

The Radioactive Drug Research Committee: Background and Retrospective Study of Reported Research Data (1975–2004)

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In the United States, human research involving radioactive drugs must be conducted under a Food and Drug Administration (FDA) investigational new drug (IND) application, unless specifically exempt from IND requirements, or under the direct oversight of a Radioactive Drug Research Committee (RDRC) as long as certain conditions are met. Research overseen by RDRCs is considered basic science research when its purpose is to advance scientific knowledge and not to determine a radioactive drug's safety and effectiveness as a therapeutic, diagnostic, or preventive medical product in humans. We retrospectively reviewed and analyzed available study data from annual reports submitted to the FDA dating back to 1976. In 1976, there were 18 studies involving 531 subjects compared with 2003, when there were 284 RDRC studies involving 2,797 subjects. In 1976, RDRC subjects were imaged 5% of the time using positron-emitting nuclides and 77% of the time with conventional γ -emitting nuclides. In 2003, this was reversed with 77% using positron emitters and 5% using conventional γ -emitters. In 1976, pediatric studies comprised 7.3% of all RDRC subjects; today pediatric RDRC studies are rarely conducted. Today the RDRC is used primarily by large medical research institutions. Although the program has a very good safety record, RDRC's 30-y-old regulations need to be revised to be consistent with current scientific knowledge and health policy.

Key Words: Food and Drug Administration; Radioactive Drug Research Committee; radiolabeled drugs; drug quality standards; radiation dose limits; basic science research; PET

J Nucl Med 2006; 47:1220–1226

A basic requirement of clinical research is the protection of all participating human subjects (1,2). In the United States, to help ensure the safety of human subjects, research

studies involving subjects administered radioactive drugs or biologic products must be conducted under a Food and Drug Administration (FDA) investigational new drug (IND) application (3), unless specifically exempt from IND requirements, or under the direct oversight of a Radioactive Drug Research Committee (RDRC), an FDA-approved body charged with the review of such studies provided that they fulfill the necessary conditions (4). It is the RDRC's responsibility to ensure that studies within their purview meet these requirements.

BACKGROUND

From 1963 until 1975, the Commissioner of Food and Drugs exempted from compliance with new drug requirements radioactive new drug and biologic products used for investigational purposes in humans, as long as these products complied with regulations issued by the then-active Atomic Energy Commission (5). In 1975, the FDA terminated the 1963 exemption, and the FDA and the newly formed Nuclear Regulatory Commission (NRC, consisting of components of the former Atomic Energy Commission) agreed that all radioactive drugs and biologic products should become subject to the same FDA requirements for investigational use as other new drugs. The current RDRC regulations, promulgated on July 25, 1975 (6), clarified under what circumstances certain radioactive drugs would be generally recognized as safe and effective (GRASE) and, thus, eligible for use in basic research studies involving humans without requiring an IND.

RDRC CRITERIA AND COMPLIANCE

To use a radioactive drug on human research subjects in an RDRC-supervised study, that drug must be GRASE, and the research conducted must be basic science in nature.

To be GRASE, radiolabeled drugs must meet 2 specific criteria, the first relating to the pharmacologic dose and the second relating to the radiation dose. The first criterion specifies that the mass dose of the radiolabeled drug to be

Received Jan. 23, 2006; revision accepted Apr. 3, 2006.

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administered must not be known to cause any clinically detectable pharmacologic effect in human beings. This definition assumes, a priori, that the drug in question has no clinically detectable pharmacologic effect on human beings; consequently, this criterion rules out first-in-humans (FIH) testing under RDRC authority. Recent FDA initiatives such as the Exploratory IND (7) may facilitate FIH testing and, thus, make some radiolabeled drugs more readily available for RDRC research. Although the November 16, 2004, public meeting on RDRC research (8) entertained suggestions about FIH testing of new drugs under RDRC authority, such testing is not currently allowed under the existing regulation (4). The second criterion for radiolabeled drugs to be GRASE involves radiation safety and requires that human subjects receive the smallest radiation doses practical to perform the study and that the radiation doses the subjects receive from a single study or receive cumulatively from several studies conducted within a 1-y period do not exceed the regulatory dose limits.

