Publication Planning in Emerging Markets: Scientific, Cultural, and Practical Issues

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Disclosure
Leslie Citrome, MD, MPH

Leslie Citrome serves as Associate Editor of the International Journal of Clinical Practice (IJCP), published by Wiley-Blackwell, and has the firm belief that IJCP is the best journal in the world.

Leslie Citrome, is a consultant for, has received honoraria from, or has conducted clinical research supported by the following:


* Denotes a relationship in effect anytime during the past 12 months
Publication Planning in Emerging Markets: Scientific, Cultural, and Practical Issues
What Are Emerging Markets?
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Mind the Gap!
What Are Emerging Markets?

Shifts in Industry-Sponsored Phase II/III Trial Sites

Figure 8. The shift in industry-sponsored phase II/III trial sites from 2006.01 to 2008.06 and 2008.07 to 2010.12. The green points represent a gain in the number of sites, while the red points a loss in the number of sites. Values taken from Table 5.

Source: Clinical Trial Magnifier Vol. 4:1 Feb 2011
www.ClinicalTrialMagnifier.com
Emerging markets may differ from the point of view of the researcher

- Not all specialties are at the same level of development
- Emergence of new countries for the conduct of clinical trials
- Emergence of greater autonomy and leadership for the conduct of clinical trials in Asia – example of the Clinical Trial Magnifier
US FDA site inspection findings during the past ICH period, 1997-2008, fail to justify clinical research globalization concerns as recently put forth in the US and EU.

In this Magnifier issue, we report, East Europe, with 150 completed US FDA site inspections, has the best overall results, with 3.3% of its site inspections having three or more deficiencies, compared with 20.2% in Europe. A significant, relatively higher number of deficiencies are also reported for European sites, notably 43.6% for “Failure to follow Investigational Plan”, compared with 33.9% for North America and 27.5% for rest-of-the-world.

It is therefore ironic that the European Medicines Agency (EMA) recently posted a strategy paper expressing growing concern about how well clinical trials are conducted from an ethical and scientific standpoint in regions outside Europe and North America, namely Africa, Asia, Latin America and Russia.

Our findings strongly imply that equal or even stronger concerns should be directed towards Western European investigator sites.

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Investigator Initiated Clinical Trial Contract Issues

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“Get your facts first, then you can distort them as you please.” — Mark Twain.

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http://www.ClinicalTrialMagnifier.com

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http://www.clinicaltrialmagnifier.com/
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<tr>
<td>Book</td>
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<tr>
<td>2010 Issue 6</td>
<td>Dec Investigator Incentives for Trial Participation (I-Incent) Report</td>
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<td>2010 Issue 5</td>
<td>Oct WHO International Clinical Trials Registry Platform – An In-depth Analysis</td>
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<td>Sep REVISIÓN DE ESTUDIOS CLÍNICOS: UNA GUÍA PARA EL COMITÉ DE ÉTICA</td>
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Growth of Biomedical Publishing

67% Growth

The number of biomedical research articles published annually between 2000 and 2009 – based on the PubMed database.

Who gained and who lost?

China, South Korea, Brazil, India, Turkey, Taiwan and Iran gained most in the proportion of articles between 2000 and 2009; together 9.0% or 79,000 articles.

The US, Japan and UK lost most in the proportion of biomedical articles published between 2000 and 2009; together 6.6% or 53,000 articles.
Rest-of-World (ROW)

- ROW contributes approximately the same number of articles as either North America (NA) or Europe (EUR)
- But 5/10 high impact journal articles are currently produced in NA, 3/10 in EUR, 1/10 in the ROW
- The ROW presently contributes almost the same number of controlled trial reports as NA and slightly fewer than EUR
- Asia is clearly the “new kid on the block”, now contributing about half of the biomedical articles produced outside of NA and EUR
- China and Iran stand out as the fastest-growing contributing countries among emerging regions, while Russia is the slowest
Growth of Biomedical Publishing

Growth in the proportion (%) of all articles between 2000 and 2009

Karlberg J. Clinical Trial Magnifier 2009;2(12)
### Growth of Biomedical Publishing

