Do N-of-1 Trials Need IRB Review?

Ruiqi Cen¹, Azad Hussain¹, Kirk J. Pak², Geoffrey Mitchell³, Jane Nikles³, Stephanie Gaudreau², Lydia A. Bazzano¹, and Joseph L. Breault²

Abstract

There is no standard policy regarding the regulatory or institutional approval of N-of-1 trials in the United States. The objective of this study was to examine whether institutional review boards (IRBs) accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) consider N-of-1 trials as meeting the definition of human subjects research (45CFR46.102) and requiring IRB approval. A questionnaire was distributed via email to 170 AAHRPP-accredited IRBs in the United States. Responses were analyzed using statistical and qualitative methods. Nineteen of 59 respondents reported viewing N-of-1 trials as research. Twelve respondents reported having a policy regarding N-of-1 trials, and in all cases, such policies did not consider N-of-1 trials as meeting the definition of research. This topic deserves wider examination in the IRB literature and community to inform policies and guidance as N-of-1 trials become more common in the pursuit of personalized, precision medicine.

Keywords

research ethics, IRB (institutional review board), human subjects research, biomedical research

Introduction

N-of-1 trials are multiple crossover, randomized controlled trials (RCTs) of interventions versus a placebo or control (Nikles, Glasziou, Del Mar, Duggan, & Mitchell, 2000). N-of-1 trials are useful clinical decision tools that apply a systematic approach to the informal trial-and-error paradigm commonly used in clinical practice to guide personalized treatment plans (Duan, Kravitz, & Schmid, 2013; Hay et al., 2008; Lillie et al., 2011). N-of-1 trials are usually applied to chronic, stable, or slowly progressive conditions which are either symptomatic or have a valid behavioral or biological marker. When aggregated, N-of-1 trials can generate population-level evidence of equivalent strength to parallel group RCTs, with much smaller sample sizes (Duan et al., 2013; Nikles et al., 2011; Senior et al., 2013; Zucker, Ruthazer, & Schmid, 2010; Zucker et al., 1997). N-of-1 trials may provide the opportunity to produce generalizable information regarding treatment plans that can influence the care of other patients (Punja, Eslick, Duan, & Vohra, 2014). Periodic crossover design and multiple episodes of treatment can address the individual effects of treatment in patients over time and increase the precision of outcome measures. By a patient crossing back and forth between two treatments several times, clinicians can identify the more effective approach for that individual with greater precision than can be achieved in ordinary practice.

Thus, the conduct of N-of-1 trials addresses the need for individualized information in clinical decision making and moves forward the goal of personalized treatment while also generating information applicable to the population at large. However, there is no standard policy regarding the regulatory or institutional approval of N-of-1 trials in the United States. Some institutional review boards (IRBs) consider them to be research meeting the definition of human subjects research (45CFR46.102), while others do not. The Agency for Healthcare Research and Quality (AHRQ) has published a discussion of the ethics of N-of-1 trials (AHRQ Effective Health Care Program, 2014). Nevertheless, there is no consensus about whether N-of-1 trials qualify as research under the federal definition “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge” (45CFR46.102), which would then require IRB review.

The objective of this study was to examine whether IRBs accredited by the Association for the Accreditation of Human

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Research Protection Programs (AAHRPP) in the United States consider N-of-1 trials to be research meeting the definition of human subjects research (45CFR46.102) and requiring IRB approval.

**Method**

**Study Participants**

The human subjects approval of this project was determined exempt by the IRB of Ochsner Clinic Foundation, USA.

We developed an online survey through SurveyMonkey™ to examine this issue among AAHRPP-accredited IRB members in the United States. Contact information for AAHRPP-accredited IRBs was identified from the AAHRPP website (http://www.aahrpp.org/learn/find-an-accredited-organization) and individual IRB websites. We identified 173 IRBs via the AAHRPP website and excluded two institutions which had outsourced their reviews to independent companies. The IRB office of the Ochsner Clinic Foundation (also AAHRPP-accredited) was excluded to avoid any conflict of interest. A questionnaire was distributed via email to 170 AAHRPP-accredited IRBs in the United States. Reminders were sent out to non-responders weekly for 3 weeks after the initial distribution.

