consider the State of the Union of the Biopharmaceutical Section (BIOP) of the American Statistical Association and also chart our course for the future. During 2015, the Section continued to thrive as the largest Section of the ASA. As part of our growth, we had a number of new volunteers desiring to actively serve the profession and the Section, and the Executive Committee put forth great efforts to enlist the assistance of all volunteers. Speaking of volunteers, the BIOP Section answered the call to serve as docents during the 2015

Joint Statistical Meetings in Seattle. The ASA Docent Program is designed to assist first-time JSM attendees with navigating all that JSM has to offer. Although BIOP Docents were instrumental in "guiding" first-timers in a non-biased manner, we could not help but highlight the many invited sessions, topic-contributed sessions, roundtables, and business/networking meetings sponsored by the Section. In addition those first-timers who expressed interest in our Section were invited and encouraged to attend the BIOP reception/mixer and open business meeting on Tues evening.

In 2015 BIOP continued the rich tradition of providing valuable webinars to the membership. Webinar topics included graphical approaches to multiple testing, interpretation of patient-reported outcomes, propensity score methods for estimating causal effects, and Bayesian methods for drug safety evaluation and signal detection, just to name a few. To increase outreach to our international colleagues, we also considered time zones during the scheduling of webinars. As another mechanism to increase our international outreach, the BIOP Report also featured a series of reports from the BIOP International Initiative Subcommittee with perspectives spanning the different regions represented by our membership. In addition to the series, the three editions of the BIOP Report served to keep the membership aware of various activities and the progress of initiatives. Featured articles in the BIOP Report included, "Estimands and Their Role in Clinical Trials", "Statistical issues in generalized linear models in clinical trials" and "Statistical Endpoint Selection for Recurrent Events in Clinical Trials". Our 2015 editor, Paul Gallo, was instrumental in advocating for a facelift for the BIOP Report, and we are excited to unveil the new masthead for the BIOP Report in this current edition. Within the new masthead, we also are showcasing and presenting the new BIOP Section logo.

In 2015, the Section continued to conduct and archive a number of podcasts, to solicit and host Scientific Working Groups, and to mentor others via our Mentoring Program. We also sponsored our ever popular annual workshop, recently renamed as the ASA Biopharmaceutical Section Regulatory/Industry Statistics Workshop. Despite the slight name change, the workshop will remain the same. We look forward to celebrating the 20th year of the workshop in 2016!

Although we have only highlighted a few of our many activities, accomplishments, and initiatives, we hope it is apparent that the State of the Section is Statistically Significant! We sincerely thank all who have given of their time and talent to maintain and promote the Section. We are certainly poised to continue our contribution to our profession, to provide enriching opportunities to our membership, and to increase the visibility of our profession to ensure the development of future statisticians. ■

AN INTRODUCTION TO GRAPHICAL MULTIPLE TESTING IN CONFIRMATORY CLINICAL TRIALS

Dong Xi, Novartis

Introduction

Increasing medical knowledge allows us to better understand the mechanism of many difficult diseases. In parallel, advancing technology provides more reliable diagnostic tools and more effective treatment options to improve the quality of life. All of these promote the evolution of clinical trials so that one can, in a single trial, investigate the multidimensional effects of an investigational treatment including multiple endpoints, several dose regimens, more than one population, and so forth.

To confirm the benefit of a new treatment in so-called phase III clinical trials, multiple inferences are made using hypothesis testing approaches where the null hypothesis is usually a statement of no treatment effect. A false positive claim, or a Type I error, is an error in data analysis where the effect of a treatment is falsely concluded in the absence of a true benefit. Since the chance of making at least one false positive claim increases with the number of hypotheses, an appropriate control of the Type I error rate plays an important role in judging the success of such trials. Regulatory guidance (ICH, 1998; EMEA, 2002) in confirmatory clinical trials requires the strong control of the familywise error rate (FWER) at a pre-specified significance level α, which is the probability of rejecting erroneously at least one true null hypothesis.

Theory on multiple comparison procedures (MCPs) is well developed to control the FWER at a desired level α and widely applied to clinical trials and other scientific research areas. However, recent confirmatory clinical trials are becoming increasingly more complex with multiple sources of multiplicity and structured study objectives. Such trials could include simultaneous inferences on multiple clinical endpoints, more than one treatment dose or regimen, several study populations, non-inferiority and superiority testing, and any combination of the above. They also bring two challenges that make it difficult to apply common MCPs including the Bonferroni test. First, study objectives can be of different relevance and thus require a structured evaluation. For example, the primary objective(s) defines the success of the trial and the secondary objective(s) is only relevant if the primary objective is achieved. Second, objectives may have different importance based on medical need and other considerations. For example, the mortality endpoint in a cardiovascular trial is more important than the hospitalization endpoint and thus the null hypothesis with the former may carry more weight.

In light of these challenges, we introduce a clinical trial example to motivate graphical approaches for multiple testing. In a diabetes trial, the investigational drug is assessed against control on two endpoints: the reduction in glycated hemoglobin (HbA1c) level and the reduction in body weight. The study success depends on the reduction of HbA1c level and thus it is the primary endpoint. Then a reduction in patients' body weight is the secondary endpoint because it may only be relevant if a reduction in HbA1c level is achieved. In addition, two different doses (high and low) of the treatment are investigated and are equally relevant for a dosage recommendation (but may be of different importance). Therefore, we have the primary and the secondary hypotheses within each of the two dose-control comparisons. The induced logical restriction requires that a secondary hypothesis be tested if and only if the primary hypothesis for the same dose-control comparison has been rejected. In this case, the Bonferroni test across all hypotheses, for instance, is not suitable because it treats all hypotheses as equally relevant.

Graphical approaches to multiple testing

There are two underlying principles in graphical approaches (Bretz et al., 2009; Burman et al., 2009). First, all hypotheses could have different importance and thus potentially unequal weights. Second, the structured testing between two hypotheses is implemented by the specific order of testing in which a less relevant hypothesis can only be tested after a more relevant hypothesis is rejected.

In fact, neither principle is new. The fixed sequence (or hierarchical) test (Maurer et al., 1995) applies to multiple hypotheses with a pre-specified order H_1, H_2,

H_3. First it tests H_1 at level α. If it is rejected, test H_2 at level α; otherwise stop testing. If H_2 is further rejected, it tests H_3 at level α. If we think through this process graphically, we can visualize it as in **Figure 1**. We start with testing H_1 at level α. The order of testing is represented via directed edges so that if H_1 is rejected, we "move to" H_2 and test it at level α. We can further "move to" H_3 and test it if H_2 is rejected. We introduce the meaning of the values in Figure 1 in the following.

