August 27, 2010: IND Process and General Responsibilities under IND and IND Exemptions

A. Accessing Investigational Anticancer Agents Outside of Clinical Trials
   Vol 55 April 1 1998 Am J Health-Syst Pharm

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   Chest 2007; 131:909-912
Accessing investigational anticancer agents outside of clinical trials

Q: What treatment options are available for cancer patients whose disease has progressed after standard therapy and who are ineligible or unable to participate in a clinical trial?

A: The Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), allows early access to investigational anticancer agents for patients who are unable to participate in clinical trials. Early access is provided through several mechanisms, including special exception, group C, and treatment referral center (TRC) protocols. Investigational agents obtained through the early access program are sometimes described as being for non-research, or compassionate, use. The ultimate purpose of this program is to make available to individual cancer patients and their physicians investigational anticancer agents that have notable clinical activity against specific malignancies.

Physicians who want to request an agent for nonresearch use must consider the following questions:

- Is the patient ineligible or unable to be treated on a research protocol? (Patients should be ineligible or unable to participate in a clinical trial for reasons other than safety.)
- Have standard therapies been exhausted?
- Is there objective evidence that the investigational agent is active in treating the disease for which the request is being made? (Published data from Phase II trials are usually required as objective evidence of activity.)
- Is the drug likely to benefit the patient while posing acceptable risk?

A request for nonresearch use may be considered by DCTD if the answer to all the above questions is affirmative. Each mechanism for nonresearch use differs in purpose and in the reporting and procedural responsibilities of the investigator.

Mechanisms for early access: Special exception

The special-exception mechanism is the functional equivalent of an emergency investigational new drug application (IND) except that any person registered with NCI as an investigator may obtain an agent directly from DCTD instead of having to have an IND approved by FDA. A request for a special exception may be considered for any investigational agent for which DCTD sponsors an IND. DCTD currently sponsors more than 200 INDs with FDA for approximately 150 different investigational anticancer agents. Approval depends on meeting the standard criteria for nonresearch release of investigational agents as previously discussed and agent availability. Requests for special exceptions are reviewed and approved by staff of the Cancer Therapy Evaluation Program (CTEP) on a patient-by-patient basis.

Group C or treatment IND

DCTD requests group C or treatment IND designation from FDA for an investigational agent that has reproducible efficacy in one or more specific types of tumors. Such an agent is considered likely to alter the contemporary treatment of a disease and can be safely administered by properly trained health care providers without specialized supportive care facilities. Typically, DCTD will seek group C classification only for those agents whose activity is well-established that FDA approval of a new drug application or biologic license application is likely in the relatively near future. If an agent meets these criteria, DCTD may initiate a formal application to FDA to authorize group C distribution for a...
specific indication. Such approval is not equivalent to formal FDA approval of efficacy of that agent for that indication. Any registered investigator may receive a group C agent. NCI has sponsored more than 20 group C protocols since 1976 (table). At the time of writing, the only active group C protocol is for azacitidine for the treatment of refractory acute myelogenous leukemia.

**Treatment referral center protocol.** DCTD may make investigational treatments available via a TRC protocol for certain highly promising agents or high-priority diseases such as breast, prostate, lung, and ovarian cancer. TRC protocols can also be used to ensure equitable distribution of agents with limited availability. Safety and efficacy data are typically collected in TRC protocols. TRC protocols are initially offered to the NCI-designated clinical and comprehensive cancer centers. All patients treated on a TRC protocol must receive their investigational therapy at an NCI-designated cancer center. NCI arranged for three TRC-protocols, now completed, that used paclitaxel in the treatment of refractory ovarian cancer (TRC-9103) and refractory breast cancer (TRC-9202 and TRC-9301).