**ROW > Europe > North America**

#### Proportion of all articles (%)

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<tr>
<th>Year of publication</th>
<th>Rest-of-world</th>
<th>Europe</th>
<th>North America</th>
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<tbody>
<tr>
<td>2000</td>
<td>24.1%</td>
<td>25.4%</td>
<td>32.2%</td>
<td>34.6%</td>
</tr>
<tr>
<td>2002</td>
<td>24.3%</td>
<td>26.6%</td>
<td>32.3%</td>
<td>34.7%</td>
</tr>
<tr>
<td>2004</td>
<td>27.6%</td>
<td>31.2%</td>
<td>31.3%</td>
<td>34.4%</td>
</tr>
<tr>
<td>2006</td>
<td>28.2%</td>
<td>31.2%</td>
<td>31.6%</td>
<td>34.3%</td>
</tr>
<tr>
<td>2008</td>
<td>29.9%</td>
<td>31.3%</td>
<td>31.7%</td>
<td>33.4%</td>
</tr>
</tbody>
</table>

** Ranking 2000**

North America; Europe; Rest-of-world

** Ranking 2009**

Rest-of-world; Europe; North America

Karlberg J. Clinical Trial Magnifier 2009;2(12)
Growth of Biomedical Publishing

Asia >> Eastern Europe > Latin America > Oceania

Proportion of all articles (%)

Asia | East Europe | Latin America | Oceania

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<td>13.7</td>
<td>14.3</td>
<td>14.8</td>
<td>15.4</td>
<td>16.0</td>
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<tr>
<td>East Europe</td>
<td>3.8</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Latin America</td>
<td>4.1</td>
<td>4.4</td>
<td>4.6</td>
<td>4.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Oceania</td>
<td>4.4</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
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</table>

Global 2

Asia contributes with over 50% of rest-of-world

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Growth of Biomedical Publishing

Middle East > Africa > Israel > South Africa

Proportion of all articles (%)

- Middle East
- Israel
- Africa
- South Africa

Year of publication


Global 3

Israel is losing its dominance in Middle East
South Africa is not alone in Africa

Karlberg J. Clinical Trial Magnifier 2009;2(12)
Growth of Biomedical Publishing

*English Remains the Lingua Franca*

Source: Clinical Trial Magnifier Vol. 2:12 Dec 2009
www.ClinicalTrialMagnifier.com

Figure 1. Number of articles by year and language, i.e. English or non-English. Values taken from Table 1.

Karlberg J. Clinical Trial Magnifier 2009;2(12)
What Are Emerging Markets?

*Point of View: The Medical Journal*

Emerging markets may differ from the point of view of the medical journal:

- Access to resources may differ
- Governmental or professional society sponsorship can make the journal a “contender”
- English and indexing = influence
- Role of the EIC may be that of a figurehead
What Are Emerging Markets?

Point of View: The Clinician

Emerging markets may differ from the point of view of the clinician

- Not all specialties are at the same level of development
- Access to the literature can differ
- Access to new medications can differ
- Access to diagnostic tests can differ
- Disparities in basic health care
Cultural Influences
Cultural Influences

- Access to medical education – who becomes a physician?
- The hierarchy – the impact of the professor
- Who provides primary health care? Are physicians the last resort?
- The acceptance of “Western” medicine
- The curious case of branded generics in China
Who is a KOL?

- Meritocracy vs. seniority
- Academic teacher vs. bureaucrat/technocrat
- Academic teacher vs. entrepreneurial clinician
- Academic researcher vs. commercial researcher
- An international reputation, often including time abroad, may trump all
Regulatory and Business Differences

- The demarcation between promotional activities and continuing medical education may not be clear in some places.
- The US legal system and the litigious culture appears unique.
- Access to health care can differ greatly.
Getting Information Out

- Paper versus on-line access
  - Adoption of on-line access to medical information can differ between countries and between practitioners and researchers
- Reprints and republications
  - Translations are popular but...the author is often the last to know
    - Authorized versus unauthorized
- Libraries
  - Affordability of subscriptions an obstacle
More About Language

- Be skeptical when told that everyone understands English.
- However, publishing in English is highly valued.
- Academics will make the effort to read English in order to further their own publishing endeavors.
- Clinicians, and their staff, likely require translated materials.
An authorized translation and republication with an unauthorized duplicate PubMed entry (eventually deleted)
Interpreting and applying the EUFEST results using number needed to treat: antipsychotic effectiveness in first-episode schizophrenia