Formally, null hypotheses H_1, H_2, …, H_m are represented by nodes and initially the total significance level α is divided among hypotheses such that the local significance levels α_i sum to α. The directed edge from H_i to H_j is denoted by the transition weight g_{ij}, which specifies the proportion of the significance level to be propagated to H_j after H_i is rejected. The transition weights g_{ij} of all outgoing edges from H_i should sum to 1. Then α_i and g_{ij} jointly define the initial graph. In this formal framework, the fixed sequence test with three hypotheses can be represented as in Figure 1. In this case, we have $\alpha_1 = \alpha$, $\alpha_2 = \alpha_3 = 0$ and $g_{12} = g_{23} = 1$.

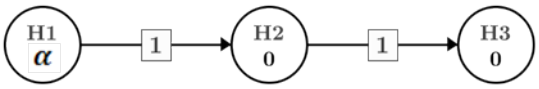

Figure 1: A graphical visualization of the fixed sequence test

Another common MCP that fits into this framework is the Holm (1979) procedure. In the case with two hypotheses, it tests the hypothesis with the smaller *p*-value at level $\alpha/2$. If it is rejected, the procedure tests the other hypothesis at level α. In **Figure 2**, we visualize the Holm procedure for two hypotheses with $\alpha_1 = \alpha_2 = \alpha/2$, and $g_{12} = g_{21} = 1$. If one uses the following algorithm to carry out the testing, it can be easily seen that the graph in **Figure 2** produces the same decision as the Holm procedure.

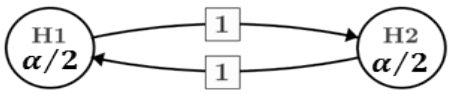

Figure 2: A graphical visualization of the Holm procedure

The last component of graphical approaches is the updating algorithm to carry out testing and to update the remaining graph after a hypothesis is rejected. Assume that the unadjusted *p*-values are p_1, p_2, ..., p_m for H_1, H_2, …, H_m. For a given graph with α_i and g_{ij}, the updating algorithm is as follows:

0. Set $I = \{1, 2, \ldots, m\}$.
1. If $p_j \leq \alpha_j$, reject H_j and continue to step 2; if no such j exists, stop testing.
2. Update the graph
   - Remove H_j from the graph and update $I \rightarrow I\backslash\{j\}$,
   - Update $\alpha_i \rightarrow \alpha_i + \alpha_j g_{ji}$ for i in I; 0 otherwise,
   - Update $g_{ik} \rightarrow (g_{ik} + g_{ij}g_{jk})/(1 - g_{ij}g_{ji})$ for i, k in I, $g_{ij}g_{ji} < 1$; 0 otherwise.
3. If I is an empty set, stop testing; otherwise go back to step 1.

The updating algorithm shows the dynamic nature of graphical approaches. After the rejection of a hypothesis, the local significance levels of remaining hypotheses are increased due to recycling the level from the rejected one. This increases the chance to make a further rejection. The algorithm, together with αi and gij, guarantees the strong control of the FWER of graphical approaches at a pre-specified level α (Bretz et al., 2009; Burman et al., 2009).

Recall that in the diabetes example, we plan to assess two doses (high and low) of the investigational drug against control on two endpoints. This gives us four hypotheses. Let H_1 and H_3 denote the primary and the secondary hypotheses comparing the high dose versus control. Similarly, H_2 and H_4 are the primary and the secondary hypotheses comparing the low dose versus control. We assume that both high dose and low dose are equally important and thus $\alpha_1 = \alpha_2 = \alpha/2$ and $\alpha_3 = \alpha_4 = 0$. This preserves the structure that the secondary hypotheses H_3 and H_4 cannot be rejected before the rejection of the primary hypotheses. If one primary hypothesis, say H_1, is rejected, we may want to test the descendant secondary hypothesis H_3. Thus 100% of the level of H_1 is propagated to H_3. Likewise, if H_2 is rejected, 100% of its level is propagated to H_4. Finally, if the secondary hypothesis in one dose-control comparison is rejected, this means that the corresponding primary hypothesis has been rejected. Then we can propagate its level to the primary hypothesis in the other comparison. The initial graph is displayed in **Figure 3** (a).