**Description of Survey**

We created a nine-item survey with questions regarding the following: IRB facility information, review of U.S. Food and Drug Administration (FDA)-regulated research, policy on N-of-1 trials, N-of-1 trials as human subjects research and IRB approval of N-of-1 trials. Selected survey items are listed in Table 1. Responses were categorical for six of the nine items and open-ended for three items.

**Statistical and Qualitative Analyses**

Frequencies of categorical responses were calculated. Survey responses were analyzed with SPSS software (IBM SPSS Version 20.0). Themes for responses to two substantive open-ended questions were analyzed and summarized with NVivo software (Version 10.0) and KH Coder (Version 2.00 [Perl 5.14.2, Perl/Tk 804.029]), via the methodological process of analyzing text and retrieving useful information from natural language, or text mining. KH Coder generated word frequency lists, as well as word cluster diagrams, linking the most persistent combinations to assess the general responses to the questions, “Why do you think they are / are not research?” and “Why do you think they need / do not need IRB approval?”

**Results**

Of the 170 possible responders, we received 59 responses, representing a response rate of 35%. Descriptive characteristics of the 170 IRBs invited to participate and the 59 which responded to our survey are shown in Table 2. The majority of IRBs which responded to the survey were from academic institutions and their geographic distribution varied with the greatest number from the South followed by the Northeast and Midwest regions and the fewest respondents from the Western region of the United States.

Frequencies of results for closed-ended survey items are shown in Table 3. Fifty-six of the 59 IRBs reported that they reviewed FDA-regulated research. Of the 12 IRBs (21% of responders) that reported having a policy regarding review of N-of-1 trials, all 12 IRBs reported that N-of-1 trials were not considered research and did not require IRB approval. Of the remaining IRBs that did not have a policy regarding review of N-of-1 trials, 19 (43%) responding IRBs reported viewing N-of-1 trials as research. Twenty-four responding IRBs (54%) regarded N-of-1 trials as needing IRB approval.

Among the 35 responders who answered the open-ended question “Why do you think they are / are not research?” 15 of them (43%) considered N-of-1 trials’ potential for generating “generalizable knowledge” as research and another
Table 3. Responses of AAHRPP-Accredited IRBs Regarding N-of-1 Trials.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes n (%)</th>
<th>No n (%)</th>
<th>I don’t know n (%)</th>
<th>It depends on a case-by-case basis n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your IRB review FDA-regulated research?</td>
<td>56 (94.9%)</td>
<td>3 (5.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does your IRB have a policy about N-of-1 trials?</td>
<td>12 (21.4%)</td>
<td>44 (78.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to the policy you have, are N-of-1 trials considered research by the definition of 45CFR46.102(d)?</td>
<td>12 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to the policy you have, do N-of-1 trials need IRB approval?</td>
<td>12 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you think N-of-1 trials constitute research using the definition in 45CFR46.102(d)?</td>
<td>19 (43.2%)</td>
<td>11 (25.0%)</td>
<td>7 (15.9%)</td>
<td>7 (15.9%)</td>
</tr>
<tr>
<td>Do you think N-of-1 trials need IRB approval?</td>
<td>24 (54.5%)</td>
<td>4 (9.1%)</td>
<td>9 (20.5%)</td>
<td>7 (15.9%)</td>
</tr>
</tbody>
</table>

Note. AAHRPP = Association for the Accreditation of Human Research Protection Programs; IRB = institutional review board; FDA = U.S. Food and Drug Administration.

Figure 1. Word cluster diagram illustrating the top 35 words occurring in the top 95 edges of responses for “Why do you think they are / are not research?”.

Note. Thicker edges represent higher frequency. FDA = U.S. Food and Drug Administration; IRB = institutional review board.

eight (19%) considered “systematic” investigation as research (Figure 1). Among the 33 responders who answered the open-ended question “Why do you think they need / do not need IRB approval?” 13 of them (40%) considered
N-of-1 trials that meeting the definition of “research” and require IRB approval (Figure 2).

