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Editorial Open Access

Impediments to the Conduct of Clinical Research in our Current System and Suggestions-Improvements

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Introduction

While the costly and lengthy gestation period for development of a new agent for human use in the United States has been well chronicled over the years, little progress has been made in breaking down barriers to success. This editorial will focus on ten main barriers faced by clinical researchers on a routine basis and suggestions for systematic changes to allow a safe, more efficient cancer clinical research structure to thrive in the current environment.

Insurance coverage

Currently, most patients have a clause restricting insurance coverage for early phase clinical trials. Some, after laborious appeals, have further clauses allowing research only for those 'without other options and death within 6 months' to enter studies. Further, there is a disproportionate impact on accrual to those with less supportive insurance plans, often affecting those in ethnic and/or racial minority groups to a greater degree and limiting the diversity of accrual on current clinical studies. This lack of national commitment to improved outcomes through clinical research is one of the clearest examples of how we are failing those in need. We all point to European examples of national databases and success, bemoaning our shortcomings, but we have yet to address this issue with a national measure. I am not aware of any good data in cancer care that 'study directed' therapy results in increased cost for the insurer (provided standard of care staging and follow up is followed as is usual). Given there are usually other chemotherapeutic options available, but with little data to support enthusiastic usage, when denied coverage for a clinical study we do not cease therapy but often embark on a series of palliative chemotherapies utilizing inpatient and outpatient resources, in conjunction with supportive care, etc. Alternatively, currently many sites don't inform insurance carriers of a patient on a protocol and as there are usually no 'research' charges sent to insurance the insurer may not learn of it at all! In discussions with colleagues, it appears this 'don't ask- don't tell' approach is commonplace at centers throughout the country. At times, when this is later discovered and the center is denied payment, patients /surviving families are later tasked with a large bill for care rendered subsequent to a study, whether it be SOC or not. This is not sustainable or a healthy way to treat patients.

Suggestions: Require that all studies allowed to proceed approved by the FDA, or sponsored by the NCI (i.e., all at designated comprehensive cancer centers or part of National Cooperative Groups for instance) be required to have standard of care tests (normal blood tests, antibiotics, blood transfusions, patient care) supported by the insurance carrier. If this is felt to be too broad, one could highlight that any study with at least 1 efficacy parameter as a primary objective be supported, however this leaves the important first in human/ phase 1 studies out of the loop. If these cannot be included in a larger agreement, one might consider that as part of the cooperative group or NCI designation some commitment by the centers be made to a certain number of phase 1 studies (or financial support) and certain annual accrual. This would require acceptance from the medical centers truly dedicated to progress, the payback being for grant support such as in fellowship grants, UO1s, SPOREs, PO1s - these efforts would be included in review and scoring much like tumor banking, institutional investment into career development, etc is required now. Further, with insurance coverage assured for the above studies, medical centers offering studies will have increased usage as patients remain there for treatment rather than returning home for 'off protocol' and 'off label' therapy. Some of this increased revenue stream should be expected to flow back to the clinical research enterprise and be used for funding this early phase research effort.

Deliverable: Enhanced and rapid accrual to most studies with a more diverse group of study subjects enrolled.

Potential subject identification

In choosing sights to run studies, currently, each center use a partial salaried employee to fill out duplicative feasibility questionnaires, submit for review, and hear back for things we've already discussed with companies. In addition, once a study is open to enrollment, a significant amount of time is wasted at the research sights filling out 'screening logs' individualized for each study.

Suggestion: The NIH could establish a 'national clearing house' database for these questionnaires with diseases treated, numbers/ yr (already reported anyways by cancer centers); study personnel available, computer capabilities, lab capabilities, etc. all updated annually and uploaded to the database once per each site; Contract research organizations and others could search the database for sights of interest and contact them. The infrastructure to do this is already available electronically.

In terms of patient screening, as each study is now listed in the national database (such as clinicaltrials.gov), it would save a great deal of staff time to have one screening log that allows patient input once, then simply 'clicking the box' for the studies open at that sight that the patient was screened for.