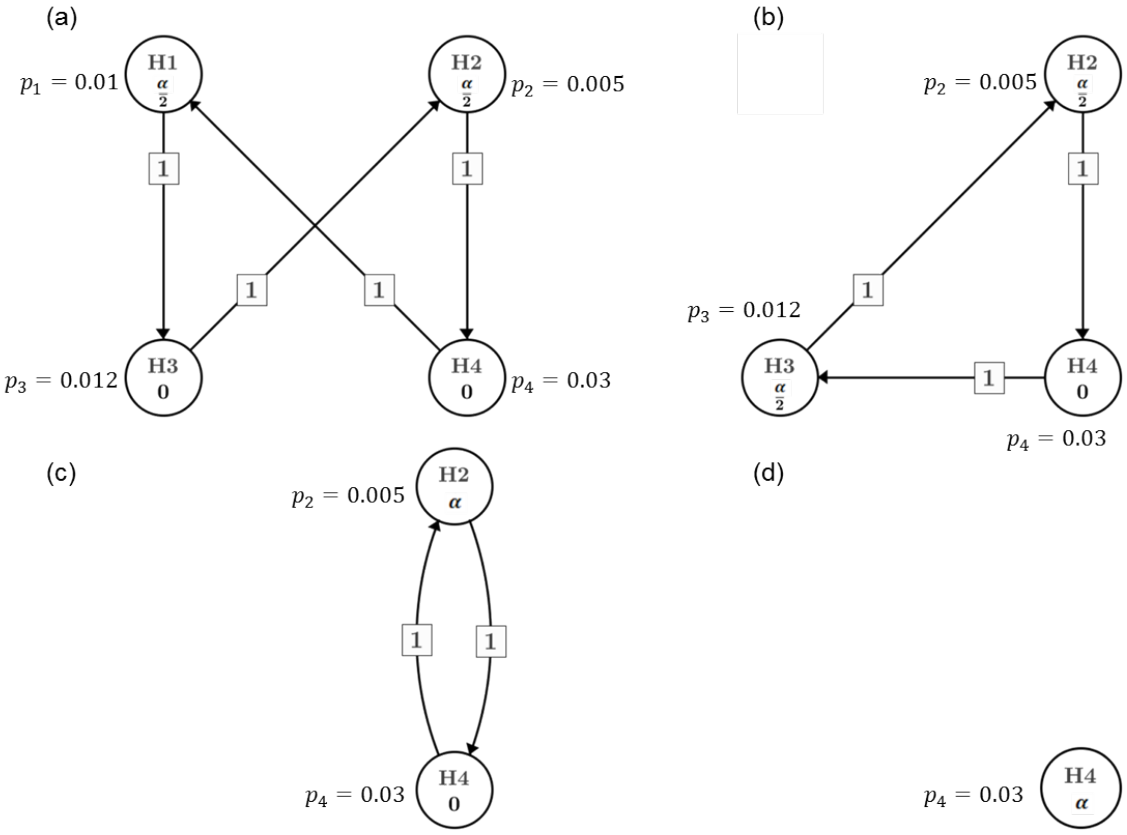

Figure 3: Visualization of the graphical MCP for the diabetes example

Assume that the one-sided overall significance level is $\alpha = 0.025$ and the unadjusted *p*-values are 0.01, 0.005, 0.012 and 0.03. The MCP based on the graph is carried out as follows.

1. In **Figure 3 (a)**, we first compare p_1 and p_2 against $\alpha/2 = 0.0125$ and thus both H_1 and H_2 can be rejected.
    - Suppose that we select H_1 and reject it. Then we remove its node and update the graph.

Then in **Figure 3 (b)**, we compare p_2 and p_3 against $\alpha/2 = 0.0125$ and choose to reject H_3.

2. Then in **Figure 3 (c)**, we reject H_2 because $p_2 \leq 0.0125$
3. Finally in **Figure 3 (d)**, we fail to reject H_4 since $p_4 > 0.025$.

In this example, we selected the rejection of H_1 in the first step as the basis for updating the graph. In fact, H_2 could be chosen instead of H_1 and the graph could be updated accordingly. However, it has been shown that the final decision (H_1, H_2, H_3 being rejected but H_4 being not rejected) does not depend on the sequence of rejections. Therefore, in each step of the updating algorithm, one can reject any hypothesis if its *p*-value is not larger than its local significance level.

One benefit of graphical approaches lies in its transparency and ease of communication. In the case of a complex MCP, it is much easier to communicate with the graph than to explain it in words, with the peace of mind of the guaranteed strong control of the FWER. Another advantage is that it is flexible to fine-tune the testing strategy by changing α_i and g_{ij} to satisfy further clinical and statistical considerations. For instance, if the high dose is expected to be clinically more beneficial than the low dose, one could increase the local significance level α_1 and decrease α_2 so that $\alpha_1 + \alpha_2 = \alpha$. On the other hand, one could add, delete or change transition weights to allow an alternative propagation of the significance level. For instance, after rejecting H_1, one could add a directed edge with a weight $g_{12} > 0$ to H_2 to increase the chance of rejecting the other primary hypothesis H_2. But to ensure the strong control of the FWER, we also need to decrease g_{13} so that $g_{12} + g_{13} + g_{14} \leq 1$. In general, one could fine-tune α_i and g_{ij} to first ensure that all clinical considerations are satisfied and then to optimize the probability of achieving certain study objectives via simulation.

Discussions and further readings

The graphical approach provides a transparent and flexible framework to design and implement MCPs. However, it is wise to keep in mind that the procedure has to be prespecified in confirmatory trials to avoid data-driven decisions. Secondly, it is important to understand the tradeoff between two alternative graphs. The requirements have to be satisfied in any graph that the local significance levels α_i sum to α and that the transition weights g_{ij} of all outgoing edges from H_i should sum to 1. Therefore, an increase in one local significance level (or transition weight) means a decrease in at least one other local significance level (or transition weight). That is to say, there is no "best" graph for all situations but there could be an "optimal" graph for a specific study objective. Therefore, it is critical to quantify the tradeoff among alternative procedures via simulation for an informed decision. Finally, it is usually a good practice to first ensure clinical and logical considerations and then to evaluate statistical operating characteristics for candidate graphs. Discussions with relevant stakeholders are essential for a better decision strategy.

The graphical approach builds on the idea of the Bonferroni and the fixed sequence tests and includes a wide range of existing procedures. It also provides a flexible tool to create and visualize more complex MCPs. It has been further extended to Simes and parametric tests and to allowing interim analyses and adaptations. A systematic review of the methodology is provided by Bretz et al. (2014). Implementation of graphical approaches has been developed to allow proper designing, evaluating and reporting of multiple comparison procedures. In SAS, an IML function is available to derive the rejection decisions (Bretz et al., 2011). The R package gMCP provides a graphical user interface to design, analyze and simulate graphical multiple comparison procedures (Rohmeyer et al., 2015). Finally, the graphical approach is one of the recent multiple comparison procedures which attempt to address the multiplicity issues in complex confirmatory clinical trials. Two recent tutorials on traditional and more advanced multiplicity adjustment methods are given by Dmitrienko et al. (2013) and Alosh et al. (2014). ■

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SUMMARY MINUTES FROM ASA BIOPHARM SECTION EXECUTIVE COMMITTEE MEETING

Ed Luo

Meeting was held on 16th October 2015 at the ASA Headquarters in Alexandra, VA.

Matilde Sanchez announced the slate of candidates for the 2016 election.

POSITION	CANDIDATE	CANDIDATE
Chair-Elect	Satrajit Roychoudhury (Novartis)	Heather Thomas (PRA Health Sciences)
Treasurer	Alan Hartford (Abbvie)	Yue Shentu(Merck)
Program Chair-Elect	Janelle Charles (FDA/CDER)	Qi Jiang (Amgen)
Council of Sections Representative	Edmund Luo (PTC Therapeutics)	Erik Pulkstenis (MedImmune)

Erik Pulkstenis highlighted the summary findings of ASA Biopharmaceutical Section Committee on Interest Groups. EC discussed the recommendations from the committee.

Jennifer Gauvin reported that the membership committee completed the member survey and made recommendations to the EC per the survey response.

Jennifer Gauvin, on behalf of Amarjot Kaur, informed the EC that the Mentoring Committee conducted a limited Pilot Mentoring program at the Sept 2015 FDA-Industry Workshop. The committee needs to work to sustain the BIOP mentoring program (3 years and beyond) and continue to make enhancements as necessary.