Research overseen by RDRCs is considered basic science research when its purpose is to advance scientific knowledge and not to determine a radioactive drug's safety and effectiveness as a therapeutic, diagnostic, or preventive medical product in humans. The intent of basic science research is to obtain basic information such as metabolism and excretion data. Such research may also investigate the biodistribution or pharmacokinetic properties of a radiolabeled drug or its physiologic, pathophysiologic, or biochemical characteristics. Other types of basic science research may investigate receptor binding or occupancy, transport processes, enzyme activity, or multistep biochemical processes. Although some of these studies may have eventual therapeutic or diagnostic implications, the initial studies are considered to be basic research within the context of the regulations.

To ensure that RDRC research complies with these requirements, the FDA vests each RDRC with the responsibility for direct oversight of the basic science research conducted at the designated medical institution, by directly reviewing and approving research protocols. The membership of the RDRC shall consist of at least 5 individuals, including (a) a physician recognized as a specialist in nuclear medicine, (b) a person qualified by training and experience to formulate radioactive drugs, and (c) a person having special competence in radiation safety and radiation dosimetry. The remaining members of the committee should be qualified in various disciplines relevant to the field of nuclear medicine, such as radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, health physics, and radiopharmacy. In addition to requiring approval by the RDRC, prospective human research study subjects must also be reviewed and approved by an institutional review board (IRB).

Each RDRC is required to submit to the FDA an annual report summarizing all research conducted under its authority by January 31st of each year for the previous calendar year. This information includes a list of the members of each

RDRC, the number of studies conducted by each committee, and, for each study, the study title, names of the investigators, radiolabeled drug(s) used, the pharmacologic and radiation doses administered, and the age and sex of each participating human subject. Additionally, special summaries must be submitted to the FDA immediately during the year whenever a study has human subjects under 18 y of age or when the number of subjects in a study exceeds 30.

This article will present observations and discuss findings of a retrospective review of RDRC study data since the program's inception in 1975.

METHODS

We retrospectively reviewed available study data from annual reports submitted by RDRCs dating back to 1976. Available physical records were reviewed for the years 1976, 1981, 1986, 1991, 1996, 2001, 2002, and 2003. The data captured from early reports were limited to the number of studies, types of radionuclides used, number of study subjects, and number of subjects under 18 y of age, who will be referred to as pediatric subjects. Data on adverse reactions were reviewed beginning in 2001. Beginning in 2002, a more comprehensive review was conducted, which additionally included the age and sex of study subjects, the radiopharmaceutical(s) used, and the subject areas of the research. Only descriptive data that could be analyzed in a consistent manner over the observed time period were reviewed. Gaps in the data resulting from possible missing files limited the types of analyses that could be performed.

OBSERVATIONS

Numbers of RDRCs and Study Subjects

Since the inception of the RDRC program in 1975, the FDA has approved a total of 201 committees. The number and status of RDRCs by 5-y reporting periods are shown in Figure 1. During the early years, over 120 medical institutions applied for and received approvals for their RDRCs to conduct research. Many of these approved committees were inactivated shortly thereafter. Table 1 shows the number of RDRC studies and the number of human subjects by year. In 1976, the first year for which RDRCs submitted annual reports to the FDA, 8 committees conducted a total of 18 research studies involving 531 human subjects. That year, the mean number of human subjects per RDRC study was 29.5. By 2003, 54 RDRCs reported conducting 284

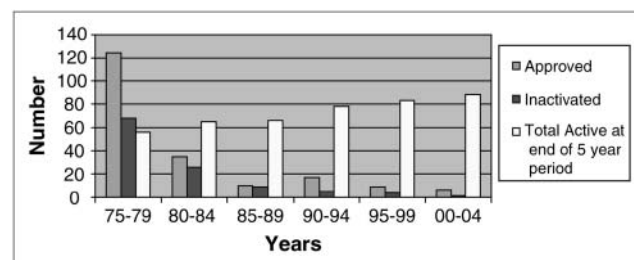


FIGURE 1. Number and status of RDRCs by 5-Year Reporting Periods

TABLE 1
RDRC Research: Number of Studies and Number of Human Subjects by Year

Year	RDRC studies (n)	RDRC subjects (n)	Studies with pediatric subjects (n)	Pediatric subjects (n)	Studies with pediatric subjects (%)	All subjects who were pediatric (%)
1976	18	531	3	39	16.7% (3/18)	7.3% (39/531)
1981	224	2,088	12	58	5.4% (12/224)	2.8% (58/2,088)
1986	207	2,310	8	80	3.9% (8/207)	3.5% (80/2,310)
1991	245	2,833	9	80	3.7% (9/245)	2.8% (80/2,833)
1996	243	1,958	6	32	2.5% (6/243)	1.6% (32/1,958)
2001	153	1,108	0	0	0	0
2002	280	2,872	0	0	0	0
2003	284	2,797	0	0	0	0