Deliverable: Immediate access to institution specific data to help target the study to the sights most likely to help in success. In fact, in coordination with suggestions below, for those utilizing this national clearing house information database', the confidentiality agreements could already be in place as well. The universal screening log would provide a simplified patient management at the sights and allow for national comparisons for study activity.

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Startup activities

As part of the national efficiency effort, we should force those that par-take of the cost and time savings above to stop 'no value- added' activities that cost sights time and money. The duplicative and time consuming sight 'pre-qualification meetings' and on sight repeated 'study start up meetings' do not have a value added. Each site that inputs data to the national clearing house will be part of an accepted national cooperative group (main or affiliate) and as such we need to invest properly in the national cooperative group auditing and monitoring efforts for these sights to be accepted as adequate partners. For those few others interested, but not part of some national research group, this national effort could offer a 'site team' to visit and qualify those sites for membership in this national effort, though also require that for continued acceptance they join one of the accepted national research groups as an institutional commitment to this national cause. Similarly- site 'pre-qual visits' and 'site start ups' and 'tours' are wasteful of time and money and add about a month to enrollment starting, just while we wait for the coordination and conduct of these visits. The details of these availabilities can be rolled into the function of the cooperative group site visits/audits.

Suggestions: Eliminate prequel visits; consider study startups as online tutorials; these do not have to wait until the final contract is signed.

Deliverable: Rapid approval for a site to perform a study and initiate accrual.

Budgeting

Budgeting is a bottle-neck for many. There are variable overhead costs and variable fee structures. These vary widely around the country, between large academic centers versus community centers.

Suggestion-implementation: We need to develop a review board composed of cooperative group, NCI, insurers, and pharmaceutical leaders to establish a standardized budget template for start-up costs and protocol conduct. Standard of care items will be determined by this team and be put in place for insurers to cover but all other costs identified by this group will be covered by the study and be uniform for all centers running the studies. The lists of standard of care items could be chosen based on accepted group standards such as the cooperative groups or NCCN guidelines.

This standardized budgeting could allow a smoother, rapid contracting process as well. For instance, we might consider budget simplification with only a 3 tier pricing of easy/medium/hard for studies, as determined by the central team that reviews and approves studies at the FDA now. Recommendations from outside sources considering, correlative analyses, study phase, number of cycles, inpatient or outpatient, infusion times, data management needs, nursing support, pharmacy dispensing, would be taken into account.

As a requirement for funding in the NCI centers or Cooperative groups, acceptance of these templates could be enforced by centers that choose to open the particular study, as the centers would have had a say in the template creation already. While contentious, it isn't all that different from other requirements we have if we want to compete for PO1s or SPOREs in terms of having compliant infrastructures and institutional support. Accepting a template budget is likely the toughest pill for our university teams to swallow.

Deliverable: Rapid completion of the budgeting process, allowing completion in parallel with study review. This allows rapid initiation of accrual as well. For many sites, this is the single most important thing to fix to allow timely 'study start up'.

Contracting process

Confidentiality agreements and subsequent contracting for each study remains duplicative and variable in requirements between companies and even within the same company or university but for different studies. Attempts have been made by some major medical centers to agree upon a 'template' and though well intentioned, these templates did not adequately account for variable restrictions placed on different companies and different research institutions. One example is some institutions have buildings constructed in part with tax free municipal bonds. This public type funding those sites cannot agree to certain publication and data restrictions. The START clauses are helpful, but unless the stakeholders are 'required' to use a standard, the timing is not likely to further improve.

Suggestions: A national effort, led by the stakeholders must meet and agree to standardized CDAs and contracts. The NCI can use the Cooperative group funding or NCI designation status and potential access to studies via the national database above as the 'stick' to assure Universities accept these standardized templates. Universities and companies with the privilege of access to the national database above for subject screening, feasibility assessments, and template budgeting would be bound by the annual CDA the researcher/university would submit for this process, minimizing regular duplication of effort. If accepting these national standardized agreements, start-up fees as an impetus for their buy-in as well. Most of this work could be done in conference calls to set the framework, and then a meeting of those parties interested could be held to finalize and agree to the final documents. As 'master's' are in place already for so many 'big pharma' companies, I suspect these meetings could start with those templates and if the parties are truly committed it could be completed within a year's time with this deliverable made important by the NCI in consideration for the coop group and cancer center funding discussions.