Olga Marchenko provided a Letter of Support and endorsed two courses for JSM 2016, 1) "Analysis of Clinical Trials: Theory and Applications" by Devan V. Mehrotra, Alex Dmitrienko, and Jeff Maca; 2) "Making Quantitative Decisions during the Clinical Development of a New Drug" by Christy Chuang-Stein. The Biopharmaceutical Section will have 4 invited sessions: 1) Innovative Trial Designs and Data Analysis Models in Rare Diseases, 2) Choosing Appropriate Estimands in Clinical Trials, 3) Issues in predictive biomarker in oncology drug development, and 4) Subgroups Analyses: Planned versus ad-hoc - How many are too many?

Richard Zink and **Wei Zhang** reported that 835 people registered for the 2015 ASA Biopharmaceutical Section Statistics Workshop. The number of short courses increased from 6 to 8, which reduced overcrowding and provided diverse topics.

Freda Cooner and **Ed Luo** reported that Steering Committee (SC) of the 2016 Workshop had the kickoff meeting at the 2015 Workshop. The website will be open for proposal submission from Oct. 30 to Dec. 4. Freda and Ed asked EC for more funding as the SC plans to add a poster session and is considering a ceremony of 20 years of workshop with band performance. The EC is generally in support of the poster session.

Dionne Price led a discussion on the new name for the Workshop. The EC decided to have an offline e-voting post meeting and the final name chosen by the EC is "ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop"

The EC discussed and clarified that the Biopharmaceutical Section members will have one free webinar in October 2015 and up to three free webinars by ENAR 2016 (regular price for non-section members) will be made to the section membership.

Paul Gallo reported that Biopharm Report had published three issues in 2015. The fourth issue is planned to be published in early December 2015 or Jan 2016 depending on the number of articles. ■

REPORT OF 2015 SURVEY OF ASA BIOPHARMACEUTICAL SECTION MEMBERS

Jennifer Gauvin (Novartis Pharmaceuticals Corporation), Mike Colopy (UCB Biosciences), Matthew Guerra (U.S. Food and Drug Administration), Soumi Lahiri (GlaxoSmithKline), Guan Xing (Gilead Sciences)

Abstract

During July and August 2015, a survey was conducted by the Biopharmaceutical Section to its members. The 26-question survey was designed to collect information on demographics, professional experiences, professional meetings, continuing education activities, and career development, as well as to solicit feedback and suggestions from the members on the services provided by the Biopharmaceutical Section. The survey was emailed to 2172 Biopharmaceutical Section members using the ASA Community website and 278 responded. Results are summarized based on 278 responses.

The results showed that a majority of members live in the United States (92.5%), are male (60.1%), are 35-64 years old (80.5%) and earned a doctorate degree in Statistics or a related field (72.7%). A majority of members have been ASA members for at least 15 years (65.3%) and Biopharmaceutical Section members for at least 10 years (57.6%). In terms of working experience, a majority of have worked or are working for industry (70.4%), followed by 13.1% for academia and 6.9% for government.

Introduction

To better serve its members, the Biopharmaceutical Section needed to update its 2012 membership profile, regarding demographics, job roles and interests, by conducting its triennial survey. The 2015 survey was revised from the 2012 survey and finalized by the Membership Committee (Jennifer, Mike, Matthew, Soumi, and Guan) in Spring 2015 after incorporating the comments from the Biopharmaceutical Executive Committee. The survey was open from July 22, 2015 to August 28, 2015. Multiple reminders were emailed to Biopharmaceutical Section members. To boost the response rate, those who completed the survey were given free access to one ASA webinar.

Method

As with previous years, the committee took a do-it-yourself approach.

In July 2015, the survey was implemented at surveymonkey.com by Mike Colopy. The survey invitation and follow up messages were sent to all Biopharmaceutical Section members via ASA's Community web email interface by Mike. Each member received a hyperlink to the online survey hosted by surveymonkey.com. At the survey close, Surveymonkey provided summary statistics for each question, and the survey results were downloaded for future analysis. Additional analyses were performed to summarize the responders' comments from the text field part of the questionnaire. Recommendations were communicated to the Biopharmaceutical Executive Committee for improving our services.

Results

On July 22, 2015, the survey invitation was sent to 2172 members' email addresses. From past experience, the committee knew some addresses to be outdated or misspelled. Before sending out the survey e-mail, the membership committee made an effort to reach out to the Biopharmaceutical Section members to correct and update their ASA account information. In addition, during the Biopharmaceutical Section mixer in JSM 2015, attendees were reminded to respond to their survey invitation. In some instances, the survey invitation was resent to members at their preferred emails which were provided at JSM. Despite these efforts, it is still unknown exactly how many addresses were outdated. When the survey was closed on August 28, 2015, 278 (13%) members had responded to the survey. Results are summarized in the following sections based on 278 responses.