research studies involving 2,797 human subjects, and the mean number of subjects per study was 9.8 (Table 1). The number of active studies and number of subjects per active RDRC for 2003 are shown in Table 2. The 10 most active RDRCs conducting research in 2003 accounted for 69% of all human subjects in RDRC studies that year, whereas 39 of the least-active RDRCs each conducted studies on less than 2% of all 2003 RDRC human subjects.

Radionuclides and Nuclide Types Used

Table 3 shows the distribution (%) of RDRC human study subjects for 2003 by nuclide type administered. Nuclides used in RDRC research may be imaging nuclides or nonimaging nuclides, used for in vitro assay studies. Imaging nuclides can be further characterized as either positron-emitting nuclides or γ -emitting nuclides. Nonimaging nuclides used in research are β -emitting nuclides.

TABLE 2
Number of Active Studies per Active RDRC in 2003

Committees conducting studies	Active studies (n)	Human subjects (n)	All 2003 human subjects (%)
A	31	266	9.5
B	34	251	9.0
C	14	242	8.7
D	14	214	7.7
E	16	211	7.5
F	25	193	6.9
G	15	162	5.8
H	12	154	5.5
I	16	121	4.3
J	5	116	4.1
K	7	87	3.1
L	14	85	3.0
M	18	80	2.9
N	8	68	2.4
O	2	66	2.4
Remaining 39 committees	53	481	17 (<2% for each remaining committee)
Total: 54 active	Total: 284	Total: 2,797	100

In 1976, 14 of 18 (78%) RDRC studies used imaging radionuclides with 433 of 531 human subjects, or 82% of all subjects that year. The 2 most frequently used imaging nuclides were the γ -emitting nuclides ^{67}Ga and $^{99\text{m}}\text{Tc}$. ^{67}Ga was used in 1 study with 166 human subjects, which represented 31% of all RDRC research subjects. $^{99\text{m}}\text{Tc}$ was used in 3 studies involving 146 subjects (27% of all subjects). Only 1 RDRC imaging nuclide study in 1976 used a positron-emitting nuclide (^{52}Fe , in a study with 25 subjects). The remaining 4 RDRC studies that year all used a nonimaging radionuclide, ^{14}C (a β -emitter), for in vitro bioassay analyses. ^{14}C was used in 4 of the 18 studies (22% of all RDRC studies) involving 98 of 531 human subjects, which also represented 18% of all RDRC participating human subjects during that reporting period.

Basic research RDRC studies in 2003 used 120 different drugs and 20 different radionuclides. Table 4 lists the percentages of specific radionuclides used in 2003 RDRC studies by imaging type and nuclide type. Radiolabeled drugs were used for imaging in 82% of all 2003 RDRC studies conducted: positron-emitting imaging nuclides were used in 77% of studies and conventional γ -imaging nuclides were used in 5% (Table 4). That year, 77% of human subjects in these studies received positron-emitting imaging nuclides, whereas only 5% were administered γ -emitting imaging nuclides (Table 3). The remaining 18% of radiolabeled drugs in 2003 RDRC studies were nonimaging

TABLE 3
Distribution (%) of RDRC Research Subjects by Year and Nuclide Type Administered

Year	Imaging nuclide (% positron emitter)	Imaging nuclide (% γ -emitter)	Nonimaging nuclide (% β -emitter)
1976	5	77	18
1981	12	32	56
1986	30	14	56
1991	37	8	55
1996	55	9	36
2001	80	4	16
2003	77	5	18

TABLE 4
Percentages of Specific Radionuclides Used in 2003
RDRC Studies by Imaging Type*

