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Registries and Databases: Toward Transparency

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Background[1]

This article outlines structural and ethical considerations of clinical trials registries and databases of results. The topic is complex. Indeed, even what to call these entities is confusing. Some prefer simply to refer to them as registries; others distinguish between registries and databases based upon differing objectives and content.

Regardless, at base, there appears to be agreement that international public confidence in the clinical research enterprise as a whole may be improved with the expansion of registries and databases. Certainly public understanding - and more effective use - of clinical research are expected to profit from their refinement and accessibility.

"*Transparency*," a term used to capture the grave concern of leadership and management across the functional areas of Good Manufacturing, Clinical, Laboratory, etc. Practice (GXPs) regarding public trust, is the ultimate goal. This larger context of transparency also includes two important challenges, both characterized by wide pendulumlike swings in the last half-century of clinical research.

One challenge arises from public opinion that has alternated between viewing the research enterprise as generating miracles and seeing it as a hotbed of greed and arrogance. The other involves how the research community has confronted human subject protections - oscillating between paternalism and self-sufficiency.

Structural Considerations[2]

In the development of effective registries and databases there are five basic sets of challenges:

- The What: . . . . .*Information*?
- The Where: . . . . . *Sources*?
- The For Whom: . . . .*Access*?
- The Who Controls:*. . . . . .Authority and Responsibility*?
- The When: . . . . . .*Timing*?

Naturally, each carries significant implications, including resource allocations.

Regarding Information, there are three fundamental considerations:

- Formats
- Fields
- Validation

So, the challenge is one of design of the registry or database that also includes what standards are to be maintained for quality assurance purposes and how to minimize redundancy while maximizing ease and efficiency of use.

Currently, there is a range of designs including those of:

- The World Health Organization
- The EudraCT/Europharm
- Individual organizations, institutes, and even countries
- Individual PhRMA companies including, among others: Roche, Eli Lilly, GSK, and Merck.

And, in the United States - but with international impact:

- Clinicaltrials.gov and GeMCRIS

The content of registries and databases is determined by the interplay of *Information*, *Sources*, and *Access*.

Sources of data can include:

- Pre-clinical explorations
- Clinical
- Post-approval surveillance

The most dramatic issues here are those of intellectual property rights and the unintended consequences of full transparency: that is, making data widely available, which in some cases, is raw or uninterpreted.

In terms of Access, there may be both intended and unintended audiences.

Intended audiences include:

- Regulators
- Healthcare Professionals
- Health Management organizations
- Public-at-risk (that is, those with a specific medical condition)

Here, there are public policy, risk management, and legal impacts, both foreseeable and not.

Unintended audiences span the following:

- Litigating Attorneys
- Competitors, a frequent user of current website registries
- Stock Analysts
- Public-at-large

The business consequences of such audiences cannot be ignored; and these consequences are not insignificant for sponsors who are primarily tasked with registering their trials and releasing results.

Yet, while certain burdens fall heavily on sponsors, Authority and Responsibility are more extensive. A fundamental debate has raged over whether the registries and databases should be mandatory or voluntary. Attendant issues include the definition of the role of already overburdened Institutional Review Boards (IRB) and Ethics Committees, as well as the question of the feasibility of mandating compliance, especially internationally, in a timely fashion since a mandatory system would require legislative action across the global community that conducts trials.

Another aspect of Authority and Responsibility has to do with jurisdiction:

- International
- National
- Local

This spectrum spans harmonization to balkanization, the latter a genuine specter in light of the possibilities that, in the U.S., 50 different versions may be legislated; and, in Europe, half that number, but often larger entities, with additional member states still to be added.

A final aspect of *Authority and Responsibility* has to do with 'hosting:'

- Government
- Industry
- Neutral third party or non-profit

Perceived and real conflicts of interest are the predominant concern.

As to matters of Timing, is a trial registered and/or its data captured:

- Simultaneously with reports to regulatory authorities?
- After internal review (sponsor)?
- After external review (peer or regulatory)?

Critical to discussions of timing is the consideration of when it becomes advantageous or disadvantageous for each stakeholder in the clinical research enterprise, from sponsor to subject (enrolled or potential)?

Ethical Considerations

In addition to these five structural considerations for designing and implementing registries and databases, there are also ethical ones. The most overarching is that of allocation of scarce resources. So, for example, the content of registries and databases - as the interplay of *Information*, *Sources*, and *Access* - becomes both a political and an ethical matter. The political dimension is self-evident: determination of the spending of public moneys. The ethical may be less so, involving as it does the principle of Justice which is also the backbone of *Rule of Law*.

In addition, there are conundrums with moral implications for various players in the research enterprise, each of whose missions themselves includes an ethical obligation:

- From the perspective of the site: What do investigators and study managers or coordinators make available to current or prospective subjects; and how do they do so? Databases, in particular, can be significant resources in decision-making regarding participation in a trial. They can also cause profound confusion; as well as be misused.
- From an Ethics Committee or IRB view: How involved does this body need to be especially in terms of adverse events review?
- Sponsors are faced with the following dilemma: If interests of stakeholders and the public are corporate social responsibilities, how does a sponsor balance the two (for examples: protecting intellectual property while addressing the public's right to know; or, juggling what may be beneficial for a public- at-risk vs. the public-at-large in terms of access to data).
- And, for the public at large: Who and how much to trust? And: What about participation in decision-making by government and industry? The latter can range from a more passive role, as in polls and surveys through more active involvement, perhaps including participation in Citizen Councils or having a wider presence on Ethics Committees.

Conclusion

To conclude, by returning to the wide pendulum-like swings of the last half-century of clinical research, two questions emerge regarding registries and databases:

- Can they serve to enhance public education about clinical trials sufficiently to overcome public distrust and, perhaps, to moderate the radical swings between public expectations of miracle cures just around the corner and vilifications of the enterprise as greedy and arrogant?
- What will their impact be on making more robust human subject protections in a fashion that encourages personal responsibility of subjects while not diminishing the enterprise's obligation to value the gift of these volunteers?

Endnotes

1. This article is based on two distinct, and distinguished, events: (1) two panel discussions at the 2006 Euro-meeting of the Drug Information Association in Paris, France which included a presentation by the author; and (2) the Fordham University Summit ("Bio-Pharmaceuticals for the 21st Century: Responsibility, Sustainability, and Public Trust," January, 2005) where the author participated as a member of the Steering Committee. In addition to those events' colleagues (especially Dr. Pierre Mermet-Bouvier, Director, Global Long Range Planning, Wyeth Research, Paris who chaired one of the panels; and Professors Celia Fisher and Falguni Sen who Chaired the Fordham Summit), the author is indebted to Dr. Brian Edwards, Senior Medical Adviser, Benefit-Risk Management, a division of Janssen-Cilag UK Ltd.
2. Additional resources include:

- The White Paper from the Fordham University Summit, which the author co-authored, is available at fordhamethics.org. See also, Fisher, C., "Clinical Trials Results Databases: Unanswered Questions," Science (13 January 2006), pp. 180-1.
- WHO International Patient Safety alliance
- Joint Commission International Center for Patient Safety
- IFPMA (International Federation of Pharmaceutical Manufacturers and Associations)
- IoM (Institute of Medicine)
- Office for Human Research Protections (OHRP) DRAFT Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others (October 11, 2005)

Also See:

JVT: FDA's Unique Device Identification System Final Rule