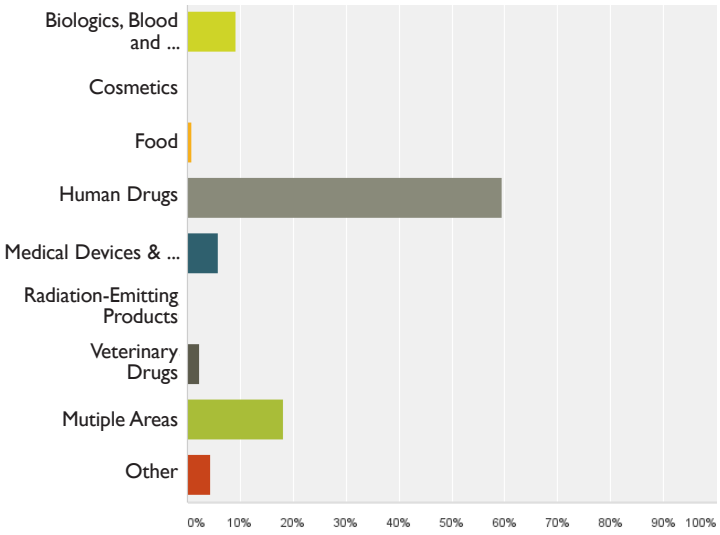


Figure 1: Primary Product Area

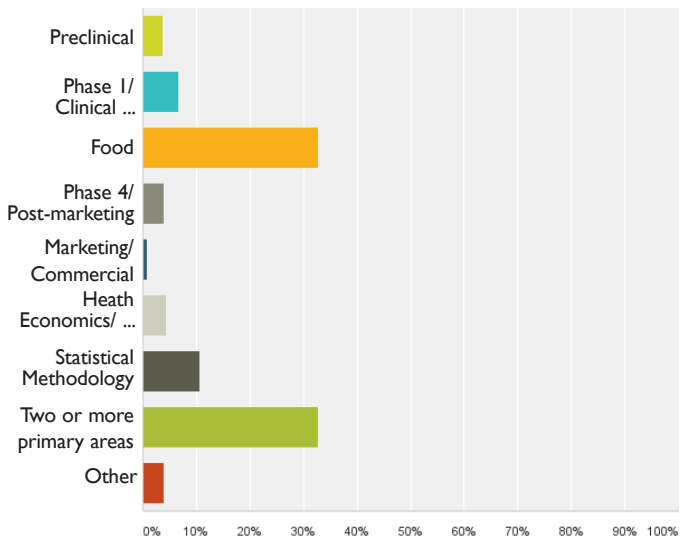


Figure 2: Primary Functional Area

Demographics

Members primarily live in the United States (92.5%); 2.9% live in Europe, 1.8% live in Canada, and less than 1% live in China, India, Japan, Mexico or Central/South America, or elsewhere. Most members are males (60.1%). The majority (80.5%) of members are between the ages of 35 and 64 years with 23.3% (35-44), 30.6% (45-54), and 26.6% (55-64); 7.8% of members are 34 years or younger and 11.8% of members are 65 years or older.

Education

Only 5.1% of members are students working part-time or full-time towards an advanced statistical degree. The majority (97.9%) of members hold an advanced degree in Statistics or related field: 72.7% with doctorate and 25.2% with masters as the highest degree.

Professional Experience

As shown in Figure 1, 59.4% work primarily in the development of human drugs, 9.2% in biologics, blood and vaccines, 5.9% in medical devices and diagnostics, and 18.1% in multiple areas. Figure 2 shows that 32.8% of the members work primarily in Phase II and Phase III development, 10.7% in statistical methodology, 6.6% in Phase I/Clinical Pharmacology, 4.4% in health economic/outcomes research/epidemiology, 4.1% in Phase 4/Post-marketing, 3.7% in pre-clinical and 4.8% in other areas (marketing/commercial, consulting, manufacturing, software etc.). More than 30% of the members work in two or more of these primary areas.

Of the members who responded to the professional sector question, 70.4%, 13.1%, 6.9%, and 9.5% have worked or are working in industry, academia, government, and other fields respectively. The majority (69.4%) of members have been a professional statistician for at least 15 years.

Professional Meetings and Continued Education

Members were asked which statistical meetings they attended within the last five years and the factors that influence them to attend the meetings. The most popular meetings are the ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop (previously known as the FDA-Industry Statistics Workshop), JSM, and ENAR, attended by 20.7%, 20.5%, and 15.5% of the members at least once, respectively, within the last five years. The most important factor to attend a meeting is funding or travel budget (48.4%) followed by invited and contributed sessions (47.3%), giving a presentation (44.0%), location (39.0%), networking (34.7%) and continuing education courses (31.4%).

To characterize attendance at short courses and workshops, members were asked how frequently they attend both external and internal statistical short courses

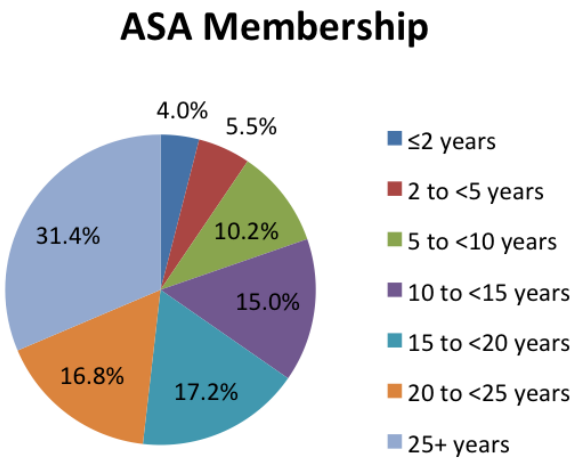


Figure 3: Pie Diagram of ASA Membership

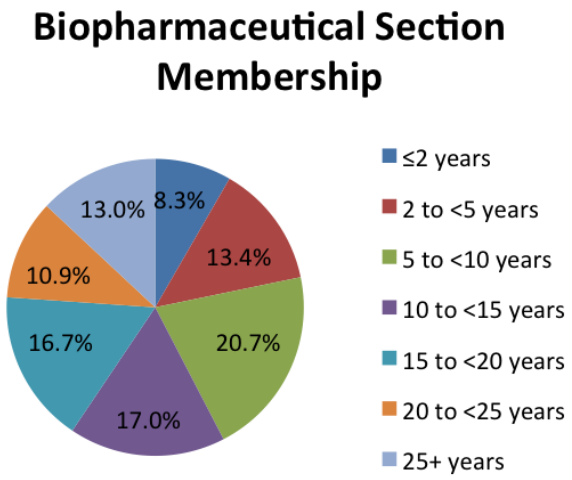


Figure 4: Pie Diagram of Biopharmaceutical Section Membership

and workshops. About half of the members reported occasional attendance at external courses or workshops (49.1%), 20% attended once per year and 11.6% never attended any external courses or workshops. A majority of the attendance (74.2%) was sponsored by the employers. More than 32% of the members reported that internal short courses/workshops are not available within their company.

With the increase in availability of online short courses and workshops (e.g. Courser, ASA webinars etc.), the survey added a new question that asked how often members attended statistical short courses and workshops online in 2014. Most the responders attended between 1 to 3 online courses or workshop in 2014 (56.9 %), whereas 10.5% attended 4 to 6, 2.5% attended 7 or more and 30.1% did not attend any of them.

Career Development

In responding to the question on importance of enhancing and updating statistical skills, our members identified statistical books (87.2%), software packages and manuals (86.9%), statistical journals (85.0%), statistical short courses (81.7%), statistical meetings (79.9%) and Biopharm Webinars (68.3%) as either "very important" or "somewhat important". Our members also identified inter-personal skills (65.2%), technical skills (51.8%) and high visibility project work (51.8%) as the most important factors for their career development. Presentation skills (34.9%), education (33.7%) and networking (32.6%) were also identified as highly important for career development.

Experience with ASA and Biopharmaceutical Section

A majority of members have been ASA members for at least 15 years (65.3%) and Biopharmaceutical Section members for at least 10 years (57.6%). Members were also asked which other ASA sections they belonged to. On average, Biopharmaceutical Section members are members of 2.8 ASA sections, including this section. Other most common sections are reported as Biometrics (37.2%), Medical Devices and Diagnostics (12.8%) and Bayesian Statistical Science (11.7%). Figure 3, Figure 4 and Table 1 provide the distribution of membership by number of years for ASA and Biopharmaceutical Section respectively. Biopharmaceutical Section appears to perform well in recruiting new members as well as maintaining the existing members based on 278 survey responders.