Imaging nuclides			Nonimaging nuclides		
Positron (total = 77%)	γ (total = 5%)		β (total = 18%)		
¹¹ C	37	^{99m} Tc	2.50	³ H	12.40
¹⁸ F	19	¹²³ I	1.30	¹⁴ C	4%
¹⁵ O	17.50	¹³¹ I	0.30	⁵⁹ Fe	0.70
¹³ N	2.60	¹³³ Xe	0.30	⁴⁵ Ca	0.30
⁶⁰ Cu	0.70	¹¹¹ In	0.20	⁵⁵ Fe	0.30
¹⁷ F	0.50			¹²⁵ I	0.30
^{94m} Tc	0.20			⁴⁷ Ca	0.20
				⁶⁵ Zn	0.20

*Radioactive drug research studies conducted in 2003: 84 committees, 284 studies, 2,797 human subjects. Values in alternate columns are expressed as percentages.

nuclide β -emitters, primarily ³H and ¹⁴C, used for in vitro bioassay studies (Table 4). Table 5 details the use of multiple nuclides in RDRC studies by year and number of nuclides used per study. The data indicate a slight trend toward multiple nuclidic studies in more recent years.

Pediatric Study Subjects

Available files were examined for all aforementioned years covered in this review. The total numbers of participating pediatric subjects as well as the number of RDRC studies using them for each review year are shown in Table 1. In 1976, 3 of 18 active RDRC studies (16.7%) involved 39 pediatric subjects, or 7.3% (39/531) of all human subjects. Overall, the use of pediatric subjects in RDRC research has declined significantly, particularly during recent years. In 2001, 2002, and 2003, no RDRC studies with pediatric subjects were reported, although in 2004, 1 such study with 4 pediatric subjects was reported to the FDA. Pediatric studies initially reported under RDRC authority but resubmitted as INDs after FDA review were not counted as RDRC studies.

TABLE 5
Use of Multiple Nuclides in RDRC Studies by Year and
Number of Nuclides

Year	Studies with 1 nuclide (%)	Studies with 2 nuclides (%)	Studies with 3 nuclides (%)	Studies with 4 nuclides (%)
1976	92.3	7.7	0	0
1981	94.9	3.4	0.6	1.1
1986	93.3	4.5	2.2	0
1991	82.1	16.4	1.5	0
1996	88.2	11.0	0.9	0
2001	72.5	23.9	3.5	0

Additional Recent Data

Beginning in 2002, more comprehensive data, including the age and sex of research subjects, specific radiopharmaceuticals used, and research topic, were available for review. In 2003, 53% of the 2,797 reported human subjects in RDRC studies were male and 47% were female. Subjects had a mean age of 46 y and a median age of 45 y. The youngest subject was 18 y and the oldest was 94 y of age. Forty-two percent of RDRC subjects were older than 50 y. There were 6,124 reported dose administrations for these subjects (i.e., each subject was administered a radiopharmaceutical a mean of 2.2 times). In 2003, the most frequently occurring topic areas for RDRC studies were neuroreceptor research (45%), followed by cancer (15%), diabetes (12%), and cardiac-related basic science research (9%). The remaining research topics consisted of studies that represented a broad range of interest, encompassing areas such as exercise, pain, obesity, acupuncture, prostheses, the gastrointestinal tract, the pulmonary system, bone, and so forth. Each of these areas accounted for 2% or less of all RDRC research for that year.

Radiation Doses

Available files were also reviewed for reported radiation doses received by human subjects to determine whether RDRC dose limits were exceeded. Data were reviewed for all years covered in this report. There were no reported instances of whole-body radiation dose limits being exceeded in any of the studies. The majority of reviewed files also showed most, but not all, committees reporting organ radiation-absorbed doses that met the regulatory limit guidelines. The current radiation dose limits for human subjects in RDRC studies are presented in Table 6. However, radiation dose reporting among the various institutions was inconsistent, with some committees failing to report doses from associated x-ray imaging procedures, whereas

TABLE 6
Radiation Dose Limits for RDRC Subjects*

Organ or system	Single dose [†] (Sv)	Annual and total dose [†] (Sv)
Whole body	0.03	0.05
Active blood-forming organs	0.03	0.05
Lens of eye	0.03	0.05
Gonads	0.03	0.05
Other organs	0.05	0.15

*RDRC: Radiation Dose Limits—Code of Federal Regulations Title 21, Part 361.1 (b) (3).

[†]0.03 Sv = 3 rem.

