Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 733 4210 Fax 646 383 9249
Email: marc.wilenzick@pfizer.com

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http://www.regulations.gov
Christine Ireland
Committee management Officer
National Library of Medicine
6705 Rockledge Drive, Suite 301
Bethesda, MD 20892-7968

Re: Expansion of the Clinical Trial
Registry and Results Data Bank
Docket NIH-2009-0002

Dear Ms. Ireland:

Pfizer, a global research-based pharmaceutical company conducting over 150 trials a year, submits the following comments in response to the National Institute of Health (NIH) notice of March 23, 2009 (74 Fed. Reg. 12,138). NIH asked for input on issues relating to providing information about the results of clinical trials and ways to enhance patient access to and understanding of the results of these trials.

Background

Pfizer has registered over a thousand clinical trials with the NIH, on http://clinicaltrials.gov (ct.gov), and posted summary results, on http://clinicalstudyresults.org (clinicalstudyresults.org), for over 850 Pfizer sponsored trials. We have submitted basic results for 36 trials to NIH.

Pfizer registers interventional trials that involve a Pfizer drug or biologic, phase I through IV, and submits results, for posting on ct.gov, following FDA approval (or, in the case of post-marketing trials, one year after study completion). We also register and post results from observational studies of Pfizer drugs that involve prospectively-defined data collection and analysis. Summary results of trials for which development has been abandoned are posted on clinicalstudyresults.org. Our policy for study registration and posting of results is available on Pfizer.com.[1]

[1] http://pfizer.com/sciencepolicy

Preparation of results summaries in the ICH E3 format, endorsed by the World Health Organization and used for results summaries posted on clinicalstudyresults.org, requires approximately five to 41 hours, per study, with an average preparation time of 18 hours. The detailed "basic" results information, required by the NIH, for trials on FDA approved drugs, so far has required about 60 hours per summary. The following chart shows our experience in preparing study result summaries, in the ICH-E3 format[2] and with the additional elements and format required by NIH for posting on ct.gov.

Type of Results summary	Range of hours required to complete		Preparation Time (average)
	Low	High	
ICH E3 Format	5	41	**18**
NIH Format	20	128	**60**

Discussion

1. Whether to require submission of results information for unapproved products.

NIH describes three situations where submission of the results on unapproved products might be required:

- Trials involving products that are never submitted to the FDA for approval or clearance,
- Trials where an application has been submitted to the FDA for approval or clearance, and/or
- Trials where FDA has rejected an application for approval or clearance.

The contribution to public health from requiring the submission of results information in the situations described above is unclear. Potentially, these results would be of interest to other researchers and product development organizations. Some also have asserted that safety data from such trials would be useful in "inform[ing] institutional review boards and others reviewing similar drugs or devices."[3]

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[2] www.fda.gov/cder/guidance/iche3.pdf

[3] Alastair Wood, *Progress and Deficiencies in the Registration of Clinical Trials*, N Engl J Med 2009;360:824-830 posted at http://content.nejm.org/cgi/content/short/360/8/824

It is, nonetheless, unclear whether and how researchers and IRBs use the results of clinical trials, already in the public domain, to inform the design and review of trials on other products, or for other purposes. This information needs to be collected before NIH can draw inferences as to the public health benefit (of requiring the submission of results from trials on products that are not commercially available). It may be, for example, that the results of certain types of trials would be of relatively greater benefit to researchers and IRBs, or patients. If NIH determines that requiring the results of trials where the product is not FDA approved is in the public interest, we recommend that the required results be a summary. Specifically, NIH should limit the required data elements to those established by the FDA and other regulators in the ICE-E3 Guidance.

The posting of *summary* results of trials where development (of the product or mechanism) has been abandoned would be reasonable. Pfizer also would support a mechanism where the Secretary of Health and Human Services could require the submission of summary results of a specific trial, or of trials using a specific technology, where the Secretary determines that the data is important to patient protection (with respect to the design of other trials) or public health.

2. Whether narrative summaries of the clinical trial and its results would be misleading or promotional.

The primary purpose of the NIH/clinicaltrials.gov database was and should be to help patients and their physicians find information about trials that are enrolling. A second important purpose was to help patients, providers, and researchers find results that allow them to make informed decisions about the use of marketed products. NIH can and should facilitate the submission of technical and non-technical summaries of trial results to make this information more useful to patients, their physicians, caregivers and consumers. A pilot or series of pilots would allow the NIH and industry to gain confidence and experience in translating study results, and learn how to best communicate that information in formats that are understandable.