When asked on what topics members would like to see more seminars, a majority (64.4%) answered "Improving Technical Programs" and 41.3% would like to see more seminars on "Improving Consulting Skills". About one-third of members would like to see more seminars on "Improving Communication Skills" and "Career Development."

Biopharmaceutical Section Services

Most of the members (88%) reported that membership in ASA Biopharmaceutical Section is beneficial to their professional development. Overall, the following services are of greatest importance to members: sponsor workshops/webinars, e-library, fellowship with other pharma statisticians, section newsletters, and sponsor relevant sessions (Table 2).

Members seem most ambivalent about the following services: student paper awards, refreshments/updates at annual meetings, and awards for best contributed papers (Table 3).

Recommendations

The section should continue supporting e-library, sessions at annual meetings and conferences, workshops and webinars as well as cultivating fellowship among its members. Based on open comments, the section should consider sponsoring more webinars. Section newsletters are useful although the frequency of section communication could be reduced. The section could consider giving members more information on awards for best paper (at JSM) and student paper awards. It might be that these offerings are not important to members due to the limited information provided through the process. Members feel ambivalent about annual updates and refreshments at meetings. Members also showed interest to get more involved with the Biopharmaceutical Section by serving different committees.

The main objective of the Biopharmaceutical Membership Committee is to identify members' needs. Important announcements, messages, reports and surveys of Biopharmaceutical Section are communicated to members through e-mail. Therefore, members are requested to update their ASA account information with valid e-mail addresses, so that we can reach our members and provide best services.

Table 1: Distribution of Membership by Experience

Years of Membership	% of ASA Members	% of Biopharmaceutical Section Members
<= 2	4	8.3
2 - < 5	5.5	13.4
5 - < 10	10.2	20.7
10 - < 15	15	17.0
15 - < 20	17.2	16.5
20 - < 25	16.8	10.9
>= 25	31.4	13.0

Table 2: Summary of Responses (%) to Services of Greatest Importance

How important for you are the following services?	Very Important	Somewhat Important	Somewhat or Very Important
Sponsor workshops/ webinars	45.8%	44.7%	90.4%
e-library	44.8%	37.8%	82.6%
Fellowship with other pharma statisticians	37.4%	43.7%	81.1%
Section newsletters	18.0%	59.6%	77.5%
Sponsor relevant sessions	29.4%	42.8%	72.1%

Table 3: Summary of Responses (%) to Services of Most Ambivalence

How important for you are the following services?	Very Important	Somewhat Important	Not Very Important or Not Important
Student paper awards	13.6%	26.4%	49.4%
Refreshments/ updates at annual meetings	8.3%	33.5%	48.9%
Awards for best contributed papers	10.4%	33.8%	48.7%

Table 4: Biopharmaceutical and ASA Membership Information Comparison

		BIOP Survey Results			ASA Information*		
	Categories	2009	2012	2015	2009	2012	2015
	Response Rate	636/2422 (26.3%)	592/2137 (27.7%)	278/2172 (12.8%)	Out of 17633	Out of 18329	Out of 19286
Demographics	Male	67.9%	68.3%	60.1%	54.4%	54.8%	55.4%
	35-64 years old	77.6%	79.4%	80.4%	45.0%	43.7%	44.9%
Highest Degree	Ph.D.	59.6%	67.4%	72.6%	45.3%	43.9%	46.9%
	M.S./M.A.	35.4%	30.8%	25.2%	25.8%	26.3%	26.9%
Employment	Industry	67.9%	66.6%	70.4%	34.0%	24.7%	33.0%
	Academia	NA	18.0%	13.1%	29.9%	29.9%	32.0%

*Missing response rate varies from 15% to 30% depending on the categories.

Comparison with Previous Member Surveys

The previous Biopharmaceutical Section membership surveys were administered in 2009 and 2012. The survey in 2009 had 36 questions compared to 22 questions in the 2012 survey and 26 in the 2015 survey. While the response rate was comparable between the 2009 survey and the 2012 survey (26.3% vs. 27.7%), the response rate for the 2015 survey was only12.8%. The lower response rate may be due to members not receiving the survey because of outdated e-mail addresses in their ASA account information. We highly encourage our members to update their e-mail addresses in ASA and complete the triennial survey.

Demographic information was generally similar in all three surveys: the majority of members lives in the United States, are male, and are 35-64 years old. The percent of members with a doctorate degree in Statistics or a related field has increased from 59.6% to 67.4% to 72.6%. In 2009, the most popular meeting was the annual JSM; however, in 2012 and 2015, the ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop (previously known as the FDA-Industry Statistics Workshop) was the most popular. Similar to 2009 and 2012, in responding to the question on importance of enhancing and updating statistical skills, our members identified statistical books, statistical journals, software packages and manuals, statistical short courses, statistical meetings and Biopharmaceutical Webinars as either "very important" or "somewhat important".

The percent of members who reported being an ASA member for at least 15 years has increased from 53.4% in 2009 to 61.5% in 2012 and to 65.3% in 2015. Similarly, the percent of members who reported being a Biopharmaceutical Section member for at least 10 years has increased from 45.5% in 2009 to 55.3% in 2012 and to 57.6% in 2015.

Comparison with 2015 and 2012 Membership Information

Table 4 presents the demographic information obtained from the Biopharmaceutical Section surveys conducted in 2009, 2012 and 2015. In addition, the table contains the ASA demographic information at the end of each respective year. Missing ASA information varied depending on the category and year ranging from 15% (gender in 2015) to 30% (employment in 2009).

While the number of ASA members steadily increased from 17633 in 2009 to 19286 in 2015, the Biopharmaceutical Section membership decreased by approximately 12% from 2422 in 2009 to 2137 in 2012 and increased slightly to 2172 in 2015. For the categories of male and 35-64 years of age, the percentages were higher for the Biopharmaceutical Section in comparison to the ASA membership as a whole. As noted previously, the percent of Biopharmaceutical members with a doctorate degree in Statistics or a related field has increased from 59.6% in 2009 to 72.6% in 2015; however, for ASA membership as a whole, the percent remained fairly constant between from 2009 to 2015 and was consistently smaller than the Biopharmaceutical Section. The per-

cent of members working in industry was higher in the Biopharmaceutical Section compared to the ASA membership as a whole.

