



Published in final edited form as:

Genet Med. 2012 April ; 14(4): 411–416. doi:10.1038/gim.2012.14.

Return of Individual Research Results and Incidental Findings in the Clinical Trials Cooperative Group Setting

Michael Ferriere, B.S.¹ and Brian Van Ness, Ph.D.²

¹Eastern Cooperative Oncology Group Coordinating Center, Boston, MA

²Institute of Human Genetics, University of Minnesota, Minneapolis, MN

Abstract

The NCI funded cooperative group cancer clinical trial system develops experimental therapies and often collects patient samples for correlative research. The Cooperative Group Bank (CGB) system maintains biobanks with a current policy not to return research results to individuals. An online survey was created, and 10 directors of CGBs completed the surveys asking about understanding and attitudes in changing policies to consider return of Incidental Findings (IFs) and Individual Research Results (IRRs) of health significance. The potential impact of the ten consensus recommendations of Wolf et al. presented in this issue are examined. Re-identification of samples is often not problematic; however, changes to the current banking and clinical trial systems would require significant effort to fulfill an obligation of recontact of subjects. Additional resources, as well as a national advisory board would be required to standardize implementation.

INTRODUCTION

This article will frame the cooperative group banks (CGBs) as an interesting case study in relation to the management of incidental findings and individual research results in response to new recommendations made by Wolf et al. (1). As previously described by Wolf et al., an incidental finding (IF) is “a finding concerning an individual research participant ... that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study.” (2). An individual research result (IRR) is “a finding concerning an individual contributor that has potential health or reproductive importance and is discovered in the course of research on the focal variables under study in meeting the stated aims of the research project.” (Id.). A brief history and discussion of the role of the CGBs in cancer research is provided. The basic structure of the CGBs in relation to the models described by Bemmels et al. (3) are presented, relevant key processes and current policies are described, and some of the potential impact of the ten recommendations made in the Wolf et al. consensus paper (1) are examined.

The National Cancer Institute (NCI)-funded cooperative group cancer clinical trials system has existed for over 50 years. Currently, ten US-based groups conduct clinical trials on experimental therapies for cancer in the United States and several other countries. As part of their research efforts, the cooperative groups have created and maintain biospecimen banks (i.e., the CGBs), the structure and governance of which are particular to each group.

Correspondence to: Brian Van Ness, 515 Delaware St. SE, MMC 206, University of Minnesota, Minneapolis, MN 55455, Phone: 612-624-9944, Fax: 612-625-4294, vanne001@umn.edu.

Conflict of Interest

The authors have no conflict of interest to disclose.

The CGBs facilitate the collection of samples and conduct of translational studies for the cooperative groups. In addition to providing clinical information (eg. demographics, disease related tests, treatment and outcome measures), trial participants submit biospecimens as a part of many clinical trial protocols. The biospecimens collected and banked are most often tissue (cancer or surrounding normal), and blood. In addition to providing clinical diagnostic information, these samples are often used for correlative research, such as developing predictive biomarkers. In some cases residual samples remain after these studies are complete. In other cases, materials are collected per protocol without a defined endpoint but for unspecified future use. All banked materials are available for use in approved research, and such research has led to a wealth of scientific knowledge and improvements to patient care (4).

The clinical scopes of the groups vary, but they share a focus on large Phase II and Phase III cancer trials where many participating sites are needed to accrue the numbers of patients necessary to meet study endpoints. Over 3,100 sites in the US and abroad participate in cooperative group trials (5), representing a wide range of sites potentially contributing specimens to the CGBs. Trial sample collections and associated research may occur through the time span of the trial. Particularly in Phase III studies, where large numbers of patients are needed to provide statistical power for study objectives and where survival is a common primary endpoint, trial completion and data maturity may take several years. In many cases, research may be done on samples years after trial completion. This length of time needed to complete trials and conduct research on samples may have an impact on the ability of the groups or CGBs to re-contact participants about their results, or the impact on their health, and will be examined in the discussion.