A current therapeutic controversy in the treatment of schizophrenia is the relative merit of using different antipsychotic medications. Recently reported are the results of the European First-Episode Schizophrenia Trial (EUFEST), where 498 patients were randomised (1). Similar to the US Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) for schizophrenia, the primary outcome measure was all-cause treatment discontinuation (2), and the study was conducted at multiple sites (50 in 14 countries), with each patient able to remain on their assigned medication for a lengthy period of time (1 year). The major differences are that the EUFEST patients were in the first episode of their illness, the study although randomised, was open-label, and the principal first-generation antipsychotic being examined was haloperidol, not perphenazine, albeit at a low dose of 1-4 mg/day. Rather than including risperidone, the study designers included olanzapine, a second-generation antipsychotic unavailable in the USA. Also, unlike CATIE, failure on randomised drug meant the end of that patient’s study participation instead of a continued study of the individual group total was used to calculate discontinuation rates, rather than the Kaplan-Meier estimate so that the respective 95% confidence interval for the NNT could be determined. The rank ordering of the antipsychotics by all-cause discontinuation was from lowest to highest rates olanzapine > haloperidol > quetiapine and haloperidol and ziprasidone > haloperidol, as reported here.

The authors found differences in all-cause discontinuation evidencing advantages for all of the second-generation antipsychotics studied in survival curve analysis, but they did not find significant differences in psychopathological rating scale outcomes among the antipsychotics used. How can one explain the apparent clinical difference among the antipsychotics in this study? One possibility is that the clinical meaningfulness of antipsychotic treatment of first-episode schizophrenia is possible but that second-generation antipsychotics are not necessarily more efficacious than haloperidol, based on the finding that symptom reductions as measured by the Positive and Negative Syndrome Scale (PANSS) were almost the same in all the groups, at around 40. Moreover, discontinuation outcomes as measured by the Calgary Depression Scale for Schizophrenia and quality of life outcomes as measured by the Manchester Short Assessment of Quality of Life Scale were also similar for the anti-psychotics tested. This may mis the point that there were identifiable differences in medication 'durable' by which patients would continue taking some of the antipsychotics for longer periods of time. Patients randomised to haloperidol had a mean time to discontinuation of 0.5 months, compared with 3.3 months for olanzapine and 6.3 months for olanzapine (Figure 1). Did patients get better relatively quickly regardless of antipsychotic but then decided not to continue for reasons that are not adequately captured?

The concept of number needed to treat (NNT) can help place the EUFEST data into clinical perspective. Defined as 'the number of patients who must receive an intervention of therapy during a specific period of time to prevent one adverse outcome or produce one positive outcome' (3, page 111), NNT is one of the essential tools of evidence-based medicine that helps us gauge effect size, or clinical significance (4).

Number needed to treat for all-cause discontinuation for the five tested antipsychotics can be presented in a 5 x 5 table (Table 1). The absolute number who discontinued divided by the individual group total was used to calculate discontinuation rates, rather than the Kaplan-Meier estimate so that the respective 95% confidence interval for the NNT could be determined. The rank ordering of the antipsychotics by all-cause discontinuation was from lowest to highest rates olanzapine > haloperidol > quetiapine and haloperidol and ziprasidone > haloperidol, as reported here.

The strongest effect sizes were olanzapine > haloperidol 

NNT yields statistically significant
gain pari-wise advantages olanzapine > haloperidol and quetiapine and haloperidol, and ziprasidone > haloperidol. The relative clinical meaningfulness of these differences cannot be captured by a discontinuation

On the other hand, it is possible that the EUFEST results for all-cause discontinuation are consistent with what has been observed in a NNT analysis of the CATIE data (5).

Number needed to treat for discontinuation because of insufficient efficacy, side effects and non-

adherence can also be calculated. Amisulpride and olanzapine had the lowest rates for discontinuation because of insufficient efficacy (14% each), and

EUFEST compared haloperidol, amisulpride, olanzapine, quetiapine and ziprasidone

The concept of number needed to treat (NNT) is the number of patients...
Resources

- World Association of Medical Editors (www.wame.org)
  - 1664 members representing more than 980 journals from 92 countries (as of February 4, 2011)
  - Active LISTSERV
Medical Publishing Insights and Practices (MPIP) Authors’ Submission Toolkit: A Practical Guide to Getting Your Research Published

