Federal Human Research Oversight of Clinical Trials in the United States

The primary federal human subjects protections (HSP) policies in the United States, including requirements for institutional review board review and informed consent, are the US Food and Drug Administration (FDA) HSP regulations1 and the Common Rule.2 The first covers FDA-regulated clinical investigations of drugs, biologics, and devices, regardless of funding source, whereas the second applies to human studies funded or conducted by 17 federal entities, regardless of the type of intervention studied. These regulations are largely consistent but contain differences. Concerns have been raised about burdens and inefficiencies for studies covered by both regulations (overlap trials),3 and about some studies that are covered by neither (gap trials).4 To inform such discussions, we estimated the numbers of active US-based clinical trials subject to these regulations.

Methods | From ClinicalTrials.gov records of active trials listing at least 1 US-based facility as of September 13, 2013, we extracted the intervention type, investigational new drug application (IND) or investigational device exemption (IDE) status, sponsor, and collaborators.5 We approximated the number of trials subject to each regulation.

Given the nuances of the FDA-HSP regulations, we determined a lower and upper bound for the number of covered trials by applying narrow and broad criteria. The narrow algorithm included all trials of drugs, biologics, and devices, regardless of IND or IDE status. The broad algorithm also included trials of FDA-regulated products (eg, dietary supplements) that are only covered when used to “support applications for research or marketing permits.”1

For the number of Common Rule trials, we counted records listing at least 1 federal entity as a sponsor or collaborator.

Results | Of the 23,936 sampled trials, our algorithms indicated that between 13,165 (55%) and 15,576 (65%) trials were covered only by FDA-HSP regulations, 1442 (6%) to 2497 (10%) trials were subject only to the Common Rule, and 4578 (19%) to 5633 (24%) were overlap trials that studied drugs and devices and have some federal funding (Figure). Five percent to 16% were gap trials that studied interventions other than drugs or devices (eg, behavioral, surgical) and had no federal funding. The characteristics of gap trials varied widely, but included research in vulnerable populations (eg, pregnant women, people with major mental illness, children) with end points that reflected potentially consequential risk to benefit profiles (eg, organ failure, depression relapse, seizure frequency, hospitalization).

Discussion | In 2001, the National Bioethics Advisory Committee noted, “An unknown amount of nonfederally funded research is completely unregulated under the federal system. This research may include experimental surgical techniques, research on reproductive technologies, some uses of approved drugs and medical devices, and research use of private, identifiable data.”6(p12) Our analysis provides the first quantitative estimate of the size of that gap in regulatory coverage, and also documents a large number of studies that are subject to both sets of regulations.

Although ClinicalTrials.gov can provide summary information about current US-based clinical trials, it has limitations for this analysis. The sampled trials were likely skewed toward those subject to federal regulation due to the high proportion of industry-funded trials of drugs, biologics, and devices and federally funded academic trials in ClinicalTrials.gov.

In addition, our algorithms did not count trials as subject to the Common Rule if they would come under that rule only because an institution had voluntarily given the federal government jurisdiction over all of its trials, regardless of funding source (currently done by approximately two-thirds of US-based institutions, though the list changes frequently). Accordingly, we likely underestimated the number of Common Rule trials (and overestimated gap trials). Other limitations include miscategorization due to errors, incomplete information in the self-reported data, and lack of certain discrete fields necessary to determine regulatory status of some trials (eg, intent of study), but we are not aware of systematic biases.

Our data are not precise measures of the current scope of different regulatory categories. Rather, they represent the best current estimates, and this analysis is intended to inform ongoing discussions about potential regulatory reforms.

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Author Contributions: Dr Zarin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Zarin, Tse, Menikoff.
Acquisition of data: Tse.
Analysis and interpretation of data: Zarin, Tse, Menikoff.
Drafting of the manuscript: Zarin, Tse.
Critical revision of the manuscript for important intellectual content: Zarin, Tse, Menikoff.
Administrative, technical, and material support: Zarin, Tse, Menikoff.
Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: Drs Zarin and Tse are supported by the Intramural Research Program of the National Institutes of Health, National Library of Medicine. Dr Menikoff is supported by the Office for Human Research Protections, Department of Health and Human Services.

Role of the Sponsor: The National Library of Medicine and the Office of the Assistant Secretary for Health had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the positions of the Department of Health and Human Services or its divisions, the National Institutes of Health, or the Office of the Assistant Secretary for Health.


COMMENT & RESPONSE

Deaths and Cardiovascular Events in Men Receiving Testosterone

To the Editor As clinicians and researchers in the testosterone field, we found surprising the results reported by Dr Vigen and colleagues1 of increased deaths and cardiovascular events in male veterans receiving testosterone following coronary angiography because these results contradict a literature spanning more than 20 years.2 Should testosterone therapy be considered unsafe based on this study? We do not believe so.

This study was not a straightforward 2-group comparison in which there were a higher number of events in men who received testosterone. Rather, this was a complex retrospective study with a messy data set, containing a serious flaw that distorted the conclusion.

The authors wrote, “... the Kaplan-Meier estimated cumulative percentages with events were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group ...” at 3 years following coronary angiography. How-

### Figure. Inclusion Criteria of Trials

<table>
<thead>
<tr>
<th>Narrow algorithm</th>
<th>Broad algorithm</th>
</tr>
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<tbody>
<tr>
<td><strong>13165</strong> (55%) Trials</td>
<td><strong>15576</strong> (65%) Trials</td>
</tr>
<tr>
<td>≥1 intervention type = “drug,” “biological,” “genetic,” “device,” OR “radiation” AND/OR IND or IDE protocol? = “yes” AND NOT Common Rule only</td>
<td>≥1 intervention type = “drug,” “biological,” “genetic,” “device,” “radiation,” “dietary supplement,” “other,” OR “procedure”</td>
</tr>
<tr>
<td><strong>2497</strong> (10%) Trials</td>
<td><strong>1442</strong> (6%) Trials</td>
</tr>
<tr>
<td>≥1 sponsor or collaborators = “NIH institute or center” OR “other US federal agency” AND NOT FDA-HSP regulations only</td>
<td>≥1 sponsor or collaborators = “NIH institute or center” OR “other US federal agency” AND NOT FDA-HSP regulations only</td>
</tr>
<tr>
<td><strong>4578</strong> (19%) Trials</td>
<td><strong>5633</strong> (24%) Trials</td>
</tr>
<tr>
<td>FDA-HSP regulations only AND Common Rule only</td>
<td>FDA-HSP regulations only AND Common Rule only</td>
</tr>
<tr>
<td><strong>3696</strong> (16%) Trials</td>
<td><strong>1285</strong> (5%) Trials</td>
</tr>
<tr>
<td>NOT FDA-HSP regulations only OR Common Rule only</td>
<td>NOT FDA-HSP regulations only OR Common Rule only</td>
</tr>
<tr>
<td><strong>23936</strong> Trials</td>
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</tr>
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FDA indicates Food and Drug Administration; HSP, human subjects protections; IDE, investigational device exemption; IND, investigational new drug application; NIH, National Institutes of Health.