Most of the CGBs operate under an Honest Broker model for their banking activities. Biospecimens received from participating sites may or may not be accompanied by individually identifiable health information as defined by the Health Insurance Portability and Accountability Act (HIPAA) (6) in the form of initials or names. Received samples typically arrive with a patient code unique to the clinical trial. Although the CGBs remove PHI and assign a unique code before transferring samples to approved researchers, most CGBs maintain a key, linking the original identifiers (again, typically a protocol-related patient code) and the bank's code. This key is provided only to cooperative group operations office staff and statisticians responsible for association studies whereby the results of laboratory studies are associated with patient information such as clinical outcome on the cooperative group trial. Laboratory researchers work with the cooperative groups, rather than the CGBs, to access clinical data. Access to samples and associated data is regulated by the cooperative groups and NCI, in addition to local Institutional Review Boards. However, because of the use of the Honest Broker model, and lack of re-identification, many projects on CGB specimens are not considered to be human subject research (45 C.F.R. 46.101).

The NCI Group Banking Committee (GBC) was formed in 2005. Per its Charter “the purpose of the Group Banking Committee (GBC), is to improve the operation of the clinical oncology cooperative group human specimen banks and to coordinate banking activities among groups conducting phase III and large phase II clinical trials” (Charter – available from GBC on request). Ten cancer clinical trial cooperative groups are GBC members. The GBC generates consensus documents, approving them by established voting processes. Approved documents are then implemented by the member groups. Groups may choose to use their own documents rather than those generated by the GBC, but agree that the principles of the approved documents will be reflected in the local documents. Therefore, an examination of approved GBC documents is an expedient way to examine broadly representative policies and processes across the cooperative groups.

Informed consent templates employed by all cooperative groups have sections or stand-alone components devoted to tissue banking. These templates make patients aware that banked specimens would be available for future research, contingent upon their consent. In 2011, the GBC finalized updates of the banking consent template in an effort to ensure that important issues were clearly and consistently represented to patients across the group templates. Foremost among the issues was a uniform way to deal with and describe genetic studies which had become an increasingly common requested use for banked specimens. The final template informs the patient that consenting to future use of supplied biospecimens allows these specimens to be used in studies involving inherited traits. The template contains the single, explicit, statement: “*Research results will not be returned to you or your doctor.*” This language was developed as a GBC consensus and drafts have been submitted for review to a number of oversight bodies during development. Therefore, it would be correct to say that IRRs and IFs resulting from projects utilizing banked tissue are not currently returned. Deviations from this general policy may of course be made on a protocol-by-protocol basis. Return of IRRs which represent clinical trial endpoints (e.g., biomarker testing to determine clinical trial eligibility) would not be included in this general statement. Although the template wording illustrates current policy, it does not preclude change based on the Wolf et al. recommendations (1), but would require a change in current policy.

The GBC Material Use Agreement (MUA) provides a template that outlines general cooperative group policies involved in use of banked tissue, covering areas such as regulatory approvals, data use, and publication policies (7). The GBC MUA, or a group-specific MUA which adheres to the same principles, must be signed by an investigator as a precondition of receiving CGB samples. Notably, the current document states investigators will not seek to re-identify subjects. Since investigators are restricted from obtaining patient identifiers or therefore attempting to contact them, the burden of returning IRRs and IFs in the current setting would fall to another entity in the CGB system. In light of the consent statement not to return results, this remains undefined.

Because the CGBs vary in structure and governance, as well as policies regarding IRRs and IFs, they likely differ in how they might adhere to the recommendations of Wolf, et al. (1). A survey of CGB directors was conducted by the authors with an aim of establishing some of the similarities and dissimilarities of general conduct of research and current opinions on treatment of IRRs and IFs in the Cooperative Group setting.