Discussion

This is the first article we are aware of that collects data directly from IRBs to examine whether members of AAHRPP-accredited IRBs in the United States consider N-of-1 trials as meeting the definition of research and requiring IRB approval. We found that although the vast majority (79%) of responding IRBs said they did not have a written policy about N-of-1 trials, almost half of the responding IRBs regarded N-of-1 trials as meeting the definition of research and requiring IRB approval. It is striking that although only 21% of respondents had a policy regarding this issue, 100% of those with policies considered N-of-1 trials as not meeting the federal definition of research and therefore not requiring IRB approval. In a systematic review of 108 N-of-1 trial protocols from studies published between 1985 and 2010, most trials (69%) reported receiving IRB approval, which is consistent with our finding (see Table 3; Gabler, Duan, Vohra, & Kravitz, 2011). These results have important implications for the conduct of N-of-1 trials and can inform future policies and guidance.

Two issues related to the conduct of N-of-1 trials are reflected in the responses to our survey questions: the primary intent of the N-of-1 study and how study findings are reported. Where the intent is to generate generalizable knowledge, IRB approval should be sought (Duan et al., 2013; Gabler et al., 2011; Hay et al., 2008; Lillie et al., 2011). Examples of this include testing the use of N-of-1 studies in improving clinical decision making overall, or aggregating multiple N-of-1 studies to estimate a clinical effect. In such cases, the report of findings would most likely include an abstract or journal article intended to disseminate
generalizable knowledge obtained from the investigation. However, if the sole intent of the N-of-1 study is to assist in the conduct of patient care, then IRB approval should not be necessary. N-of-1 studies in this context are a scientifically valid version of what most clinicians do every day—testing an approved therapy in a particular patient to see whether it works or not for that individual. The difference is that N-of-1 studies systematically collect information to deliver an irrefutable answer in a particular individual. The findings of such studies, whether or not they are published in abstract or journal report, relate to a particular individual and do not represent generalizable knowledge.

AAHRPP-accredited IRBs were chosen to be surveyed because we thought those IRBs would be more sophisticated and likely to have developed policies that address more than just the basics required by FDA auditors. In addition, there is a list of AAHRPP-accredited IRBs, so the target population was well-defined. There may be thousands of small hospital IRBs that would be both hard to identify and unlikely to have ever heard of N-of-1 trials. The AAHRPP-accredited IRBs would give a picture of what the best IRBs are thinking and doing about N-of-1 trials.

An inquiry was made directly to the Office for Human Research Protections (OHRP) about this issue by one of the authors, and their response stated,

The regulations do not define a minimum number of subjects needed to constitute research. The regulations recognize research development as an activity that falls within the definition of research. One can make a distinction between “case reports” which, in the clinical context, typically consist of retrospective descriptions and discussion of one individual’s condition and treatment; and “n of 1 case studies,” which generally use qualitative research methods to study an individual or group, and may fit the regulatory definition of research. For example, an “n of 1” might in some cases be sufficient to refute a generally accepted rule.

Limitations of our study include the response rate of 35%. However, considering that the response rates for email or online surveys among health professionals range between 8% and 50%, the response rate for our study conforms to better end of this typical response range. From our survey design, we were unable to identify the roles of the respondents for each IRB, who may be stating a collective opinion, or might be stating their personal views. Even with these limitations, this survey does provide an interesting insight into the variety of views held by IRB offices in the United States about N-of-1 trials.

Conclusion

The issue of whether N-of-1 trials constitute research under the federal definition is not universally agreed on by the IRBs that responded to our survey. The majority of N-of-1 trials are conducted in Europe or Australia, rather than the United States. Although many IRBs appear to consider N-of-1 trials to be human subjects research, others clearly do not. The distinction between N-of-1 studies as part of routine clinical practice intended to benefit an individual by determining whether a therapy is efficacious for that particular person, and those studies designed to advance generalizable knowledge, may be subtle at times and could be underappreciated by IRBs. It requires careful consideration to make such a distinction in most cases. This topic deserves wider examination in the IRB literature and community to inform policies and guidance as N-of-1 trials become more common in the pursuit of personalized, precision medicine.

Declaration of Conflicting Interests

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