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Editorial

How to Build a Successful Phase I Clinical Trials Unit: Lessons Based on the MD Anderson Cancer Center Experience

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In 2004, I (Razelle Kurzrock) was charged with founding a phase I unit at MD Anderson Cancer Center. MD Anderson Cancer Center is routinely ranked as the number 1 cancer center in the nation, but it lacked a phase I unit. The head of medicine—Waun Ki Hong, MD—had only one directive: it must be "the best phase I unit in the world." At that time, I had broad experience in clinical trials, and had spent parts of my career doing both malignant hematology and solid tumors, so that perhaps qualified me as a choice to lead, because phase I trials often include an expansive array of solid cancers and lymphomas.

The phase I unit was enormously successful and became the Department of Investigational Cancer Therapeutics in 2007, and I was asked to be the department chair. Within 5 years, it was one of the largest units of its type in the world and, by the end of 2012, when I was recruited to the University of California, the department was enrolling more than 1200 patients on therapeutic trials each year.

In the past decade, under new leadership, including David Hong (co-author) who was one of the first faculty recruits to the department and currently serves as department vice chair, and the new chair Funda Meric-Bernstam, the phase I unit has continued to flourish and has

sustained its position at the forefront of development of many new drugs and their Food and Drug Administration (FDA) approvals; the operational and scientific structures have shown strength and durability.

There are several aspects, some counterintuitive, that made this phase I department one of the most successful of its type in the world, both in number of patients enrolled and in its ability to help patients and also to affect development of new drugs for lethal cancers. This commentary outlines our view on the ways to build a successful phase I unit (Table 1).

FIRST PRINCIPLES: ALWAYS DO WHAT IS BEST FOR THE PATIENT

It is important to have a guidepost for all decisions. For the phase I unit and for us, that guidepost was always to do what is best for the patient. This should be obvious but is often not followed. In making small daily decisions, and big directional decisions, often the decisions are based on what is best for staff, or for administration, or for leaders, or for sponsors. However, the purpose of clinical trials is (or should be) to find new treatments that improve the lives of patients with cancer. Therefore, for each fork in the road, the question of which direction would be best for patients should be asked, and that direction followed.

UNWAVERING SUPPORT FROM LEADERSHIP

Building a new unit requires unwavering support from leadership. This support includes both guarantees of financial backing as well as all other types of support. MD Anderson leadership provided strong support. As an example, in the first 2 years from the time the unit was founded, when growth in staff and faculty occurred at a breathtaking rate, I went to leadership (specifically Waun Ki Hong, MD; head of cancer medicine at the time) and expressed concerns that I was spending money quickly, and that although I felt we would be financially solid at some point, I could not be sure. The answer was firm: "you have our guarantee to cover any financial needs." This guarantee freed us to build in the way that was best for the unit and for patients. It is only in retrospect that it is possible to realize how special leadership was—because the guarantee was a verbal one that no one had witnessed, and it never even occurred to me to ask for the financial guarantee in writing. I was absolutely confident that leadership would be true to its word, and that gave me the confidence and security to build. (In the end, our financial status always remained immensely favorable, but without leadership's guarantee of support, and the mutual trust that existed, the unit could not have grown in the stunning way it did during the early years).

Importantly, backing from leadership went all the way to the top of the institution, including the visionary president at that time—John Mendelsohn, MD, and the Vice President for Clinical Research Maurie Markman, MD, both of whom worked with us continuously to ensure the success of the department.

EXPLOIT THE BEST SCIENCE

In 2004, when the MD Anderson Cancer Center phase I unit was established, the human genome had just been sequenced, at a cost of approximately $13 billion per genome.[1] Furthermore, at the time, phase I studies were considered to have the objective of finding toxicity—whether or not phase I studies could be therapeutic was still considered a matter of debate.

It quickly became apparent that the newly developed targeted drugs required a target, and therefore we instituted hot spot genomic testing for approximately 12 genes in about 2007, as well as a master protocol (the first version of Profile-Related Evidence Determining Individualized Cancer Therapy [PREDICT] as well as IMPACT), so that patients could be matched to drugs based on the biomarkers in their tumor, regardless of whether or not that was called for in the clinical trial itself. When next generation sequencing (NGS) became clinical grade (and affordable) in 2012, we started performing such sequencing on all patients. In addition, we activated the first tissue-agnostic clinical trial (to our knowledge), using the mammalian target of rapamycin (mTOR) inhibitor temsirolimus for patients with PI3k/Akt/mTOR pathway aberrations.