**NCI treatment referral center.** All requests for early access to DCTD-sponsored investigational chemotherapy agents are conducted through NCI's TRC. The TRC is managed by the Pharmaceutical Management Branch (PMB). CTEP, DCTD. PMB is composed of nine clinical research pharmacists. The TRC is coordinated by a PMB pharmacist. Each PMB pharmacist has experience fielding TRC questions. The TRC is a means for NCI to provide information to community oncologists and other health care professionals about therapeutic options for cancer patients. The TRC uses several resources, such as Physicians Data Query and the CTEP information system, to maintain a referral list of the most current active research protocols. The first priority is to refer patients to cooperative group or cancer-center clinical trials. If a patient is unable to participate in a clinical trial, a nonresearch mechanism might be considered. Health care professionals may contact the TRC about potential therapeutic options—clinical trials or nonresearch programs—by telephone (301-496-5725) or by fax (301-402-4870).

**Procedures.** NCI has attempted to simplify the acquisition and management of investigational anticancer agents for each nonresearch program previously described. NCI has designed policy and procedures to expedite the review, registration, approval, and distribution of nonresearch agents and the protocols for treating patients with these agents. The CTEP home page (http://ctep.info.nih.gov) contains current information, policies, and procedures related to DCTD nonresearch activities and other programs. Extraneous paperwork has been eliminated, and, when possible, standard reporting methods are used. PMB pharmacists can assist health care providers in addressing the medical, regulatory, and administrative requirements associated with nonresearch protocols. All investigational agents are provided by DCTD at no cost to the physician or patient (shipping costs are borne by the receiver).

**Submission of request.**

While group C and TRC protocols have set criteria to determine patient eligibility, each request for a special exception is assessed on its own merit. The following information is required for NCI to properly evaluate each request: patient identifier (initials or identification number), age, sex, diagnosis, previous cancer therapy, current clinical status, intended dosage and schedule of the requested agent (according to the current literature), potential concomitant therapy, and pertinent laboratory data.

Each case is reviewed and assessed on the basis of established guidelines developed by staff oncologists and derived from published literature. Staff oncologists are consulted about requests that fall outside the guidelines. Every attempt is made to provide requesters with a response as quickly as possible. Typically, requesters are notified of a decision the same day, and, if use of an investigational agent is approved, they can often obtain the agent via a nonresearch mechanism within three to five days. In the event of a medical emergency, investigational agents may be shipped for next day or even same-day delivery. All established NCI policies on drug accountability and storage of the agent must be adhered to. A separate drug accountability record should be maintained for each nonresearch protocol.

**Treatment guidelines for group C and TRC protocols are provided.** Occasionally, treatment guidelines are also provided for special-exception protocols. The health care providers requesting the investigational agents are required to complete a special-exception protocol document if treatment guidelines are not available. The special exception protocol document includes a brief patient history, a description of the treatment plan, dosage modifications, and monitoring variables. Patient treatment should be based on published reports. The completed special-exception protocol document should be signed and returned to the PMB within 10 working days. A copy of the special-exception protocol is submitted to the appropriate IND file.

**FDA form 1572.** FDA and NCI policy requires all people functioning as investigators who participate in a DCTD-sponsored trial, including nonresearch studies, to have an FDA form 1572 (statement of investigator) and a current curriculum vitae on file with the PMB. Investigators are asked to provide their office, shipping, and institutional review board (IRB) addresses on the form. CTEP has attempted to expedite and simplify investigator registration as much as possible. When necessary, new investigators can obtain registration within 24 to 48 hours.

**IRB and informed consent.** FDA and NCI require that approval by an IRB and informed consent be obtained before a patient is treated with an investigational agent. NCI provides model informed-consent forms for group C, TRC, and some special-exception protocols. The IRB requirements differ slightly for each nonresearch mechanism. Approval by an IRB is required before activation of a TRC protocol at a participating institution. A waiver of the requirement for IRB approval may be obtained from FDA for group C protocols. Group C pro-

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Questions & Answers

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 protocols are reviewed and approved by NCI’s IRB. Although local IRBs are not required to review group C protocols, they retain the right to do so. Registered investigators are encouraged to contact their local IRB to determine the institutional policy on IRB review of group C protocols.