Summaries of clinical trial results could be prepared by the NIH, by the sponsor of the trial, or by a third-party working for the sponsor or the NIH. There is no reason that such results cannot be provided in a truthful and non-misleading fashion. The results should follow a format established by the NIH and be based on the pre-specified study protocol and data analysis plan. If they follow the protocol and data analysis plan, the results are not likely to be "promotional". This is not to say that all subjectivity could or would be removed as to what is said in a narrative. But the risk of a misleading or promotional narrative can be minimized by establishing clear guidelines for these narratives. Additionally, the narratives could require the signature of a qualified physician and statistician, to confirm the accuracy and balance of the summary.

Given the importance of improving the transparency of clinical trial results, Pfizer has an ongoing initiative to assess mechanisms for facilitating access to study results. We are collaborating with the Center for Information and Study on Clinical Research Participation (CISCRP), a non-profit educational organization, to develop and test non-technical summaries of results from two Pfizer studies. The goal of that pilot is to assess the difficulty of preparing such results, how well the summaries are understood by the trial participants, the interest that patients in the two trials have access to the results, and the role that the trial investigators may want to play in communications of the results to the patients. The pilot involves two trials: a trial with a positive result and a trial that showed that the drug was not effective in the condition being studied. Should NIH want to participate in or observe the pilot, we would certainly be pleased to include your staff.

In conclusion, we believe that the NIH should encourage the submission of truthful study results, in patient-friendly language, and we welcome the development of guidance on the content, structure, and on procedures for quality assurance.

3. **What nontechnical language should be required to assist patients.**

Nearly half of all American adults – 90 million patients, care givers and consumers, have trouble understanding and using health information and the average reading level in the U.S. is at the 8th grade level. While there is considerable scholarship on how to make scientific and medical information understandable to consumers,[4] translating trial results into patient friendly summaries is likely to be challenging.

We recommend that the NIH establish a format that allows sponsors to voluntary report clinical trial results to NIH, in a consistent manner, for posting. That format should ensure that the summary:

- Explains the purpose of the summary of the results
- Incorporates simple layouts in presentation of the information.
- Utilizes text and plain language that is understandable at an appropriate reading level, to the extent possible.
- Provides information as to how the results of the trial should be understood in the context of the FDA approved prescribing information and other generally accepted standards of medical practice.

[4] Information on ensuring clear health communications includes Pfizer's clear health communication principles, posted at http://www.pfizerhealthliteracy.com/.

A good framework for the NIH to develop such summaries might be in a frequently asked questions (FAQ) format. A non-technical summary in such a format could for information such as:

- What drug or treatment was studied?
- How many patients were involved?
- What kind of trial was this?
- What were the results of the trial?
- Have the trial results been confirmed by other studies or are they preliminary?
- What side-effects were observed?
- Where can I find more information about the trial results?
- Where can I find more information about the medicine or treatment studied?
- What information or questions should I discuss with my physician?

It may be that the best approach to creating a successful framework for the posting of non-technical summaries, is for the NIH to make participation voluntary. This would help facilitate a partnership between the NIH and sponsors, and encourage collaboration. Additionally, given the importance of ensuring that non-technical summaries of study results are done in a manner that best supports patient understanding, it would also be very useful for the NIH to consult with FDA's Risk Communication Advisory Committee, as well as external communication experts, in formulating the guidelines.

4. Whether to require submission of the full clinical trial protocol

The information required for registration of trials with the NIH including purpose, study design, and eligibility criteria, is sufficient for evaluating the results of the trials. It seems unlikely that submission of the protocol would significantly assist patients or practicing physicians in evaluating the results of a trial or the completeness of the results. In addition, Pfizer and other sponsors already make protocols and pre-specified data analysis plans available to journal editors and regulators -- the constituencies who are likely to be interested in reviewing such information.

If NIH were to require submission of the full protocol, it is important that NIH provide an opportunity to upload this information as a .pdf file (i.e., NIH should not require manual data re-entry).

5. Procedures the agency might consider for quality control.

A periodic audit, by a third-party or perhaps an independent group such as the Institute of Medicine, would be an appropriate and useful mechanism to provide quality assurance and help ensure that the information posted is truthful and non-misleading, as well as being "non-promotional". It would also be useful for the NIH to define what it considers to be "non-promotional" and whether that means that such a summary need to be truthful and balanced or something different.