The results of such testing and a master protocol to match patients with drugs showed that, even within the phase I setting of treating patients with highly refractory cancers, patients whose tumors were properly matched to the cognate drug did much better.[2,3] Today, biomarker testing, to include NGS plus transcriptomics, immunomics, and more, is widely available and should be foundational for all patients in a phase I unit (and, in our opinion, for all patients with cancer).

OPERATIONAL PROCESSES REQUIRED FOR ACTIVATION TIMELINE OPTIMIZATION

Quality Without Speed is Not Quality

A rate-limiting step for drug development is site trial activation, especially for first-in-human studies. Three to 6 months can elapse between investigational new drug (IND) approval by the FDA and the entry of a first patient. In some academic institutions, the timeline for clinical trial activation exceeds 1 to 2 years.[4,5] For both industry and academia as well as clinical trial sites, processes converge on approval of an IND by the FDA. In general, a reasonable goal should be activation within 100 days from protocol receipt/completion. With planning, clinical site activation should be able to occur within days of IND approval.

Table 1. Building a successful phase I unit

Principles	Comment
First Principles	
Always do what is best for the patient	
Guaranteed support, including financial, from leadership	
Exploit the best science	Master protocols for the unit Reflex NGS, transcriptomics, immunomics, etc.[1, 2, 3]
Operational Processes Required for Activation Timeline Optimization: Goal is 100 Days from Protocol Receipt Completion[4–11]	
Process trial approval steps *in parallel* rather than in series (otherwise known as eliminating "we won't do this until you do that")	Eliminate "we won't do this until you do that."[6]
Limit the number of committees overseeing the protocol and use efficient *central* internal review board (IRB)	Avoid redundant reviews, such as *institutional* IRB review even in the presence of *central* IRB review.
Team meetings: weekly with PI and administrative/regulatory staff	Team meetings • Activation timeline meetings (weekly meetings reviewing each protocol to ensure that bottlenecks are quickly addressed).
Operational Processes for Accrual Optimization	
Need for tissue-agnostic specialists and units/departments	Early-phase trials often cross disease boundaries.
Need for reflex NGS and other omic testing on all patients	Many trials are now biomarker based and diagnostic NGS screening is crucial.
Ensure that there are adequate numbers of overlapping protocols (counter to conventional wisdom)	Although conventional wisdom posits that overlapping protocols negatively impact accrual, robust supporting studies for this assumption have not been reported, to our knowledge. Our experience suggests that, with the numerous exclusion criteria of each trial and the limited openings, competing trials are necessary to increase the chance of eligibility of patients.
Prescreen clinic patients and create a patient-centered service.	Consistent with all operational decisions being made to first benefit patients, coordinators prescreen patients the day before their clinic visit. Coordinators wait in clinic for patients—patients should not wait for coordinators to be called.
Team meetings: weekly protocol review meetings with PI and coordinators	Team meetings • Protocol review including accrual, responses, toxicity, deviations, amendments, etc., weekly.
Operational Processes for Best Practices	
Align responsibility and authority - institute physician/PI-led research teams	The FDA clearly indicates that the PI is responsible for clinical trials; hence, the PI must be the team leader.
People, people, people	Because early-phase studies and the patients they serve are complex, faculty and staff should be dedicated to the early-phase unit and not doing phase I clinical trials along with another focus. Phase I should not be a "side hobby."
Ensure regular meetings to foster accountability and follow-up	Team meetings (see also above) • Activation timeline meetings • weekly (also see above under activation timeline optimization) • Administrative/regulatory/financial meetings weekly • Protocol review including accrual, responses, toxicity, deviations, amendments, and so forth weekly (also see above under accrual optimization) Departmental meetings • Meetings between faculty and chair monthly • Grand rounds that include discussing scientific topics of interest and presentation of all new protocols monthly, as well as review of exceptional responses and important toxicities • Molecular tumor board/treatment planning for patients weekly (with additional electronic just-in-time molecular tumor board that can be activated by email within 24 hours for adjudication of patients who cannot wait Response and toxicity corner review weekly
Education	Must be an iterative process for the lifetime of faculty/staff employment in the unit with scheduled education on regulatory issues, as well as scientific issues, and automatic addition of modules if deficits are noted.

FDA: Food and Drug Administration; NGS: next generation sequencing; PI: principal investigator.

Project Zero Delay Demonstrates the Importance of Parallel Processing and Eliminating "We Won't Do This Until You Do That"

Project zero delay was a demonstration project at MD Anderson Cancer Center, with a first-in-human study activated and the first patient identified/enrolled 46 days from completion of the final study protocol and approximately 48 hours after FDA IND approval, while meeting all clinical good practice guidelines.[6] Parallel processing of trial approval processes was critical. As mentioned previously, support of leadership is crucial, and in this case the project was conceived together with and supported by the vice president for translational research—Dr Robert Bast.