IRB approval is also required for special-exception protocols. NCI does not specify how or in what form IRB approval is to be obtained (e.g., full IRB, IRB chair only). The local IRB may set whatever policy it determines is appropriate for approval of special-exception protocols. However, NCI policy requires that written documentation of IRB approval and a signed informed-consent form be retained in the patient’s medical record for future reference.

Adverse drug events. Investigators are required to submit adverse event reports to CTEP for all agents obtained via a nonresearch mechanism. Investigators should use the Phase II and III guidelines, included with the special exception packet, for reporting adverse drug reactions. The NCI common toxicity criteria table should be consulted for adverse event reports.

Final report. NCI requires a final report for all patients treated on nonresearch protocols. The information required for a final report is usually minimal. Standard data collection forms have been developed for group C and TRC protocols and several special-exception agents. A generic data-collection form (Report of the Independent Investigator), also included with the special exception packet, can be used for most special-exception protocols.

Publication of a patient’s experience. The principal purpose of DCTD’s nonresearch program is to increase patient access to promising investigational anticancer agents, not to obtain clinical data, since limited information on drug efficacy and safety can be obtained from this type of research design. NCI has, however, published the results of several group C and TRC protocols. Because the eligibility criteria for group C and TRC protocols are usually much less stringent than those for a clinical trial, the results are often described as being more representative of typical practice settings. Given that each special-exception request is reviewed on its own merit and considered a separate protocol, publication of special-exception data should be limited to case reports and anecdotal data and should be accompanied by a clear statement that patients were treated on separate special-exception protocols.

Cancer Therapies Provided through the Group C Treatment Protocol Mechanism

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<td>Carmustine</td>
<td>Jun ‘63</td>
<td>Apr 76</td>
<td>May 77</td>
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<td>Feb ‘68</td>
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<td>Dec ‘65</td>
<td>Aug 76</td>
<td>May 80</td>
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<td>Jan ‘71</td>
<td>Aug 76</td>
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<td>Semustine</td>
<td>Jan ‘71</td>
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<td>Streptozocin</td>
<td>Mar ‘67</td>
<td>Aug 76</td>
<td>Jun ‘82</td>
</tr>
<tr>
<td>Asparaginase (from Escherichia coli)</td>
<td>Jan ‘68</td>
<td>Oct 76</td>
<td>Apr ‘78</td>
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<td>Jul ‘71</td>
<td>Jul 77</td>
<td>Dec ‘78</td>
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<td>Hexamethylenimine</td>
<td>Jun ‘63</td>
<td>Jul 77</td>
<td>Feb ‘91</td>
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<tr>
<td>Asparaginase (from Erwinia species)</td>
<td>Mar ‘71</td>
<td>Feb 78</td>
<td>IND withdrawn</td>
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<td>Etoposide</td>
<td>Sep ‘78</td>
<td>Oct 80</td>
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<tr>
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<td>Aug ‘71</td>
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<td>Interleukin-2 and LAKc cells</td>
<td>Feb ‘84</td>
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<td>May ‘92</td>
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<td>Chlorodeoxyadenosine</td>
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<td>Mar 92</td>
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<td>Paclitaxel</td>
<td>Apr ‘84</td>
<td>Jul ‘92</td>
<td>Dec ‘92</td>
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aIND = investigational new drug application
bNDA = new drug application
cPreviously known as streptozocin
dLAK = lymphokine-activated killer


Michael J. Montello, M.S., Head, Protocol and Information Office
Jay J. Greenblatt, Ph.D., Head, Regulatory Affairs Drug/Section
Alfred Fallavollita, M.S., Chief, Pharmaceutical Management Branch
Dale Shoemaker, Ph.D., Chief, Regulatory Affairs Branch

Cancer Therapy Evaluation Program Division of Cancer Treatment and Diagnosis National Cancer Institute Executive Plaza North Room 707 Bethesda, MD 20892
April 3, 2009

IND 55,830
TORISEL (Temsirolimus, CCI-779) Intravenous
Serial Number 1018

Robert Justice, MD, Director
Division of Oncology Drug Products (HFD-150)
Attn.: Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Justice:

Wyeth Pharmaceuticals, Inc. hereby authorizes the Food and Drug Administration (FDA) to reference IND 55,830 for TORISEL in support of an Investigational New Drug Application (IND) to be requested by MD, UC Davis Cancer Center, 4501 X Street, Sacramento, CA 95817 to conduct the following protocol:

Protocol 3066K1-1207, “Phase I Trial of Pazopanib Plus Temsirolimus in Advanced Solid Tumors, with Emphasis on Renal Cell Cancer.”