For research subjects under 18 y of age at last birthday, the radiation dose does not exceed 10% of adult dose. Radiation doses from x-ray procedures that are part of the research study shall be included.

others used incorrect or outdated radiation dose terminology. The magnitude of these reporting inconsistencies made analysis of radiation-absorbed doses to organs extremely difficult; therefore, a credible and accurate estimate of the number of RDRCs that exceeded specific radiation dose limits was not possible.

Adverse Reactions

A review of available RDRC files dating back to 2001 found no reported adverse reactions in human subjects attributable to the administration of a radioactive drug. This is consistent with the findings of other such analyses (9).

DISCUSSION

RDRCs actively conducting research have increased from a modest 8 committees in 1976 to 84 committees in 2003. As previously mentioned, 120 RDRCs were approved during the program's early years, although many of those committees were inactivated shortly thereafter. The high number of initial approvals may have been related to the uncertainty associated with the new program and to a concern that the research not be jeopardized. RDRCs are used primarily as research tools by a few major medical research institutions. The vast majority of studies conducted by these committees use radiolabeled drugs for imaging, with positron-emitting radionuclides clearly the preferred type of imaging agent used today. Nonimaging, *in vitro* bioassay studies constitute approximately one fifth of all RDRC studies.

Research using positron-emitting radionuclides in human subjects is currently conducted more frequently under RDRC regulations than under IND regulations. A review of annual IND reports filed with the FDA in 2003 found that 8 clinical research studies used positron-emitting radionuclides in 496 human research subjects, for a mean of 62 subjects per IND study for the reporting period. By comparison, for the same period, 218 of 284 RDRC studies used positron-emitting radionuclides in 1,756 human subjects (mean of 8 subjects per RDRC study). The smaller mean number of subjects per RDRC study is not surprising, as RDRC studies are basic science in nature, and such studies do not generally require a large number of subjects. If a preliminary hypothesis needs to be tested—sometimes referred to as a “proof of concept study”—such a study can be done with a minimal number of subjects. Once the hypothesis has been tested under RDRC oversight, either the study will be terminated because the results failed to support the hypothesis or the hypothesis will be investigated further under IND authority, where a specific diagnostic or therapeutic endpoint may be desired. Sometimes basic science research studies may require large numbers of subjects. In these cases, any time the number of human subjects in a study exceeds 30, the RDRC must submit a special summary report to the FDA immediately rather than delaying notification until the annual report.

Today, research studies involving pediatric subjects are very rarely conducted under RDRC authority. One possible

reason for this is that the radiation dose from positron-emitting radionuclides (the type used most frequently today in RDRC studies) is much higher than the dose from conventional radionuclides. This inhibits the use of pediatric subjects in RDRC research, because regulations limit the allowable radiation dose for pediatric subjects to 10% of the allowed dose for adults. The safety of pediatric subjects has always been a concern in RDRC research; however, variations in the standards and terminology of current regulations for conducting human research, especially with pediatric subjects, may cause some confusion (10). This issue surfaced at the November 2004 RDRC public meeting (8), where one viewpoint held that current RDRC regulatory radiation dose limits for pediatric subjects were too restrictive and should be relaxed, whereas another viewpoint suggested that pediatric research not be allowed under RDRC authority, invoking the IRB regulations. In fact, both the RDRC and the IRB must separately review and approve prospective human research subjects. However, RDRC regulations use the term “without significant risk,” while IRB regulations refer to “minimal risk” and “greater than minimal risk” in relation to the risks of daily living. A recent article by Wendler et al. (11) focused on these ambiguities, identifying the need for a more quantifiable risk standard that can be related to the risk of daily living and applied in a more consistent way by the research community.

RDRC regulatory radiation dose limits need to be revised using current scientific information and safety criteria. RDRC dose limits differentiate between adult and human subjects under 18 y of age on the basis of concerns and information from 1975 that radiation-induced risks were higher in younger humans than in adults. Today, these risks are better and more specifically documented (12). The current RDRC regulations limit the radiation dose for human study subjects under 18 y of age to 10% of the adult dose; however, an anomaly of these regulations is that a 1-mo-old infant and a 17-y-old subject have the same dose limit, whereas an 18-y-old subject can receive 10 times the radiation dose that a 17-y-old subject can. Adhering to these regulations does not provide an equal level of risk for all human research subjects.

