Defining Professionalism in Medical Publications: Transparency, Objectivity, and Ethics

5th Annual Meeting of ISMPP
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Global Standards

Elizabeth (Liz) Wager
Sideview
Global Standards and Expectations for Medical Publications

Transparency’s Moving Target

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Transparency, Objectivity, and Ethics

Philadelphia, PA, USA
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'Whenever the people are well informed, they can be trusted with their own government.'

‘Whenever things get so far wrong as to attract their notice, [a well-informed people] may be relied on to set them to rights.’

Thomas Jefferson
1743-1826
What is the effect on science when it is put in the public domain for scrutiny?

How can we best incorporate the evolving US, EU, and international standards for transparency in clinical trial registration and results publications into our medical writing requirements regarding objectivity and ethics?
Transparency in Medical Publishing

- **Trust** is the cornerstone of medical research and practice
- We trust what we can see (know)
- Science is a **written activity**; we need to trust the writers and the publishers
- Society is in search of a **basis** for trusting science and the products of science
- Clinical trial registration and results publication are responses to a lack of trust (the ‘trust deficit’)
- How can we use the standards of transparency to increase **objectivity and ethics** in our medical writing?
The Background to Transparency

- an increasing interest by scientists, sponsors, and the public to have both studies and their results published
- an increasing need to share knowledge in health research (Cochrane Groups, NICE UK, US?)
- a growing concern with data, data management, and data access
- **EU Directive 2001/20/EC**
- The medical journal industry and the ICMJE Requirements: www.icmje.org
- The role of www.clinicaltrials.gov
- The role of the World Health Organization’s ICTRP
- The role(s) of pharma-bio and academic sponsors & researchers
- The roles of patients and ethics committees (IRBs)
‘Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.’

Declaration of Helsinki 2008 paragraph 19
National Clinical Trials Databases (1)

- www.ClinicalTrials.gov
- EudraCT, EudraVigilance, EudraPHARM
- India
- China
- Australia
- Brazil
- Argentina
- Chile
- Canada
- Croatia
- France
- Spain
- The Netherlands
- Italy
- Switzerland
National Clinical Trials Databases (2)

- Germany
- Turkey
- Cuba
- Iran
- Latin America (PAHO)
- Sri Lanka
- South Africa
- Taiwan
- Israel
- New Zealand
- (United Kingdom)
- Japan
EU Directive 2001/20/EC

‘OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use’
EudraCT Characteristics

- A database of all clinical trials commencing in the European Union after 1 May 2004
- The EudraCT number – legally required before commencing a clinical trial in the EU (and now at times in 3\textsuperscript{rd} countries)
- Accessible only to the EMEA, ‘competent authorities’ (and sponsors)
- A unique experiment – and challenge
The EU Paediatric Regulation


Published in the OJ 27 December 2006 Effective 26 January 2007
Transparency in EU Paediatric CTs

- ‘information shall be made available to the public, on how clinical trials results shall be submitted and be made public and on the European Medicines Agency (EMEA)'s responsibilities and tasks in this regard’
Objectives of the EU Requirements for Transparency in EU Paediatric CTs

a) to increase the availability of information on the use of medicinal products in the paediatric population

b) to avoid unnecessary repetition of studies in the paediatric population which do not add to the collective knowledge
The Information Made Public (adult)

- The European Commission ‘List of Fields Contained in the EudraCT Clinical Trials Database to be Made Public, in Accordance with Article 57(2) of Regulation (EC) NO 726/2004 and its Implementing Guideline 2008/C168/02’

  (Brussels, 04.02.2009 ENTR/F/2/SF/jr D (2009) 3687)

The European Commission ‘List of Fields to Be Made Public from EudraCT for Paediatric Clinical Trials in Accordance with Article 41 of Regulation (EC) NO 1901/2006 and its Implementing Guideline 2009/C28/01’

(Brussels, 04.02.2009 ENTR/F/2/SF/jr D (2009) 3698)

Protocol-related Information to Be Made Public (1)

- Identification of the clinical trial and its protocol
- Sponsor
- Source of funding
- Contact point for public use
- Identification and description of the treatment arms of the study (IMPs) to be used
- Therapeutic objective of the trial (disease under investigation)
- Trial population
Protocol-related Information to Be Made Public (2)

- Trial design
- Major objectives and endpoints
- Inclusion/exclusion criteria
- General information on the trial including the countries in which it is to be conducted
- Trial status (per country or region as applicable), and if refused for ethical reasons the reasons for refusal
Results-related Information to Be Made Public (1)