METHODS

A 29 item survey was created by the authors. Questions were formulated to accomplish two goals: to gather data on the current policies of the CGBs, and to solicit initial impressions of CGB leadership on the ability of the CGBs to adopt the recommendations of Wolf et al. in terms of IF and IRR return. A brief background was provided to respondents. Respondents were not provided with a draft of the Wolf et al. paper. The survey was not intended for statistical analysis and was not created in consultation with a statistician or survey tool expert. It was administered on-line using *Google Docs*TM. Personal email invitations were sent to all 13 Directors of CGBs, representing 14 distinct CGBs. The initial invitation was sent to directors of banks known to the author through the GBC and represented banks from nine GBC member groups. Ten surveys were completed, representing seven national cooperative groups. Personal email follow-up requests for survey completion were made up to twice during the time span the survey was open. The survey was conducted under the assurance that results would be anonymous; although names and CGB positions were collected to confirm which banks were represented in the results. As this did not involve any human subjects information, no Institutional Review Board approval was necessary. No follow-up with responders was attempted after survey completion.

RESULTS

The complete survey tool and results are available as supplemental materials. A summary of results follows, presented in broad categories relevant to issues of returning IRRs and IFs.

Types of specimens and data

All ten survey participants indicated that their bank houses samples such as tissue, blood or sputum received directly from the institution which has collected the materials, as well as derived material, including DNA. Five banks indicated they generate or receive genotype data while five did not.

Patient Identifiers

Four responders indicated their CGB receive PHI along with specimens; six did not. One responder indicated a sample recipient might receive such PHI along with samples, while the remaining nine indicated PHI was not released. Similarly, nine replies indicated researchers always received de-identified samples.

Operational and regulatory structure

Eight of those surveyed indicated “someone else in the cooperative group” was responsible for providing clinical data (such as outcome) associated with supplied specimens to researchers. One responder indicated this responsibility was the CGB’s. Similarly, eight stated that someone else in the cooperative group performed clinical associations, with two responders choosing the response “other.”

Nine of ten banks operate under and Honest Broker model. Eight indicated they maintain a distinct IRB approval for their cooperative group-related banking operations and all ten noted a requirement for investigators who receive specimens to obtain a distinct IRB approval at their own (as opposed to the bank’s) institution.

Current IF and IRR policy

Asked whether there is an established method for disclosure of IF and IRRs for the CGB, four responded that there was not, one noted the investigator was responsible, and two responses indicated the cooperative group was responsible. Three submitted a response of “other.”

Eight surveyed indicated that during the application process for banked specimens, there was no collection of a list of anticipated IFs or IRRs; of the other two responses, one indicated such collection was performed and the other chose “unknown.”

Nine of ten responders indicated they receive information on IFs and IRRs from investigators using banked samples after their research is complete, while one indicated they did not. Seven stated their CGB had never returned IFs or IRRs for a cooperative group study; two did not know if this has ever occurred. One responder chose the “other” response.

Five responders indicated their CGB had a policy on return of IF and IRRs while five did not have a policy. Regarding the presence of a policy within the bank’s governing institution, six indicated they did not know whether there was one, as it would not affect the CGB samples.

Answers to the question “Does any consent form used as part of your Cooperative Group Banking function indicate that research results may be returned to patients of treating physicians if warranted for health reasons?” were mixed; please see table 1 for results.

Opinions

Participants were asked what entities *should* be responsible for disclosure of IFs and IRRs, and which entities were *best positioned* for disclosure, with results noted in table 2.

Seven of those surveyed felt a requirement for CGBs to disclose IF and IRR would add costs to banking, two had no opinion and one thought no costs would be added.

Interestingly, seven expressed interest in participating in the assembly of databases to allow comparison of approaches for IF and IRR return.

At the end of the survey participants were asked to rate how much they agreed with six statements concerning return IFs and IRRs by the CGBs. Talled results appear in table 3.

DISCUSSION

In this section, selected survey results are discussed with consideration of the ten consensus recommendations of Wolf et al. (1) in light of the background information presented, personal experience with the cooperative group system and the survey results. In general, bank directors recognized the potential benefits of returning IRRs and IFs, but raised significant concern over the complexities of implementation, with the cooperative group setting.