Site timelines are driven by multiple processes including, but not limited to, disease team approval, scientific review, institutional review board, budget and contracting, feasibility review, determining which procedures are standard of care versus research, and building order sets.[7] For both industry and academia as well as clinical trial sites, processes converge on approval of an IND by the FDA.

In the context of a strategic alliance between MD Anderson Cancer Center and a major pharmaceutical company, a concerted effort was made to eliminate delays in initiating clinical trials. The efforts focused on multiple factors, but the most important was tackling administrative processes in parallel, rather than sequentially. Simply put, no process could be held up in the "we won't do this until you do that" rule that causes inevitable delays. All processes must proceed in parallel, and that includes applying for an IND, which should not hold up protocol processing. (In case the FDA requests changes in the protocol, those can be put through the institutional review board [IRB] as an amendment.)

Although processing protocol activation steps in series is the general modus operandi because those involved in each step of the process do not want to waste their time on a step if the protocol will not go through due to a prior step, in essence, the processing in series causes multiple bottlenecks and, ultimately, there is a much greater waste of time for all involved because the length of time to activation becomes excessive, with the protocol completing or near completing at more efficient sites, and time to activation of more than 1 year correlating with study failure to accrue.[8] Most importantly, patients with lethal diseases, for whom time is a limited commodity, risk losing the opportunity to participate in a clinical trial at the involved sites.

Limit the Number of Committees/Decision Steps Overseeing the Protocol (Reduce Regulatory Mud) and Use Efficient Central IRBs

The current regulatory burden in the activation of clinical trials is to the war on cancer what World War I mud was to trench warfare. The deep and sticky mudscape jammed rifles, trapped vehicles, and weighed down uniforms, causing the soldiers to stumble and fall. Similarly, the regulatory trial activation burden is onerous, misguided, and expensive, with little value added.[9] Once in place, it is very difficult to remove committees/steps, similar to any administrative bureaucracy (https://hbr.org/2018/11/the-end-of-bureaucracy). Currently, many protocols are put through multiple steps, in spite of FDA scrutiny and approval. Each of the steps has the well-meaning purpose of "ensuring success." However, the opposite occurs: multiple committees dilute innovation, discourage investigators from even trying, and result in regulatory gridlock.

Just a few of the routine processes for protocol activation, as mentioned earlier, include disease team approval, scientific committee review, IRB, budgeting, contracting, feasibility review, determining which procedures are standard of care versus research, site initiation visits, obtaining an IND by the FDA, and building order sets. (Building order sets has now become a large team process that often takes weeks; before the era of electronic computerized orders, an order set was initially built with the help of a PharmD specialist and took ~30 minutes, once a patient was identified; further order sets for other patients copied the template of the first order set and took just minutes to generate; hence electronic computerized systems, which were supposed to improve the process, instead hobbled it.)

It has been estimated that opening a phase III cooperative group therapeutic trial requires 769 steps, 36 approvals, and a median of approximately 2.5 years from formal concept review to study opening.[10] According to Dilts and colleagues,[10] time to activation at one group ranged from 435 to 1604 days, and time to open at one cancer center ranged from 21 to 836 days (and the current authors' experience suggests that these excessive timelines are seen at many other cancer centers as well, and that timelines on the shorter end are rare and, at many centers, nonexistent).

Solutions include strict limits on the number of committees and steps overseeing a protocol, as well as parallel processing of all steps (as mentioned previously), and, importantly, use of resources such as central IRBs, which have extensive experience and often can approve studies in a few days. (For instance, the National Cancer Institute central IRB lists 1800 organizations and Advarra IRB lists 3500 organizations: https://www.ncicirb.org and https://www.advarra.com/review-services/institutional-review-board/). The central IRB also helps with the issue of re-reviewing a protocol multiple times (i.e., at each site) by providing one central review. Importantly, many institutions that permit the use of central IRBs still have their own institution's IRB sign off on the protocol; this redundancy does not add value, but does cause delays, which in turn can harm

patients with aggressive cancers who need access to clinical trials in a timely manner

Weekly Meetings Between the Physician/Principal Investigator and the Regulatory and Administrative Staff to Move the Activation Process Ahead

Weekly meetings are essential if a protocol is to be shepherded through the activation process in a timely fashion. These meetings foster accountability and ensure follow-up, and also permit bottlenecks to be addressed by the physician/principal investigator (PI) in a timely fashion. Sometimes these bottlenecks require the physician/PI to initiate direct contact with the sponsor or clinical research organization or with stakeholders in the institution.

