From:	OC GCP Questions
To:	[redacted]
Cc:	CDER DRUG INFO
Subject:	Does an Observational Data Collection Study meet the definition of a Clinical Investigation?
Date:	Friday, August 21, 2015 9:11:23 AM
Importance:	High

Good morning –

Below is some information that might be helpful to you.

There are no FDA regulations that specifically speak to studies that involve chart review studies. However, if the results of such a study are for submission to FDA to support a change to conditions of approval for an approved medical product, e.g., to support a labeling change, it could be considered an FDA-regulated study. In such a case the requirements for informed consent would apply. As stated in 21 CFR Part 50 - Protection of Human Subjects (see below). If the study will not support an application to FDA, e.g., a user preference study, it may not be FDA-regulated. (As you mention, the study does not directly involve use of a medical product.) If you are uncertain, you can also request advice from the group in the FDA Center that would review the medical product involved. You can determine who to contact from FDA's website (www.fda.gov/). Choose the Center responsible for the medical product in question and then use the link to information about the Center to determine which group to contact.

There are no provisions for waiver of informed consent in an FDA-regulated study, as informed consent is required by the Federal Food, Drug, and Cosmetics Act. (The regulations in the Common Rule - 45 CFR 46, Part A, which regulates government-supported basic research, does allow for waivers of informed consents under certain circumstances.) However, since the retrospective chart studies can be considered minimal risk, they can undergo expedited review by IRBs.

Sec. 50.1 Scope.

(a) This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.

If the study is an FDA-regulated study under an IND the 1572 form would need to be signed by the clinical investigator. Please see the guidance document below.

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

It might be helpful to consult the Office of Human Research Protections (OHRP) as this office oversees 45 CFR 46.

Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Toll-Free Telephone within the United States: (866) 447-4777
Telephone: (240) 453-6900
Fax: (240) 453-6909
E-mail: OHRP@hhs.gov

I hope this information is helpful. Please contact us again at gcp.questions@fda.hhs.gov should you have additional questions.

Kind regards,

Doreen M. Kezer, MSN
Senior Health Policy Analyst
Office of Good Clinical Practice
Office of the Commissioner, FDA

From: [redacted]
Sent: Thursday, August 20, 2015 4:14 PM
To: CDER DRUG INFO; OC GCP Questions
Cc: [redacted]
Subject: RE: Does an Observational Data Collection Study meet the definition of a Clinical Investigation?
Importance: High

Hello: I'm writing in follow-up to the email below, which was sent last Friday. If I should direct my inquiry to another individual, could you please provide me with the appropriate contact information?

Thank you,
[redacted]

From: [redacted]
Sent: Friday, August 14, 2015 7:35 PM
To: 'Druginfo@fda.hhs.gov'
Cc: [redacted]
Subject: Does an Observational Data Collection Study meet the definition of a Clinical Investigation?
Importance: High

Greetings: I am the administrator for an Institutional Review Board and seek assistance in determining whether FDA would consider a non-interventional study designed to collect retrospective data in support of an IND to be a clinical investigation or otherwise eligible for a waiver of informed consent.

My IRB is working with a PI on submission of an industry-sponsored non-interventional, retrospective data collection study (Study #2 below). The Sponsor has separated the research into two separate protocols:

1) A Phase III, open-labeled, multicenter study of the safety and efficacy of [study drug]

in treatment of [Condition]

2) A Multicenter Non-Interventional Study to Obtain Retrospective Data for Subjects Previously Diagnosed with [Condition] to serve as Matched Historical Controls for [the Phase III Study]

The rationale for seeking historical controls for Study #2 was provided as follows:

> The [non-interventional, retrospective data collection] study is designed to create an ethically appropriate control group for the [Phase III] study. The data collected from retrospective chart review in [Study #2] will serve as a historical control group to demonstrate the comparative effectiveness of [the study drug] versus standard of care treatment for [Condition] in immunocompromised patients. This study involves a retrospective medical chart review of medical records starting from January 1st 2004. The study is for data abstraction purposes only, and does not in any way alter the course of treatment or involve risk to patients…[Study #1] study does not allow for a placebo or active control; specifically, placebo is not a viable option because investigators have been reluctant to participate in placebo-controlled studies of patients with [Condition] as the disease is often rapidly fatal (mortality rates as high as 80%) even with therapy that is standard of care. An active-control Phase 3 study is also problematic because the standard of care, [off-label drug], is not approved for the [Condition] and carries a black box warning for restriction to its indication. For this reason, [Study #2] is designed to provide a matched historical control group for subjects enrolled in [Study #1] to demonstrate the comparative effectiveness of [study drug] versus standard of care treatment for [Condition] in immunocompromised patients.

The Sponsor has asked the PI to request approval for a waiver of consent for the non-interventional retrospective data collection study (Study #2), arguing the study does not meet the definition of a clinical investigation because the retrospective data collection study does not involve a test article.

However, the Sponsor also requested the PI provide a completed Form FDA 1572 for Study #2. To my understanding, FDA Form 1572 is required when there's a clinical investigation. FDA's Guidance on 1572s (item #3) states:

> ***3. When must this form be completed and signed by an investigator?***
> Whenever a sponsor selects a new investigator to participate in a clinical investigation that is being conducted under an investigational new drug application (IND), the sponsor must obtain a completed and signed 1572 before permitting the investigator to begin participation in the clinical investigation (21 CFR 312.53(c)). The investigator should sign the form only after being given enough information to be informed about the clinical investigation and to understand the commitments described in Section #9 of the 1572. Having enough information about the study typically means that the investigator has received copies of, has read, and understands the protocol and investigator's brochure (if required[2]), and is familiar with the regulations governing the conduct of clinical studies.
>
> The investigator's signature on this form constitutes the investigator's affirmation that he or she is qualified to conduct the clinical investigation and constitutes the investigator's

written commitment to abide by FDA regulations in the conduct of the clinical investigation

The Sponsor is arguing that Study #2 is not a clinical investigation so the PI may request the waiver of consent, yet the Sponsor is requiring the PI to provide a 1572, which pertains to clinical investigations. When questioned about this, the Sponsor stated that **while Study #2 does not fall under the definition of clinical investigation, the Phase III study does and data from Study #2 will be submitted with the Phase III study data under the IND.** This seems inherently contradictory to me.

I am also aware FDA's recent draft guidance on informed consent discusses review of patient records and the need for a case-by-case determination on whether it meets the definition of a clinical investigation (excerpt below). I recognize this is only draft guidance at this point.

> **A. Review of Patient Records**
>
> Sponsors and investigators may seek to review patient medical records for a variety of reasons related to a clinical investigation. Whether the record review is considered part of the clinical investigation, as defined under FDA's regulations at 21 CFR 50.3(c) and 21 CFR 56.102(c), is determined on a case-by-case basis. If the record review is part of the clinical investigation, then informed consent from the subject for the record review is required under 21 CFR part 50….

Practically speaking, Study #2 is a low risk, retrospective data collection study that (if not deemed a clinical investigation or otherwise subject to FDA regulations at 21 CFR 50 and 56) would likely qualify for expedited review under 45 CFR 46 and makes complete sense to do with a waiver of informed consent.

Would FDA consider Study #2 to be a clinical investigation or otherwise subject to FDA regulations making it ineligible for a waiver of informed consent? Is there another avenue I should pursue to ascertain this information? I am grateful for any guidance you can provide for this case.

With appreciation for your consideration,

[redacted]