The cross-reference will apply for all relevant clinical, preclinical toxicology and pharmacology information, as well as chemistry, manufacturing and controls information submitted to our IND. However, the information in our IND remains confidential; this letter of authorization is not intended to permit the above-mentioned parties or any others to access the data in our IND, or any component of it without the expressed written consent of Wyeth.
This submission is provided entirely in eCTD format, therefore no table of contents is being provided. The FDA Viewer will display the content of the submission in its correct CTD location. Information related to the electronic format of this submission is provided immediately after the signatory page.

Because this submission contains highly confidential information and trade secrets, we request that it be withheld from disclosure under the Freedom of Information Act pursuant to 21 CFR § 20.61. We further request that if the FDA tentatively determines that any portion of the submission is disclosable in response to a request under the Freedom of Information Act, that we be provided with the opportunity for prior consultation in accordance with 21 CFR § 20.47.

Should you have any questions regarding this submission, please do not hesitate to contact Elena Spanjaard at (617) 665-7365 or me at (484) 865-5237.

Sincerely,
David K. Ellis, PhD
Assistant Vice President
Global Regulatory Affairs

cc: MD

This electronic submission is approximately 2 MB in total size. All files were checked and verified to be free of viruses using VirusScan Enterprise, Version 8.0.0 with a virus definition date of March 23, 2009.

Technical questions, related to the electronic submission format, should be directed to Taryn Stevens at (484) 865-8027.
Is an Investigational New Drug (IND) Application Required?

Note: Studies involving drugs but exempt from IND requirements still are subject to other FDA regulations including 21 CFR part 50 (human subjects protections), part 54 (conflict of interest requirements), and part 56 (IRB requirements).

No INO is required.

Will a drug be used, administered, applied, or implanted to subjects?

Y

No INO is required.

Is the study an exempt study of an in vitro diagnostic biological product?

Y

No INO is required.

Is the drug under study lawfully marketed in the U.S. but under investigation for off-label indications and meets other exemption requirements for off-label research use?

N

Is the study an in vivo bioavailability or bioequivalence study?

Y

Refer to the in vivo bioavailability/bioequivalence study decision tree.

N

An INO is necessary.

A product that is (i) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and acts through metabolism, chemical reactions, or the like; (ii) recognized in the US Pharmacopeia, official Homeopathic Pharmacopoeia, National Formulary; (iii) intended to affect the structure or function of the body and acts through metabolism, chemical reactions, or the like; or (iv) a component of any of the above is a drug.

Foods and dietary supplements generally are not regulated as drugs. However, those that are intended or promoted to be used in the diagnosis, cure mitigation, treatment, or prevention of disease are considered drugs.

If the product (i) is blood grouping serum, reagent red blood cells, or anti-human globulin; and (ii) is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure, it is exempt from IND requirements as long as it is shipped with special labeling requirements. See 21 C.F.R. § 312.160.

The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

- If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

- The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

- The investigation is conducted in compliance with the requirements of 312.7.

Note: If the study involves the use of a placebo and is otherwise exempt, it does not require an IND.
Date: May 5, 2009

Study Title: UCDCC#218: Assessing PSA Response in Low Dose Ketoconazole in Hormone Refractory Prostate Cancer Patients Who Have Failed at Least One Prior Systemic Chemotherapy Regimen

UCD IRB No: 200916901

Principal Investigator: Primo N. Lara, Jr. MD

Co-Investigator: Jennifer Marie Suga, MD

Subject: Investigational New Drug (IND) Application Status as Determined By Investigator – IND Exemption UCDCC#218 (under 21 CFR 312.2(b)(1))

In accordance with the Guidance for Industry IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer*, it has been determined that the Investigator-Initiated Study UCDCC#218: Assessing PSA Response in Low Dose Ketoconazole in Hormone Refractory Prostate Cancer Patients Who Have Failed at Least One Prior Systemic Chemotherapy Regimen meets all of the following conditions for IND Exemption Status.