ASA Sections Resources, Activity and Interest Groups

The section's Working Group on Statistical Interest Groups (Erik Pulkstenis, Kjell Johnson, Jared Lunceford, Bill Pikounis, Weili He and Mike Colopy) asked three additional questions to explore emerging interests within the Section and to gauge awareness regarding Section benefits and resources. Their results showed that only 22% of responders were familiar with resources and venues available to our members, while a surprising 66% were vaguely familiar and 12% were not familiar with our resources and venues. Sixty-six percent of members felt the section's current activities and interest groups sufficiently represented their specialties. Only 35% felt the section should create new formal interest groups to support special topics. Suggested topics included preclinical statistics, biomarkers, pharmacology, health technology assessment, real-world data and big data. New interest groups can provide new opportunities for members to become involved and contribute to the section.

Acknowledgement

We would like to thank the Biopharmaceutical Section members who completed the survey. In addition, we would like to thank Donna LaLonde for obtaining and tabulating the ASA demographic information. This article reflects the views of the authors and should not be construed to represent the FDA's views or polices. ■

UPDATE FROM THE PUBLICATIONS OFFICER

Richard Zink (SAS Institute, richard.zink@jmp.com)

Hi, Folks! I wanted to take this opportunity to provide a quick update on Publication Team efforts. What is the Publication Team? The Publication Team includes any individuals on the Section Steering Committee with responsibility for communicating, developing or identifying content for Section activities. This includes:

1. The Biopharmaceutical Report
2. Webinars
3. Webpage (***http://community.amstat.org/BioP/home***),
4. Podcasts (through the website, but all episodes are available here: ***www.buzzsprout.com/16296***)

Obviously, you are holding the new issue of The Biopharm Report, which sports a new redesign. I'd like to thank past and current editors for such great work in updating the look of our magazine!

There are a number of forthcoming webinars: March includes a presentation on biosimilars from Sujit Ghosh of NC State, while Michael Kosorok of UNC–Chapel Hill will present on machine learning in April. One item of note for webinars is that the Section is currently offering a pilot initiative to make webinars free for Biopharm members. Based on feedback so far, this appears to be very popular - the February webinar on Bayesian methods for evidence synthesis and network meta-analysis experienced record registrations. Since registrations are free and the Biopharm Section encourages groups to view webinars in conference room settings using a single registration, I hope this encourages biostatistics, statistics and data science departments to promote Biopharm Webinars to their students and faculty. It is a great way to gain insight into some of the challenges faced by statisticians in medical product development. Not yet a member of the Biopharm Section? Section membership is only $10, and you can contact the ASA office to join.

There are a number of podcasts slated for spring, including conversations with the Caucus for Women in Statistics, the organizers for the Women in Statistics and Data Science Conference and statisticians on incorporating patient preferences into medical product development.

Website content is receiving a much-needed update, and we are discussing ways in which we can better communicate the activities of our section, as well as the activities of other organizations that may be of interest to our members. We want our website to be the first stop for individuals curious in the available activities for their personal and professional development. Finally, blogs will be a future offering of the Biopharm Website!

Finally, and I can't emphasize this enough, the Publication Team cannot do it alone. We need YOUR help! Are you publishing a book or have you recently organized a section for a scientific meeting? Consider writing a brief summary on the topic for an upcoming issue of the Biopharm Report. Have a short course idea? We can always use presenters for Webinars. Want to get something off of your chest, educate our members on a new topic (e.g. data transparency, patient perspectives, biosimilars), or promote an upcoming conference or initiative, please consider a podcast or blog. We'd love to hear from you. ■

BIOPHARMACEUTICAL SECTION POSTER COMPETITION AT 2016 JSM

Judy Li

If you will be attending the 2016 JSM and plan to present a poster, you may consider participating in the Poster Competition sponsored by the ASA Biopharmaceutical Section. You do not need to be a member of the Biopharmaceutical Section to participate. All authors who present posters sponsored by the Biopharmaceutical Section are qualified to compete for this award. Three awards with cash prizes of $1000, $600 and $400 will be given for 1st, 2nd and 3rd places, respectively.

The entry criteria for the Poster Awards are:

- Topics in statistics which are applicable to biopharmaceutical research. Suitable topics include but are not limited to: methodological issues in preclinical or clinical trials, epidemiology studies of drug safety (device or biological), genetic studies predicting drug (or biological) response, laboratory and toxicological data analyses, methods for high-dimensional data from high-throughput screening, and non-linear pharmacokinetic modeling.

- This year we are going to evaluate each poster based on both social media and committee members' evaluation. Posters will be judged based on the following criteria
  - ❑ Innovation
  - ❑ General applicability in pharmaceutical research
  - ❑ Appropriate example(s)
  - ❑ Effectiveness of presentation (well written, well organized, etc.)

Authors who compete for the Poster Awards cannot also compete for the Student Paper Awards.

The process is as follows:

1. You must have submitted an abstract through the Biopharmaceutical Section by February 1, 2016.
2. Submit your poster to Judy Li, Chair for the Poster Awards, through email (Judy.Li@fda.hhs.gov) by June 10, 2016.

At this time, let's congratulate the 2015 JSM poster award winners:

First Place:

"*A Simulation Study Using Inverse Probability Weighting To Adjust For Multiple Types Of Bias In Observational Studies*" by **Xie Diqiong**, FDA

Second Place:

"*Data-Driven Prior Distributions For A Phase-2 Copd Dose-Finding Clinical Trial*" by **Shuyen Ho**, PAREXEL International

Third Place:

"*Modeling And Prediction Of Accrual In Multi-Regional Clinical Trials*" by **Yi Deng**, Department of Biostatistics and Bioinformatics, Emory University

PRELIMINARY ANNOUNCEMENT: 2016 ASA BIOPHARMACEUTICAL SECTION REGULATORY-INDUSTRY STATISTICS WORKSHOP

Freda Cooner and Ed Luo, Workshop Co-chairs

Year 2016 marks the 20th anniversary for the *ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop*, formerly known as *ASA Biopharmaceutical Section FDA/Industry Statistics Workshop*. The Workshop is sponsored by the ASA Biopharmaceutical Section in cooperation with the FDA Statistical Association (FDASA).

The Workshop will take place September 28-30 (Wednesday–Friday) at the Marriott Wardman Park Hotel in Washington D.C. The main body of the Workshop, on the latter two days, will contain invited sessions co-organized and co-chaired by statisticians from industry, academia, and regulatory agencies. In addition, short courses on important related topics are offered on the first day. The Workshop has grown steadily in popularity over the years, attracting more than 800 participants in recent years.