The first recommendation of Wolf et al. is that “... *Overarching responsibility for assuring that the biobank research system fulfills IF/IRR responsibilities should generally lie with the biobank*” (1). From this recommendation a number of logistical and administrative issues arise. In particular, recommendation #4 suggests a Central Advisory Board to work with bodies responsible for identifying and assessing IFs and IRRs, while recommendation #10 suggests there is an important role of bank funders and regulators in the handling of IFs and IRRs (1). These types of recommendations will be complicated for the CGBs by virtue of the Cooperative Group and CGB structure.

The cooperative groups are governed by central executive committees that determine policies and methods for implementation. As such, the biobank management does not have independent jurisdiction on handling samples, or determining policies for recontact of IFs and IRRs. Because the biobanks are a widely distributed resource, within the clinical trial operation, as well as in distributing samples to multiple secondary researchers, governance responsibilities must be central to the cooperative group management structure that oversees bank operations.

Similarly, the creation of an oversight body such as a Return of Results Oversight Committee as recommended in Wolf et al (1) should be sensitive to the governance of the bank and include representatives of all stakeholders in the biobank. The creation of an expert, multidisciplinary, advisory Committee or Board would be unquestionably beneficial, but issues of governance, scope and finance complicate the issue. Some cooperative group banks may be housed in an institution where such a board already exists (e.g., Mayo Clinic) in relation to one or more programs or projects. It is unlikely that such an existing board would already have governance over the bank. In our survey, seven banks indicated that the IF/IRR return policy of their governing institution would *not* apply to the CGB project. The decision of whether an independent or shared board needs to be created to oversee IFs and IRRs related to the CGBs should be decided jointly by each relevant cooperative group and governing institution, and a suitable relationship formed. The scope of a board, or boards, in deciding if results should be returned, what results would be returned and how they be returned would be decided at this time. The cooperative group or its member institutions

would be expected to be a party in dissemination of IFs and IRRs and may therefore require representation on the oversight board.

Maintaining an oversight board would represent an additional operating expense for the cooperative group or the CGB's governing institution. Since decisions would need to be archived indefinitely as well as made available to IRBs on a regular basis, additional administrative tasks are created. These duties would need to be accounted for in terms of training and percent effort of some staff, either within the CGB, the governing institution or the cooperative group. The governing institution and Cooperative Group would need to agree on the financing, scope, make-up, etc. of such a group. Alternately, a Federal body with advisory capacity to all CGB could be explored.

The development and maintenance of a roster of IFs and IRRs by the CGBs as recommended (1) represents a commendable idea. Creation and maintenance of a database for this roster would require funding. Assumption of this responsibility by a federal body, such as the NCI in the context of the CGBs, would relax the burden. A centrally maintained, web-accessible database with a simple update system for adding new findings would be preferable to the development and maintenance of independent systems across the CGBs. The benefits to such a system include: 1) reduction in overall costs by eliminating redundant system development, 2) a stable, publicly funded environment for the database, and 3) a wealth of information from participants across the NCI available to other patients and other interested users and researchers. Well-recognized organizations such as the National Cancer Institute's GBC or Office of Biorepositories and Biospecimen Research (OBBR) should be asked to recommend specifics of such a system, including architectural advice facilitating future data sharing.

Other recommendations of Wolf et al. (1) deal with the question of whether banks should be set up to even allow re-identification (i.e., recommendations #2 and #6) and when they are, if there is a responsibility for recontact and other dissemination of research results (i.e., recommendations #7 and #9). For most cooperative banks, re-identification is technically possible in many cases, although logistically challenging in the current system. Re-linking of results with a Cooperative Group study and case identifier can often be done via coordination between the CGB and the Cooperative Group. This re-linking could potentially be extended to re-identification, assuming the ability and cooperation of the Group in the endeavor. However, challenges are noted below.