RDRC radiation dose limits currently consist of a 2-tiered set: the whole-body dose limit and organ dose limits (Table 6). Organ dose limits are more constraining, as this limit may be reached before the whole-body limit is reached. Findings of our retrospective review corroborated this, as the study data indicated that whole-body radiation dose limits were not exceeded, whereas organ dose limits sometimes were.

The International Commission on Radiological Protection (ICRP) recognized this anomaly in radiation dose standards in 1977 (i.e., the disparity between a radiation dose to the whole body and a radiation dose to individual organs [tissues], each with different, organ-specific radiation sensitivities). To remedy the situation, the ICRP introduced a new concept of radiation dose that incorporated the

individual organ doses and their relative radiation risks into a single whole-body radiation dose metric, “effective dose equivalent” (H) (13). In 1991, the ICRP further refined this concept as “effective dose” (E) (14). Effective dose, like effective dose equivalent, requires knowledge of specific organ doses. The FDA’s current RDRC radiation dose limits are outdated. The limits are based on NRC 1975 occupational radiation dose limits, which have themselves also undergone change during the intervening years (15). Consequently, users of radioactive materials in the United States must comply with different sets of regulatory dose concepts for organs and for the whole body. This dilemma is further compounded by the fact that the NRC’s current dose limits are still based on the ICRP’s 1977 concept of effective dose equivalent (H), whereas the rest of the scientific and international community uses the 1991 concept of effective dose (E), itself currently undergoing a revision based on newer scientific information. Confusion on how to report dose has been further compounded by the FDA’s own reporting form, Form 2915, which used incorrect and outdated terms for dose. These have recently been corrected. It is possible that all of these factors contributed to the inconsistency of the various committees in reporting radiation doses to the FDA, as noted in our review.

Although a review of RDRC study reports since 2001 revealed no adverse reactions attributable to radioactive drugs in human subjects, it should be noted that adverse reactions, or their absence, are not the sole metric for ensuring the safety of human study subjects. To ensure the safe production and use of radioactive drugs in RDRC research, there also must be sufficient safeguards to ensure the quality and purity of such drugs, and the RDRC has this responsibility. In the November 16, 2004, public meeting on the use of radioactive drugs in research (8), the FDA reported that there had been 2 cases at 2 major medical institutions conducting RDRC research wherein the quality of the radiolabeled drug(s) used in human research subjects was highly suspect. In the first case, in which a labeled biohazard was administered to human subjects, there was inadequate documentation of processes to clear viral contamination from human biologic source material as well as inadequate informed consent of the subjects. In the second case, involving a laboratory that produced radioactive drugs for RDRC research, an unknown compound was administered to human subjects. A follow-up inspection by the FDA revealed additional problems, such as failure to follow established procedures, failure to perform quality controls before product administration, analytic equipment that was neither maintained nor calibrated, and failure to conduct proper sterility testing in the laboratory where these research drugs were produced (8).

Although the safety record for research conducted under RDRCs has been good if one considers the lack of reports of adverse reactions in human subjects given radioactive drugs, this lack of adverse reactions is to be expected

because of inherent RDRC safety criteria in place. The mandate that the pharmacologic radioactive drug dose administered must not be clinically detectable ensures with a high degree of confidence that the drug is safe. Nevertheless, the recent examples of serious issues involving the quality and purity of radioactive drugs given to human research subjects are a cause for continuing safety concerns.

CONCLUSION

RDRCs, a tool used primarily by large medical research institutions, have for more than 3 decades enabled such institutions to conduct basic science research in a relatively safe manner. Research conducted by RDRCs is relatively efficient and productive, with many more basic research studies using radiolabeled drugs in human subjects conducted under RDRC authority than under comparable INDs.

Nevertheless, 30-y-old regulations need to be revised to render them consistent with current scientific knowledge and health policy, especially with regard to drug quality standards and radiation dose limits. There is also a need for more consistent and clearer guidance for IRBs in assessing all research-related risks to human subjects, not just risks associated with radiation. The need for objective risk and safety criteria is especially important in RDRC basic science research involving humans, as the benefit from such studies will accrue to society rather than to participating human subjects, who will derive only incidental and negligible benefits, if any.

ACKNOWLEDGMENTS

The authors thank Diane S. Hackett for her assistance in the review and editing of the final manuscript as well as Sara Madanikia for her assistance in the analysis of the archived files.

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