- Administrative information and trial identification
- Trial design
- Scientific background and explanation of rationale for the trial
- Participants in the trial – information on the subject population including inclusion exclusion criteria and demographic information
- Interventions - the treatments used
- Objective(s) of the trial
Results-related Information to Be Made Public (2)

- Outcome measures
- Randomisation implementation
- Blinding
- Statistical methods
- Patient disposition
- Protocol deviations
- Recruitment
- Baseline data
- Trial interruption
Results-related Information to Be Made Public (3)

- Trial interruption
- Outcomes and estimation
- Ancillary analysis
- Adverse events
- Trial termination
- Discussion and interpretation of study results (interpretation of trial results by [the] sponsor, if available and by competent authority, if available)
- A declaration of the submitting party on liability for the accuracy of the submitted information
International Clinical Trials Registry Platform (ICTRP) - WHO

- WHO Technical Consultation on Clinical Trials Registration Standards
  WHO Headquarters, Geneva, 25-27 April 2005
- ICTRP Scientific Advisory Group Meeting
  WHO Headquarters, Geneva, 17-18 November 2005
- ICTRP Scientific Advisory Group Meetings
  WHO Headquarters, Geneva, 26-28 April 2006; WHO Center, Kobe, Japan; 29-30 November 2006
WHO ICTRP

To set international norms and standards for trial registration and reporting within which trial registers and databases worldwide can operate in a coordinated fashion, while upholding scientific and ethical principles.
The Publication Industry and Transparency

• ‘Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication’ (ICMJE), 9 September 2004, October 2008 (The Vancouver Group 1978 → ICMJE)

• ‘Altruism and trust lie at the heart of research on human subjects.’

• The high road on registration, the low road on publication practices

• Reports questioning the relationship between medical journal editors and pharma manufacturers
FDAAA Requirements (PL 110-85, 27 September 2008)

Food and Drug Administration Amendments Act of 2007 (FDAAA), Title VIII – Clinical Trial Databases, Section 801 Expanded Clinical Trial Registry Databank
Enacted on September 27, 2007

Requires Trial Registration (Dec 2007)
- Phase II-IV drug and device trials for all diseases
- Data elements: ClinicalTrials.gov + ~ WHO/ICMJE

Requires Results Reporting (Sept 2008)
- Trials of FDA-approved or cleared drugs and devices
- “Basic” Results: Baseline Characteristics, Primary & Secondary Outcomes, Statistical Analyses
- Adverse Events (Sept 2009)
- “Expansion” of results by rulemaking (Sept 2010)
Key FDAAA Milestones

- 27 September 2008
  - ‘Basic Results’ reporting requirements effective
- 20 April 2009 – Public Meeting
- 27 September 2009 – Adverse Events
- 27 September 2010 – Rulemaking Due
NIH Public Meeting Issues for Discussion

1. Post results of unapproved products?
2. Post data summaries without being misleading or promotional?
3. Post non-technical summaries? What information? Who should write them?
4. Post full protocol?
5. Procedures the Agency should consider for QC
6. Increase results posting timing to 18 months after LSLV of Primary Outcome?
7. Post results for studies registered before effective date of the regulation?
8. Appropriate timing for registration updates
9. Standard format for submission of required basic results
10. Statement that should accompany voluntary registrations
11. Other
PhRMA Principles Updated

- Announced at the NIH Public Meeting NLM, 20 April 2009
- Effective: 1 October 2009
- Register all clinical trials involving patients
- Post results summaries for all clinical trials involving patients for approved medicines as well as medicines whose research programs are discontinued.
The Challenge of Transparency for the Medical Writer

A lack of a harmonised approach

- between countries
- among international organizations
- between sponsors of research
- among editors and publishers
For transparency, objectivity, and ethics, who is the medical writer’s audience?
Transparency Check
Audience Response Session

Francis P. Crawley
Good Clinical Practice Alliance - Europe
Do patients benefit from the publication of the results of clinical trials for medicines not approved by the US FDA (or another national regulatory agency, e.g., Health Canada, EMEA, SFDA, DCGI)?

1. Yes
2. No
Question…

Should the reports of all clinical trials be publicly available for patients and researchers, without fees, regardless of where they are published?

1. Yes
2. No
Question…

Has the 2008 revision of the Declaration of Helsinki affected your practice with regard to transparency in medical writing?

1. Yes
2. No
Should medical publication professionals develop their own standards for transparency, objectivity, and ethics in medical writing using an inclusive process?

1. Yes
2. No
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