- The studies are not intended to support FDA approval of a new indication or a significant change in the product labeling.
  Study Investigator(s) are not seeking FDA approval of a new indication for Ketoconazole or a significant change in the product labeling for Ketoconazole.

- The studies are not intended to support a significant change in the advertising for the product.
  Study Investigator(s) are not seeking to support a significant change in the advertising for the product, Ketoconazole.

- Investigators and their IRBs determine that based on the scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the use of the drug product.
  Study Investigator(s) and the University of California Davis Institutional Review Board have determined that there is no significant increase in the risk associated with the use of drug product, Ketoconazole. A sampling of published data on this topic is attached.
The studies are to be conducted in compliance with IRB and informed consent regulations, pursuant to parts 50 and 56.

This study will be conducted in compliance with University of California, Davis IRB policies and guidelines. See attached IRB Notice of Approval and IRB-approved informed consent.

The studies will not be used to promote unapproved indications, in compliance with § 312.7.

This study will not be used to promote unapproved indications, in compliance with § 312.7.

Primo N. Lara Jr., MD
Principal Investigator

Jennifer M. Suga, MD MPH
Co-Investigator

* Guidance for Industry IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer Page 5 Section IV. Determining Application Status B. Investigator Determination.
Dear Dr.

We acknowledge receipt of your Investigational New Drug Application (IND), submitted September 03, 2008, for Tarceva (Erlotinib, OSI-774) in a study entitled "Phase II Study of Gemcitabine and Intermittent Erlotinib in Advanced Pancreatic Cancer."

After reviewing the information contained in your submission, we have concluded that your study meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.

The IND regulations [21 CFR 312.2(b)] state that clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements for an IND if all of the following apply:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.

2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.

3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.

4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50).

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold.
In addition, 21 CFR 312.2(b)(5) exempts from the IND requirements a clinical investigation that involves use of a placebo if the investigation does not otherwise require submission of an IND.

We remind you that exemption from these requirements for an IND does not in any way exempt you from complying with the requirements for informed consent under 21 CFR 50.20 and initial and continuing Institutional Review Board review under 21 CFR Part 56.

For additional information, you can check our web site at http://www.fda.gov/cder for the IND regulations.

If you have any questions, call Frank H. Cross, Jr., CPMS, at 301-796-0876.

Sincerely,

Robert Justice, M.D.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
IND 066123

Attention: 

v, M.D.
University of California Davis Cancer Center
4501 X Street Suite 3016
Sacramento, CA 95817

Dear Dr. :

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Yelcade.

We also refer to your July 14, 2010, letter requesting that this IND be withdrawn.

We remind you that you must notify all clinical investigators of the withdrawal of this IND.

We would also like to remind you that any unused drug must be disposed of properly.

The withdrawal procedure is now considered complete. If this drug is again subjected to clinical investigation, it is required that we be notified. This may be done by submitting a new IND. Information in this withdrawn IND may be included by specific reference. Withdrawal of an IND does not constitute abandonment of the application as provided by 21 CFR 312.130(b). A determination of abandonment is only made at the time a request is received under the Freedom of Information Act and after consultation with you.

If you have any questions, call me, at (301) 796-1381.