The most recent information about a patient is housed elsewhere within the cooperative groups' operations offices, which may be distantly located from the CGB. For example, reports that a patient has died, moved or changed treating institutions, are sent to an operations office rather than to the CGB. Therefore, although the bank may have some information regarding identification of the patient, close coordination with the cooperative group data center would be required to identify a patient and their current status for follow-up, or relevant treatment site to contact. Yet, the cooperative groups do not collect direct contact information for patients such as addresses, emails, or telephone numbers; they rely on the member sites to contact patients. The groups would need to either effect substantial changes in their policies and procedures in this regard (e.g., directly collect patient contact information), or work closely with participating sites to re-identify patients.

It should not be a difficult matter from an informatics standpoint to implement such changes prospectively. However, the idea of not being personally identified by research is central to the current tissue banking consent process and the impact of a change to this paradigm should be considered and studied. Fears of genetic results being used against a person when applying for employment or various types of insurance, whether well founded or not, may

be a negative stimulus to patients to participate in tissue banking. Conversely, the idea of a possible warning against future health issues might be an enticement to others to participate. Given that only about 3% of adult patients participate in clinical trials (8), the pool of those supplying tissue to the system is small and policy changes must be carefully considered so as to create a positive impact or minimize negative impact on the goals of cooperative group clinical trials.

Alternative methods of re-identification exist, and should be explored. Aggregate results can and should be widely publicized, as suggested in recommendation #9 by Wolf et al. (1). Results could be accompanied by invitations to former participants to initiate their own re-contact. A drawback of this method is that not all patients would be reached in this way. However, a reversed re-contact process would have the benefits of reaching those patients most interested in learning about results, and limit expenses in pursuing patients effectively lost to the follow-up process. Some resources, such as a study-specific re-contact web site, would be required, but might be supplied by existing communication structures associated with the NCI Cooperative Group system. The Coalition of Cancer Cooperative Groups's web site, <http://www.cancertrialshelp.org>, maintains a clearinghouse of cooperative group research-oriented press releases and resources for patients, advocates, and care givers. The NCI's clinicaltrials.gov web site operates under a mandate to provide access to trials and to provide the results of those trials in lay language. There are also patient advocacy and patient representative structures within the groups, which are proven to be energetic and effective in accessing the patient population. However, while these mechanisms can be used to disseminate aggregate results, interacting with individuals requires expert and readily available staff. This role is unlikely to be filled by researchers themselves or public relations staff who would be most likely to create the announcements and web sites. Again, the issue of available resources to supply such staff is raised. Based on the survey results, the CGB leadership polled did not feel they presently have the expertise or resources to most effectively return findings.

Another complicating factor in whether CGBs should be responsible for disclosing individual results is introduced by virtue of the patient having no clinical relationship with the bank. The CGB will rarely be at the treating institution, since there are a handful of CGBs and hundreds of participating institutions. Patients are not given much information about the CGB itself in the current consent template, which focuses on security safeguards and potential future testing of biospecimens. A re-contacting role for the bank would probably require additional information in the consent form about bank personnel, their preferred methods of re-contact, etc.

The lack of a relationship between CGBs and patients is an important consideration if a patient might expect further clinical explanations and options for action. Foremost, the bank has no information as to whether the condition has already manifested or testing has already been conducted for another reason. Addressing this issue would require dissemination of health care information from one or more treating sites. In many instances, when research on banked tissue is conducted, the patient will have completed their involvement with the clinical trial and may no longer be in the care of a cooperative group-related physician. Therefore, neither the contributor nor their current caregiver may have a relationship with the CGB staff responsible for contacting them. This presents a difficulty in the CGB providing informed clinical referrals, as per recommendation #7 of Wolf et al., which suggests biobanks should have plans in place to re-contact contributors (1). Due to lack of familiarity with individual patients and the geographical disparate nature of the participating sites contributing to CGBs, providing a reasonable referral would be improbable in the majority of cases.