The theme for the 2016 Workshop is "Statistical Innovation: Better Decisions Through Better Methods". Short courses and parallel sessions that will be included in the final program cover a variety of topics of current importance that illustrate innovative study designs and statistical methodologies in diverse fields, from CMC, pre-clinical, and clinical programs to post-marketing safety studies and research. In particular, the topics include adaptive designs, Bayesian methodology, biosimilars, modeling and simulation, big data, and more. Plenary sessions will feature prominent speakers from both industry and regulatory agencies to present the impact of statistical innovation in drug and device development. As it has for a number of years, the Workshop will again offer roundtable luncheon discussions on the first day where attendees can exchange ideas and opinions. This year a poster session has been added to the second day schedule, where presenters can showcase their recent research projects, newly developed statistical models, etc. The deadlines for roundtables and poster submissions are March 15, 2016 and April 1, 2016, respectively.

More than 100 participants attended the Organizing Committee meeting on February 8, 2016 to provide input into selecting the program sessions and short courses. Forty-two parallel sessions were accepted to the program and are under full development. The following 8 half-day short courses will be offered.

Title	Instructors
Introduction to Clinical Trial Optimization to Enable Better Decision Making	Alex Dmitrienko, Quintiles
Bayesian Biopharmaceutical Applications Using SAS®	Fang Chen, SAS Institute; Guanghan Liu, Merck
An Overview of Methods to Assess Data Integrity in Clinical Trials	Richard Zink, SAS Institute; Marc Buyse, IDDI; Paul Schuette, FDA
Statistical methods and software for multivariate meta-analysis	Haitao Chu, University of Minnesota; Yong Chen, University of Pennsylvania
Writing Clinical Trial Simulators	Scott Berry and Anna McGlothin, Berry Consultants
Use of Biomarkers for Surrogacy and Personalized Treatment Selection	Tianxi Cai, Harvard School of Public Health; Layla Parast, RAND Corp.
Structured Benefit-Risk Evaluation and Emergent Issues	Weili He, Merck; Qi Jiang, Amgen; John Scott, CBER FDA
Design and Statistical Analysis of Biosimilars	Shein-Chung Chow, Duke University

Registration will open on June 1, 2016. Make sure to register early! More information is available at ***www.amstat.org/meetings/biopharmworkshop/2016***.

BOOK DRIVE TO BENEFIT RESEARCH LIBRARY

Dear Statistics Friends,

Want to help African and Arabic researchers?

As you probably know research productivity in Africa is poor where only 3% of the scientific literature comes from these countries. A primary reason is that 80% of the articles in science are turned down as the result of poor statistics. We build the research methods library of science as a one stop shopping center to find answers to statistical questions. We have 1000s of lectures, materials, etc. available

Mary Shann from BU called me with a brilliant idea. She offered to donate 2000 books on research methods and statistics to the Library of Alexandria. The library was thrilled about this, and we have started to collect research methods and statistics books from across the world with the goal of reaching 10,000 books which would make the library of alexandria the largest virtual and book library in Arabic and african countries. Each of Mary's books will have a sticker on it indicating that she donated it, and BU will become a regional center for the library of alexandria.

It is most difficult to donate your books, as our books are like our babies. When I retired, I sadly pruned and tossed my books.

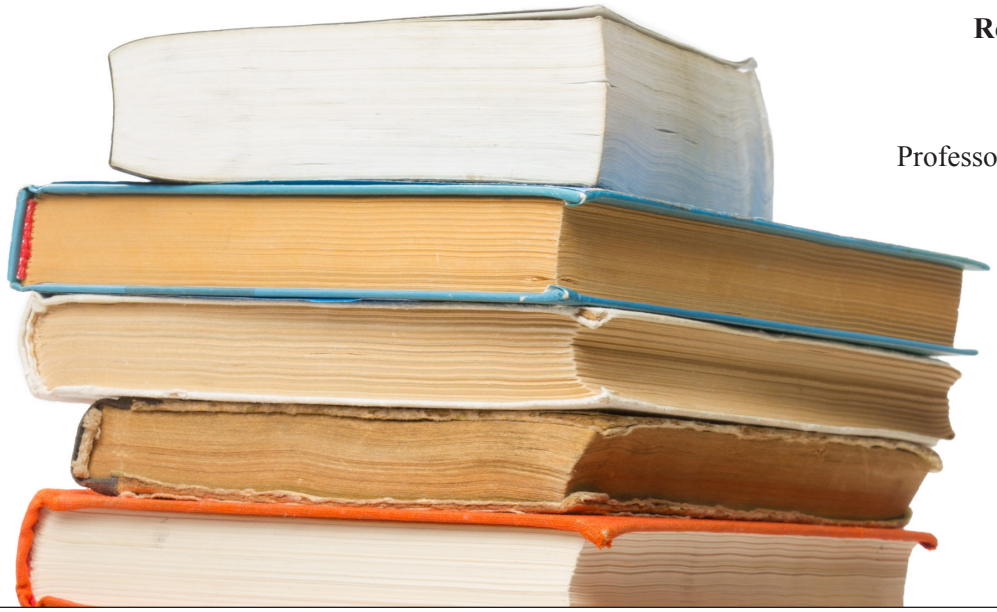
I would like you to look up from your computer to your book shelf. Identify the books that have not been opened in 5 years. In my case it was about 80%

Don't you think it would be better for those books to be teaching, rather than sitting there having their papers go yellow? We are therefore asking you to contribute the research methods and ,statistics books to Africa and Arab countries at the Library of Alexandria. Degroot's text book on statistics costs $220.00, a two month salary in many African countries. Yet our unopened 5 year statistics books gather mold in our bookshelf. Perhaps you could help 19 year olds in Mali the Sudan, and Niger with your donation.

It is almost no lose. You have many text books that you have not been opened in a decade, the Library of alexandria till take these off your hands at no cost. You will be recognized at the library of Alexandria, you will get a tax break, and you will feel really, really good.

If you would like to contribute your statistics and research methods books, please tell Mary Shann *shann@bu.edu* or myself *ronaldlaporte@gmail.com*.

I am a professor emeritus of epidemiology and former director of a WHO Collaborating Center in Pittsburgh. I have 550 publications in Nature, Science, PNAS, Lancet, BMJ. Please check out this short video if you would like future information about what have developed.



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