Impact of National Cancer Institute (NCI)-mandated scientific review on cancer clinical trial protocol development

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ABSTRACT

Background
The National Cancer Institute (NCI) requirement that all clinical trials involving cancer patients at NCI-designated cancer centers undergo a scientific protocol review before Institutional Review Board (IRB) review is unique among all medical specialties. Little is known about the impact of scientific review on protocol development. Given heightened interest in the quality and timeliness of oncology clinical trials, we evaluated the scientific review process at an NCI designated center.

Methods
We collected data on all oncology clinical trials that underwent full board review by the UT Southwestern Harold C. Simmons Cancer Center Protocol Review and Monitoring Committee (PRMC) from January 1, 2009, through June 30, 2013. The following data were collected: trial characteristics, PRMC decisions, protocol clarifications and changes requested by PRMC, and subsequent protocol modifications. We analyzed the association between trial characteristics and PRMC protocol modifications using Chi-square testing, Fisher's exact testing, and logistic regression.

Results
A total of 226 trials were included in our analysis. Of these studies, 23% were institutional (investigator-initiated) trials. Initial PRMC initial decisions were: approved (40%), approved pending response (52%), defer (7%), and disapprove (1%). Across the 226 trials, the PRMC requested 270 changes; total number of requested changes per protocol ranged from 0 (66% of trials) to 17. The number of requested changes per protocol was significantly associated with trial type (mean 0.7 for industry-sponsored versus 3.0 for investigator-initiated; *P*<0.001) and study year (mean 0.7 in 2009 versus 2.4 in 2013; *P*=0.03). Forty-nine percent of requested changes applied directly to trial protocols, with the remainder related to consent form (13%) or other documentation (38%). Protocol-related requested changes were as follows: design (53%), intervention (24%), evidence-background-rationale (14%), and population (11%). Compared to those for industry-sponsored trials, PRMC requested changes for investigator-initiated trials were more likely to be implemented (91% versus 83%; *P*=0.08). A pronounced difference was noted for requested changes related to trial design: among 154 industry-sponsored trials, 28 changes to study design were requested (average 0.2 per trial), and 8 changes (29% of requests) were implemented; among 52 investigator-initiated trials, 39 changes to study design were requested (average 0.8 per trial), and 35 changes (90% of requests) were implemented.

Conclusion
To our knowledge, this is the first study to evaluate the impact of NCI-mandated scientific protocol review in cancer clinical trial development. While this process appears to have a substantial impact on investigator-initiated trial protocols, effect on industry-sponsored trials is less clear.

INTRODUCTION

- National Cancer Institute (NCI) mandates any clinical trials involving cancer patients to undergo formal scientific review before implementation at NCI-designated cancer centers.
- This process is unique among medical fields. Clinical trials that do not involve cancer patients or clinical trials that involve cancer patients but are not conducted at NCI-designated centers are not subjected to this review.
- Timeliness to activate cancer clinical trials is essential in providing treatment options to patients, for trial accrual, and to prevent study objectives from becoming obsolete.
- Efforts are underway to identify study activation barriers and to accelerate the process in activating cancer clinical trials.[1,2]
- Studies of the clinical trial activation process have focused on timeframes of individual components of the process (eg, ethical review, budget, contract, site visit, supply shipment) and comparisons among institutions. [3,4]
- There is a dearth of information on the effect such review committees have on protocol design and content.

Table 1. Characteristics of studies undergoing scientific review at the Harold C. Simmons Cancer Center, UT Southwestern Medical Center, 2009-2013. Institutional trials included investigator-initiated trials with a local study chair or a study chair at another institution. Interventional studies included therapeutic, prevention, supportive care, screening, detection, and diagnostic studies. Non-interventional studies included epidemiologic, observational, and correlative studies.

Characteristic	Number (%)
Total studies	226
Sponsor	
Industrial/Commercial	174 (77)
Institutional/Investigator	52 (23)
Study Type	
Interventional	186 (82)
Non-interventional	40 (18)
Study Phase	
1/pilot	46 (20)
2	76 (34)
3	75 (33)
None designated	29 (13)
Cancer Type	
Breast	28 (12)
Gastrointestinal/Genitourinary	56 (25)
Hematologic	44 (19)
Upper Aerodigestive	49 (22)
Other	49 (22)
Year	
2009	48 (21)
2010	44 (20)
2011	42 (19)
2012	53 (23)
2013	39 (17)

Figure 1. Initial (green) and final (blue) scientific review committee decisions according to trial characteristics. Non-approval decisions include approval pending response, deferred and disapprove. Percentage approval plus % non-approval decisions equal 100%. Green and blue *P* values compare initial and final % approval decisions between trial characteristics, respectively. Abbreviations: Ind, industry; Inst, institutional; ND, none designated; UAD, upper aerodigestive; GI/GU, gastrointestinal/genitourinary; Heme, hematologic.