Conclusions

Because of the need to track ongoing treatment outcomes, cooperative group clinical trials typically maintain identifiers at the site of trial treatment, so re-identification is often not problematic. However, changes to the system and increased effort would be required to fulfill an obligation of re-contact of subjects on the part of the CGBs. Existing cooperative group policies and related documents would need to be updated to reflect and implement such a shift. Fundamental cooperative group processes, such as patient enrollment, consent, and follow-up would be significantly altered. The processes of application for use of banked materials, requires regulatory approvals, and material transfer agreements would need to be mindful of the IRR and IF issues. Adequate resources for re-contact would need to be in place, such as specialized training for responsible bank personnel or access to such individuals from other aspects of the bank's home institution.

Expected resource needs, both incremental and substantial, have been a common theme throughout the examination of expected impact of the ten recommendations of Wolf et al (1). Some central assistance by the NCI would alleviate some of the anticipated regulatory and administrative burden, but real impact on the CGBs in the actual re-contact of patients would be unavoidable. Given their complicated organizational structures and importance based on the vast inventories of well-annotated, re-identifiable samples, the CGBs should be an important component of further discussion on handling IFs and IRRs in the modern research environment.

Acknowledgments

This study was coordinated by the Eastern Cooperative Oncology Group (Robert L. Comis, M.D.) and supported in part by Public Health Service Grants CA21115, CA114737 and from the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

Supported by NIH/NHGRI Grant Award #2-R01-HG003178-03 on "Managing Incidental Findings and Research Results in Genomic Biobanks & Archives" (PI Susan Wolf). The authors wish to thank the NCI Group Banking Committee, particularly those individuals who completed the survey reported in this article. The authors are members of the Eastern Cooperative Oncology Group (ECOG) and wish to thank the leadership of ECOG and ECOG's tissue banks for support and guidance. However, the authors are solely responsible for the content and opinions expressed in this article.

References

1. Wolf, et al. Genetics in Medicine. this issue
2. Wolf SM, Lawrenz FP, Nelson CA, et al. Managing incidental findings in human subjects research: analysis and recommendations. J Law Med & Ethics. 2008; 36(2):219–248. [PubMed: 18547191]
3. Bemmels, H.; Wolfe, S.; Van Ness, B. Genetics in Medicine. this issue
4. <http://cgb.cancer.gov/about/scientific.impact.html>
5. National Cancer Institute. FactSheet, NCI's Clinical Trials Cooperative Group Program. <http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group>
6. <http://www.hipaa.com/2009/09/hipaa-protected-health-information-what-does-phi-include/>
7. <http://cgb.cancer.gov/access/forms.html>
8. http://www.nap.edu/openbook.php?record_id=12879&page=191

Table 1

Responses to “Does any consent form used as part of your Cooperative Group Banking function indicate that research results may be returned to patients of treating physicians if warranted for health reasons?”

Answer choices	Number of responses
Yes	1
No	3
Sometimes/protocol dependent	4
Unknown	2
Other	0

Table 2

Opinions on Entities Which Might be Expected to Return IFs and IRRs

Answer choices	Responses regarding the entity which <i>should</i> be responsible for return	Responses regarding the entity which is <i>best positioned</i> for return
Bank	0	0
Cooperative Group	4	4
Investigator	1	2
None of the above should be responsible	3	1
Other	2	3

Table 3

Responses to “How much do you agree with the following statement?”

Statements	Number of responses per category				
	1 Completely Disagree	2	3	4	5 Completely Agree
The CG Bank should be responsible for collection of IFs and IRRs from investigators	6	2			1
The CG Bank should be responsible for disclosure of IFs and IRRs to patients	10				
The CG Bank has access to staff qualified to disclose IFs and IRRs to patients	9				1
The CG Bank has access to perform CLIA-approved validation testing of returned results where necessary	4	3	1	1	1
The CG Bank is adequately funded to disclose IFs and IRRs	9				1