6. Whether the 1-year period for submission of basic results information should be increased to a period not to exceed 18 months.

There will be some instances where a delay in posting basic results may be warranted; however, a 12 months from study completion period is a reasonable time frame for submission of basic results.

7. Whether clinical trial information should be required for trials for which "basic results" information is submitted before the effective date of a regulation (requiring submission of summaries of clinical trial results).

Requiring additional clinical trial summaries (for studies for which basic results have already been submitted to the NIH website) would be better assessed, *after* a format and guidance on the preparation of such summaries is finalized. We also recommend that the NIH first establish a mechanism and process for migration of the thousands of clinical study result summaries available on the clinicalstudyresults.org site to NIH's website, ct.gov.

8. The appropriate timing and requirements for updates of clinical trial information and procedures for tracking such updates.

Under FDAAA, NIH requires that changes to clinical trial information be made at least annually, except for changes to the recruitment status and notification of the completion of the trial, which must be communicated to NIH within 30 days.[5] Changes are tracked in the database with an audit trail. The schedule of updating clinical trial information at least annually and tracking changes in the databank with an audit trail seem reasonable and appropriate.

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[6] *See* Sec. 801(a)(2)(j)(4)(C), Food and Drug Administration Amendments Act of 2007, Public Law 110-85.

9. The format for the submission of clinical trial information including adverse event information, and additions or modifications to the manner of reporting of the data elements established under the basic results reporting provisions of FDAAA.

Pfizer supports having a standard format for the submission of clinical trial information. In particular, we would recommend that NIH follow the ICH E3 format for reporting clinical trial information, and the Clinical Data Interchange Standards, established by CDISC.[6] We do not believe that NIH should establish additional standards unique to the NIH database, without coordinating with FDA, other regulators, the World Health Organization, biomedical journal editors, and industry.

10. A statement to accompany ''voluntary submission'' of primary and secondary outcome measures for clinical trials.

A statement to accompany the voluntary submission of clinical trial information for voluntary submissions (of trials that are either not phase 2-4 controlled trials or that were initiated prior to December 26, 2007) could be as follows:

> "The results of this trial have been voluntarily submitted by [responsible person] and results will be submitted for each applicable clinical trial included in any application by the [responsible person] for licensure, approval or clearance of the use of the drug or device being investigated in this trial."

11. Other issues associated with Section 801 of FDAAA that will inform the rulemaking.

- Currently NIH does not provide for the uploading of data tables when posting study results to clinicaltrials.gov. This makes the posting of study results (and the quality assurance review of individually entered study endpoints), difficult, time consuming and inefficient. We strongly recommend that NIH allow for data tables to be uploaded, utilizing existing CDISC standards, so that sponsors can focus resources on the quality of the submissions and minimize the use of limited resources for the re-entry of data.

- FDAAA provides for a delay, with submission of a certification, in submitting results for trials supporting the initial approval of a drug or device or of a new use of a drug or device.[7] Some trials involve new formulations of existing drugs, for which a new

[7] http://www.cdisc.org/

[8] Section 801(a)(2)(j)(3)(E), Food and Drug Administration Amendments Act of 2007, Public Law 110-85.

drug application will be submitted to the FDA. For example, a drug delivered by mouth might be developed for use in a topical, patch formulation. Another example involves a new combination of two or more approved chemical moieties. Please clarify that new formulations and new combinations of approved drugs, where a new drug application, 21 CFR Section 314.54, is planned, are within the scope of the certification provision (FDAAA Section 801(a)(2)(j)(3)(E)(iv)).

- NIH currently takes several weeks, and in some cases, months, to complete its quality assurance process, before posting study results. NIH posts a note that the study has been completed but that results have not been posted. Often the reason that results are not posted is because the NIH is requesting additional information or changes to study results. We request that this note indicate that results have been submitted in a timely manner, when the sponsor or responsible person has submitted results to NIH on time.

Conclusion

Pfizer appreciates the opportunity to provide comments to the NIH on its efforts to enhance patient access to and understanding of the results of clinical trials. We hope to be able to work with the NIH staff in partnership on achieving these shared goals.

Sincerely,

/s

Marc Wilenzick