Sincerely yours,

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
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Registering a Clinical Trial in ClinicalTrials.gov

Deborah A. Zarin, MD; and Alla Keselman, PhD

(CHEST 2007; 131:909–912)

Key words: compliance; computer; epidemiology

Abbreviations: ICMJE = International Committee of Medical Journal Editors; IRB = institutional review board; NIH = National Institutes of Health; PRS = Protocol Registration System

The registration of clinical trials has been the focus of attention within the medical literature, as well as in the lay press and the US Congress. Clinical trials registries are Web-based databases of clinical trial information that serve both ethical and scientific functions. Registries serve the ethical function of ensuring that the public has information about ongoing and previously conducted trials. Registries also provide researchers, journal editors, and reviewers with the context for understanding research results; by providing a complete list of clinical studies, they can alert researchers to studies that do not have published results. Trial registries differ with regard to a number of criteria, including the sponsoring organization, the focus (general vs disease specific), and the trial information that they contain. Many groups, including the International Committee of Medical Journal Editors (ICMJE), endorse the principles that registries should be managed by a nonprofit organization and should be free of charge for both registrants and users. Trial registries differ from results databases: the former generally include protocol and recruitment information, whereas the latter include study results.

Currently, the largest international clinical trials registries that satisfy the ICMJE criteria are US-based ClinicalTrials.gov, which has approximately 35,000 trials, and the UK-based International Standard Randomised Controlled Trial Number Register, which has approximately 5,050 trials. This article focuses on registering a trial in ClinicalTrials.gov. However, most of the principles discussed will apply to the registration of trials in other registries, so that the information is clear and useful.

BACKGROUND

ClinicalTrials.gov is a registry that is operated by the National Library of Medicine of the National Institutes of Health (NIH). The registry contains listings of publicly and privately funded clinical trials from around the world. ClinicalTrials.gov was initially developed to help potential subjects with life-threatening illnesses find trials in which they might want to participate. Since that time, the registry has come to serve many other purposes for a variety of users (Table 1). Registering trials with ClinicalTrials.gov is free of charge for both US and non-US registrants. Use of the registry is freely available to anybody with Internet access.

WHAT POLICIES REGULATE CLINICAL TRIALS REGISTRATION

A number of policies and regulations create specific incentives for trial registration. Some key policies are listed in Table 2. In addition, the NIH registers all trials that it funds. Although this is generally done by the NIH staff, investigators should check their trial records to ensure the accuracy and completeness of the information.

WHICH TRIALS SHOULD BE REGISTERED

ClinicalTrials.gov accepts (and encourages) the registration of any biomedical or health-related re-
search study that is conducted in human beings as long as the following conditions exist: (1) the study has been approved by an institutional review board (IRB) [or equivalent]; and (2) the study conforms to the regulations of the appropriate health authority, when applicable. Trials that are currently under review by an IRB can be registered pending IRB approval. The registry currently includes both observational and interventional studies of any intervention type (eg, drugs, devices, procedures). However, only a subset of these trials is required under the policies shown in Table 2. Trials may be registered at ClinicalTrials.gov at any time, including after completion. However, many policies require registration prior to enrollment of the first subject.

**How Do I Register My Trial?**

The ICMJE statement requires that trials are registered "at or before the onset of patient enrollment." Other policies mentioned in this article require registration within 21 days of the first patient's enrollment.

ClinicalTrials.gov uses a Web-based protocol registration system (PRS) [http://prsinfo.clinicaltrials.gov]. In order to minimize the chance of duplicates, and to ensure quality control, trials are generally registered through "organizational accounts." The PRS Web site provides a list of current organizational accounts and will guide the user through the process of identifying the appropriate trial account. For example, if the trial has received external funding from either a public source (eg, NIH), a private source (eg, a pharmaceutical company), or a foundation, then that organization's account should be used. New accounts can be set up as necessary, according to the instructions in the PRS. Many trials are conducted at multiple locations. It is critical that these trials be registered only once, with all locations listed. Investigators and sponsors need to coordinate and be clear about who will be registering the trial. Inquiries about problems with identifying or using accounts should be directed to register@clinicaltrials.gov.