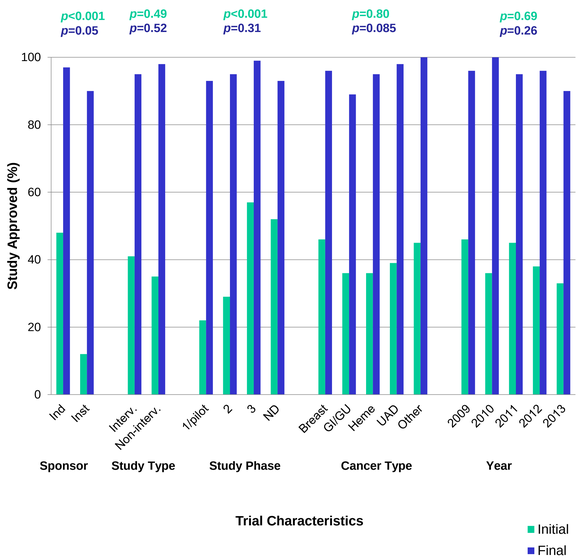

Figure 2. Number of scientific review committee changes requested (green) and made (blue). PRMC requested a total of 270 changes, with mean of 1.19 changes per study. 149/226 trials had no change requested. Maximum change requested was 17. Changes made by primary investigator (PI) can be less or more than requested changes. Green and blue *P* values compare requested and implemented changes between trial characteristics, respectively. Abbreviations: Ind, Industry; Inst, institutional; ND, none designated; UAD, upper aerodigestive; GI/GU, gastrointestinal/genitourinary; Heme, hematologic.

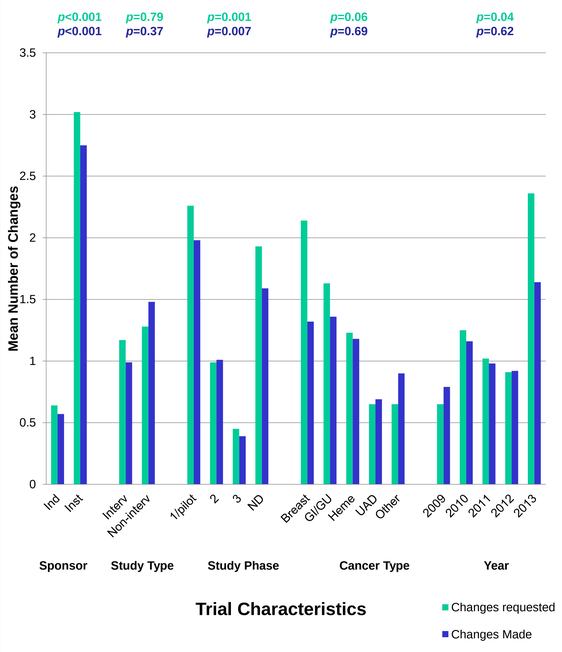

Table 2. Comparison of changes requested and made for institutional/investigator-initiated and industrial/commercial trials. Protocol-related points were categorized as study design (which included issues related to blinding, inclusion of placebo, randomization, stratification, selection of treatment arms, assessments, monitoring, and statistical analysis plan), intervention (which generally referred to treatment dose and/or schedule), population (inclusion/exclusion criteria), rationale (which included requests to obtain or clarify preclinical and other evidence used to support study design). The non-protocol-related group included points related to the consent form or the PRMC submission form.

	Trial Type (total 226 protocols)				
	Investigator Initiated Trials (N=52)		Industry Sponsored Trials (N=174)		
Type of Changes	Change requested	Change made	Change requested	Change made	p-value
Protocol	80	80	52	29	0.037
Non-Protocol	77	63	61	71	0.15
Total	157	143	113	100	

METHODS

- All clinical research at UT Southwestern involving cancer patients are reviewed by the UT Southwestern Protocol Review and Monitoring Committee (PRMC).
- We collected the following documents for each study that underwent full PRMC review from January 1, 2009, through June 30, 2013: PRMC submission form, study protocol and consent form, reviewer evaluations, PRMC decision letter, principal investigator response letter, and any revised documents.
- For each study, we recorded the following characteristics: year, disease under study, phase and type (interventional/non-interventional), sponsor type (institutional/industrial).
- From the PRMC decision letter, we recorded all protocol changes and clarifications requested. These were broadly grouped as protocol-related or non-protocol-related.
- All data collection was performed by a single investigator (N.N.). Ten percent of studies were randomly selected for data review by an experienced clinical investigator and long-term PRMC member (D.E.G.).
- We analyzed the association between trial characteristics and PRMC protocol modifications using Chi-square testing, Fisher's exact testing, and logistic regression.

SUMMARY and CONCLUSIONS

- A total of 226 studies were included in our analysis. Majority of the studies were interventional (82%) and were sponsored by industries (77%). **Table 1**
- Initial and final PRMC decisions differed significantly according to study sponsor, with more initial approvals (48% versus 11%; *P*<.001) and final approvals (97% versus 90%; *P*=0.05) for industry-sponsored than for institutional trials. **Figure 1**
- For 149 studies, no changes were requested by the PRMC. The maximum number of requested changes was 17. The requested and made changes differed significantly according to study sponsor , with more requested (3.02 versus 0.64; *P*<.001) and made (2.75 versus 0.57; P<0.001) changes for institutional trials than industry sponsored trials. **Figure 2**
- Changes made sometimes exceed requested could be do to new study team idea in the process of resubmission, in response to clarification, or one requested change results in more than one change made.
- Of the 270 PRMC requested changes,132 (49%) were protocol-related (mean 0.58 per study); 138 (51%) were non-protocol-related (mean 0.61 per study). **Table 2**
- To our knowledge, this is the first study to evaluate the impact of NCI-mandated scientific protocol review in cancer clinical trial development. While this process appears to have a substantial impact on investigator-initiated trial protocols, effect on industry-sponsored trials is less clear.

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