Deliverable: With standardization and once annual updates, start up costs will significantly drop.

IRB reviews

Current review times for major centers with an NCI designation are too long. The dictum for multiple required levels of review to be compliant with the cancer center's designation is unclear. How much is needed vs what overlaps with the IRB? What is truly 'value added' given that most of these studies come already having been through the FDA and with little ability for our centers to meaningfully alter them? When is the best time to have patient advocates involved? We need a clearer understanding of what the regulatory goals are and what the local sites need to be held responsible for versus centralized functions in the study approval process and why. (This is separate from safe study conduct, with which of course we must remain vigilant).

Suggestions: Allow studies that are through the FDA approval process to have 'expedited or exempt local IRB review' as well as expedited cancer center review. Allow studies through the Cooperative groups that are approved centrally to have 'exempt' review status, not just expedited. This saves time as well as annual local reporting costs. In addition, it allow centers to more easily adopt central IRB approval processes whereby again the trial would be exempt from local IRB oversight and reporting. Companies using this central function could do this as they submit to local sites for review and thus cut the review times dramatically. Depending on local function vs. the central IRBs,

sites could choose if they want to allow central approval for their studies as adequate.

Deliverables: Rapid 'IRB' approvals could occur within 4 weeks of delivery to a major medical center. Study start up timing will also decrease when the budgeting, feasibility, and contracting pieces are coordinated as suggested. This leads to less effort and money spent on these efforts, rapid study start up, and rapid initiation of accrual.

National electronic database for case report forms

We have discussed this issue for over two decades, though we still haven't put them into practice in our clinical research community on a broad scale. The common data elements, CA Trials, etc. need to be a reality to assist in timely completion of our data.

Suggestion: One agreed upon system for data entry would allow data management to focus on getting the data correct and not on learning a new system for each study; Further, it would be particularly helpful with 1 system if there were tie-ins to automatically download pathology, radiology, and lab results from centers involved.

Deliverable: Rapid primary data submission for review, quality assurrance, and publication is crucial. Further, it allows the continuous learning loop / data mining sought with the clintrials.gov and others to be a more valid approach than is currently a reality.

Safety reporting

Currently, we are responsible for submitting to our IRB of record every SAE and later, in summary, all AEs from worldwide use of any agent currently on an active study. These are even being reported years after study enrollment closure (when open only for long term survival follow up etc).

Suggestion: Create as part of the national database a central SAE electronic report (now available for many already). Centers with an active study related to this agent will be part of the national database already and thus the information once loaded 1 time to the FDA could be disseminated to each site IRB the SAE and determination of any action (again the contact info would be part of the annual institutional data upload to which we all agree) with the appropriate protocols highlighted in the dispersement. Annual reporting can be done centrally via this mechanism as well.

Deliverable: Saving for each center not repeating what is already collated and reviewed at the national level will ensure accurate reporting in a less costly manner by not duplicating it at every sight running the study.

Clintrials.gov reporting

Listing all studies by disease type and major inclusion with contact information has been a wonderful advance that many patients and practitioners benefit from. The unfortunate current reality is that the study closure reporting aspect is meaningless. The data points are often not accurate or interpretable, the lack of common definitions means many times reports are not interpretable. This is intended as a searchable database for all illnesses with available data. As constructed, there is significant risk of the queries being errant in nearly every conceivable way. As data points do not have a Q/A audit associated with them or across study validity in definition, the chance for someone to believe what they read and skewing public and the scientific community perception and misdirecting ongoing clinical research is enormous.

Suggestion: This reporting feature should be part of a more structured effort to do it properly, possibly linked to the national database effort noted above.

Deliverable: Real time, valid, and therefore interpretable date from the most current studies will help patients and practitioners decide on the best interventions for each individual patient circumstance.

Summary

In summary, this is an amazing time to be involved in health care with the privilege of working with patients in the area of clinical research. However, barriers concerning costs, time-lines, regulations, and lack of insurer or institutional support hamper progress and enthusiasm for the future. To the degree we believe that health care is best advanced through clinical research, whatever system emerges over the next 5 years for health care delivery needs to address our shortcomings in this area.