### Table 1—Trial Registry Purposes for Various Groups

<table>
<thead>
<tr>
<th>Registry Purpose</th>
<th>Group That Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulfill ethical obligations to participants and community</td>
<td>Patients, general public, research community</td>
</tr>
<tr>
<td>Provide information to potential participants and referring clinicians</td>
<td>Patients, clinicians</td>
</tr>
<tr>
<td>Reduce publication bias</td>
<td>Users of the medical literature</td>
</tr>
<tr>
<td>Help editors and others understand the context of study results</td>
<td>Journal editors, users of the medical literature</td>
</tr>
<tr>
<td>Promote more efficient allocation of research funds</td>
<td>Granting agencies, research community</td>
</tr>
<tr>
<td>Help IRBs determine appropriateness of a research study</td>
<td>IRBs, ethicists</td>
</tr>
</tbody>
</table>

### Table 2—Trial Registration Policies

<table>
<thead>
<tr>
<th>Policy Name</th>
<th>Policy Mandate</th>
<th>Trials Covered by Policy</th>
<th>Policy Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food and Drug Administration, section 113&lt;sup&gt;3&lt;/sup&gt;</td>
<td>US legal mandate</td>
<td>Intervention trials</td>
<td>Mandates registration with ClinicalTrials.gov of all investigational new drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs only</td>
<td>efficacy trials for &quot;serious and life-threatening diseases&quot;</td>
</tr>
<tr>
<td>ICMJE statement&lt;sup&gt;5,9&lt;/sup&gt;</td>
<td>Policy of journals as condition for publication of research results</td>
<td>Intervention trials with at least one prospectively assigned concurrent comparison arm</td>
<td>Covers all trials that are &quot;clinically directive&quot;; uses &quot;minimum data set&quot; defined by WHO</td>
</tr>
<tr>
<td>World Health Organization International Clinical Trials Registry Platform&lt;sup&gt;1,9&lt;/sup&gt;</td>
<td>Statement of WHO policy principles</td>
<td>Intervention trials</td>
<td>Calls for registration of all interventional clinical trials and defines a &quot;minimum dataset&quot;</td>
</tr>
<tr>
<td>Association of American Medical Colleges, &quot;Principles for Protecting Integrity in the Conduct and Reporting of Clinical Trials&quot;&lt;sup&gt;1,9&lt;/sup&gt;</td>
<td>Statement of principles</td>
<td>Intervention trials with at least one prospectively assigned concurrent comparison arm</td>
<td>Calls for registration of all trials meeting ICMJE requirements</td>
</tr>
</tbody>
</table>

*Examples include drugs, surgical procedures, devices, and behavioral treatments.
†Defined as "all trials whose primary purpose is to affect clinical practice."
Once the account has been identified and the account administrator contacted in order to receive log-in information, the “quick start guide” can be viewed, which will “walk” the user through the process of trial registration.

A list of all the data elements in ClinicalTrials.gov can be found by clicking on Trial Registration Requirements link at the PRS information page [http://prsinfo.clinicaltrials.gov]. The user will note that some data are required by ClinicalTrials.gov; registration cannot be completed unless the appropriate information is entered in these fields. Other elements are optional but may be required under other policies (eg, the ICMJE). We encourage users to complete all data elements because this will provide the most information about the trial. Registrants report that this process takes from 10 to 20 min.

Once entry of data elements is finished, the quality assurance staff at ClinicalTrials.gov will review the submission. The applicant may be asked to clarify some items or to make corrections. Following this, the record will be public within 2 to 5 business days.

Records contain information about recruitment status and therefore must be updated as often as necessary. ClinicalTrials.gov staff will prompt the user to update the record every 6 months during the recruitment phase, but records should be amended as soon as recruitment status or protocols are changed, or when other information becomes available (eg, links to publications). All changes are dated and tracked on an archival site, which is available to the public at [www.clinicaltrials.gov/archive]. The record on ClinicalTrials.gov main site displays the information from the most recent update.

**KEY ISSUES TO CONSIDER WHEN REGISTERING A TRIAL: AVOIDING MOST FREQUENT PROBLEMS**

Clinical trials registries may be used by people with many different backgrounds and interests, as described in Table 1. For example, patients may want to consider participating in the trial and/or may want to consider all of their possible options. In general, potential participants will find a trial by searching by condition or intervention; therefore, it is important that this information be accurate and complete.