- Published in June 2010 in Current Medical Research and Opinion
- Summarizes tips and “best practices” to increase awareness of editorial requirements, journal selection, submission processes, and effective communication with editors
Resources

Commentary

Authors’ Submission Toolkit: A practical guide to getting your research published

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Michelle Evangelista
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AstraZeneca, Chester, UK

Trish Groves
Inn, London, UK

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Current Medical Research and Opinion Informa, New York, NY, USA

Bernadette Mansi, Charles Miller
GlenSmithKine, King of Prussia, PA, USA

LaVerne A. Mooney
Piper Medical, New York, NY, USA

Ann Murphy
The Endoclyst, Durham, NC, USA

John Shelton
Journal of Clinical Psychiatry, Physicale, Postgraduate Press, Inc., Memphis, TN, USA

Philip D. Watson
Clinical Therapeutics, Hanover, Germany

Al Weigel
International Society for Medical Publication Professionals (ISMP), Butterworth-HEINEMANN, Pharmacists, Ridgefield, CT, USA

Abstract

Biomedical journals and the pharmaceutical industry share the goals of enhancing transparency and expanding access to peer-reviewed research; both industries have recently instituted new policies and guidelines to effect this change. However, while increasing transparency may elevate standards and bring benefits to readers, it will drive a significant increase in manuscript volume, posing challenges to both the journals and industry sponsors. As a result, there is a need to: (1) increase efficiency in the submission process to accommodate the rising manuscript volume and reduce the resource demands on journals, peer reviewers, and authors; and (2) identify suitable venues to publish this research. These shared goals can only be accomplished through close collaboration among stakeholders in the process.

In an effort to foster mutual collaboration, members of the pharmaceutical industry and the International Society for Medical Publication Professionals founded a unique collaborative venture in 2008—the Medical Publishing Insights and Practices Initiative (MPIP). At an MPIP roundtable meeting in September 2009, journal editors, publishers and industry representatives identified and prioritized opportunities to streamline the submission process and requirements, and to support prompt publication and dissemination of clinical trial results in the face of increasing manuscript volume. Journal and sponsor participants agreed that more author education on manuscript preparation and submission was needed to increase efficiency and enhance quality and transparency in the publication of industry-sponsored research. They suggested an author’s guide to help bridge the gap between author practices and editor expectations.

To address this unmet educational need, MPIP supported development of an Authors’ Submission Toolkit to compile best practices in the preparation and submission of manuscripts describing sponsored research. The Toolkit represents a unique collaboration between the pharmaceutical industry and biomedical journals, and reflects both groups’ perspectives on how authors can help raise standards and increase efficiency in publishing industry-sponsored studies. The information provided in the toolkit can be useful to help authors navigate the manuscript preparation and submission process, and should improve the quality and timeliness of publications.

Introduction

Purpose of the toolkit

Industry-sponsored clinical research has become more open and transparent in recent years due to changes in policy, regulation, and technology, as well as a general trend toward increased information access and sharing. The goals of greater transparency and expanded access to data are also driving a significant increase in the volume of manuscripts being developed and submitted to journals, which poses challenges to both the journals and the pharmaceutical industry. As a result, there is a need to improve efficiency in the submission process to accommodate this increased manuscript volume and mitigate resource demands...
Universal Challenges for Readers

• Finding the “right” paper
  – If it is indexed it can be found, if you have access
• Having the “right” paper find you
• Keeping up
• Sorting out the newsletters, eTOCs, and alerting services
• Is it “free”?  
• Where do I put all this stuff?
Harvesting the Literature

Step 1a: Automated search results
- eTOCs
- Prespecified e-alerts
- Amedeo
- PeerView Institute
- Search engines and other aggregators

Step 1b: Manual search done to augment Step 1a
- PubMed
- HighWire
- Other search engines

Step 1c: Newsletters
- Recommended background articles

Step 2: What to keep? What to discard?
- Is the abstract of interest?
- Has the article been endorsed by other resources?
  - Bandolier
  - BMJ Evidence Center
  - Other EBM resources
- Paper resources
  - Scan what you want to save and throw out the paper

Step 3: Storing, indexing, backup, future retrieval and viewing
- Copernic, Google Desktop Search, Other indexing programs
- Backup with portable hard drive and synchronization software
- View with a large LCD monitor (or two)

Step 4: Sharing
- CiteULike
- Connotea
- Other workflow tools
Questions?
nntman@gmail.com