IRBs may use the registry to help evaluate a particular trial. The registry could provide a listing of past research (published or unpublished) that is relevant. In addition, the registry could help them to identify ongoing research (eg, prior to publication) that may overlap or be relevant to the protocol under current consideration.

Journal editors and reviewers may use the registry to determine whether or not a submitted manuscript adheres to the protocol design that was described in the initial registration (protocol amendments are also recorded in the registry, and are publicly accessible). In addition, journal editors may wish to understand the research context, which would include ongoing and previously unpublished research on the same topic.

Systematic reviewers may use the registry to identify all published and unpublished research on a given topic and to identify key protocol elements, such as specific intervention. The quality of the information in the registry and the efficiency and logic underlying the search engine are critically important for making the registry useful to these different types of users. Here we discuss some frequent problems that arise with trial registration:

**Deciding Whether or Not To Register a Study**

It is sometimes unclear whether a specific clinical study must be registered according to the law, or according to ICMJE or other policy mandates. As long as the study meets the ClinicalTrials.gov requirements (human subjects with health or biomedical outcome measures), it is generally better to register it. If there is doubt about the applicability of a study to the registry, contact [register@clinicaltrials.gov].

**Multisite and Complex Study Designs**

A multisite study is generally regarded as a single study if the sites use the same protocol, and if the data are intended to be pooled for analysis. Each such study should be registered only once, regardless of the number of sites. For some studies, it may not be clear whether or not they should be registered as one or several studies. For example, some vaccine studies re-randomize participants from the first phase for possible participation in a subsequent phase. When questions arise about how to register a study, contact [register@clinicaltrials.gov] for guidance.

**Study Type**

Registrants must note whether their trial is interventional or observational in design. This item is critical because it determines what other design features are queried by the registry. Detailed definitions are available in the data element definitions at [http://prsinfo.clinicaltrials.gov]. Interventional studies are those in which the investigator intervenes and prospectively assigns subjects to receive a specific intervention. The assignment process may or may not be random. In observational studies, the investigator simply observes the outcomes in a predefined
group of subjects but does not determine what interventions they receive. This item frequently confuses investigators because either study type may involve the use of medical interventions. In addition, diagnostic, therapeutic and other types of interventions could be studied with either interventional or observational designs.

**Condition**

One or more conditions that are the focus of the study should be listed here. Medical subject headings (ie, MeSH) terms should be used whenever possible. Medical subject headings are a controlled terminology developed by the National Library of Medicine for indexing medical texts. Prevention studies should generally list the condition that is being prevented. Health services research studies do not always involve a specific medical condition. The focus of the study should be used; examples include "medical errors," "number of prescription medications," or "discharge rates."

**Intervention**

Randomized controlled trials, or other trials with two or more arms, should list the interventions separately for each arm of the study. Drug interventions should be identified by a generic name if available; when there is not yet a generic name, the company serial number or the chemical name may be used. Devices should be described as fully as possible, using a formal nomenclature whenever appropriate (eg, Global Medical Device Nomenclature; GMDN; Radley, Oxford, UK). Biologics, including vaccines, should also be fully described. Although "pneumococcal vaccine" may seem specific, there can be multiple versions of such a vaccine, and it would be important to know which version is being tested. In all cases, once a marketed name is available, the records should be modified to include the marketed name (along with previous names).

**Primary and Secondary Outcome Measures**

Outcome measures should include the specific measure (eg, a specific rating scale) along with the time of measurement. For example, "cardiovascular mortality at 1 year" is superior to "mortality" as an outcome measure entry. Although entries in this field are highly variable, we have found that using the outcome measure description that one would use in a structured abstract of a journal article typically provides an appropriate level of detail.1

**Conclusion**

The registration of clinical trials serves many different purposes. Sponsors and investigators are encouraged to register their trials and to provide the most informative entries possible so that the public has access to a full listing of medical or health-related research involving human subjects.

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