OPERATIONAL PROCESSES FOR ACCRUAL OPTIMIZATION

There are several issues that limit accrual. It has previously been shown that time to trial activation of more than 1 year correlates with failure to accrue.[8] Similarly, time from trial activation to first participant of more than 70 days is also associated with inadequate accrual.[11] Finally, reflex NGS testing and physician expertise in immunotherapy and genomic biomarkers is needed (because tissue-agnostic basket studies are often biomarker driven).

Need for Tissue-Agnostic, Molecular-Based Specialists and Departments

Many if not most phase I trials accrue patients with different tumor types. In addition, increasingly, these trials have multiple expansion arms with numerous tumor types. Furthermore, tumor-agnostic, molecularly driven basket trials are increasingly being used because of their likelihood, when based on robust biology, of high response rates.[12,13]

One of the major challenges in conducting phase I dose-escalation and expansion trials as well as histology-independent basket trials is that most academic centers are tumor focused and, with the exception of a few major cancer centers such as MD Anderson or Memorial Sloan Kettering, establishing histology-independent divisions/departments is difficult. The difficulty lies in several issues: (1) the fact that physician specialists in organ-focused departments have significant and highly specialized expertise in their tumor, and (2) the territorial nature of many academics. Community practices may in reality be better able to handle such trials because their oncologists often see multiple tumor types. Regardless, the reality is that centers that desire robust phase I trial programs/divisions/departments/disease teams need a home for that program, and that home should include oncologists who see multiple tumor types, and also have specialized expertise in genomic and other omic biomarkers so that they can properly oversee tumor-agnostic studies.

Need for Reflex Next Generation Sequencing and Omic Testing on All Patients

This issue has already been addressed earlier (see section "Exploit the best science"). Because many newly developed drugs target alterations seen in less than 1% of patients with cancer, accrual on such early-phase or tissue-agnostic studies is simply not possible unless all patients undergo advanced omic testing for their tumors.

Ensure That There Are Adequate Numbers of Overlapping Protocols (Counter to Conventional Wisdom)

Conventional wisdom posits that overlapping protocols should be avoided because they limit accrual on each study. However, we could find no published study that provides data to support this contention. Furthermore, our experience suggests the opposite—competing clinical trials result in more robust accrual for each trial. The reasons for this are several fold. First, competing clinical trials are generally only superficially competing—with the innumerable eligible criteria for each trial, a patient not eligible for one trial may be eligible for another. Second, patients are referred to centers where they are likely to be able to enroll in a trial; if the number of trials in a particular space is limited, the chance that any individual patient will be able to enroll, based on inclusion/exclusion criteria and opening availability is small, but if there are many trials, the chances increase substantially. Third, especially in the phase I dose-escalation phase, openings are extremely limited and often competitive—so patients realistically only have a chance to enroll on a specific type of trial that matches their tumor portfolio if several trials are simultaneously active.

Prescreen Clinic Patients and Create a Patient-Centered Service

To ensure accrual, a process needs to be set up to prescreen clinic patients for eligibility. The most important part of the process is *putting the patient at the center.* Any process that involves a physician who is seeing the patient calling a coordinator to screen a patient cannot be functional, as this means having the patient hanging on without a plan in clinic—multiply that by multiple patients and there is a clinic traffic jam. Therefore, the only workable process is to have coordinators prescreen clinic patients, preferably the day before. Any new patient, and any patient with scans showing progression, or without scans, should be prescreened. Patients with recent scans showing response should not be prescreened. A list of possible protocols with openings for which the patients in clinic are eligible should be prepared for the physician and be ready before clinic in the

morning. If a coordinator has a patient who is eligible for a protocol, that coordinator should be in clinic waiting for the patient (rather than have the coordinator called after the patient is seen, so that the patient waits for the coordinator).

There are now multiple computerized programs that can also prescreen clinic patients. Although we are confident that they are becoming usable for phase II studies, such as tissue-agnostic therapies that might be given to patients with rare alterations in an early-phase unit, they are not (yet) well adapted to phase I dose-escalation studies, wherein openings for study are limited and competitive with multiple sites and can change minute by minute or hour by hour. We anticipate that in the future, computerized programs will be able to take on this task.

Weekly Protocol Review Meetings

Weekly formalized review of patients on protocol between the PI and the coordinators allows close follow-up and resolution of accrual issues, as well as optimization of type of patient recruited to the study, based on up-to-date response and toxicity information.

OPERATIONAL PROCESSES FOR BEST PRACTICES

Align Responsibility and Authority—Institute Physician/PI-Led Research Teams

The FDA is clear in its guidance regarding the responsibility for the study (https://www.fda.gov/media/77765/download)—the investigator is responsible for the conduct of the study. Excerpts from the guidance are quoted below.

"In conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, the investigator is responsible for:

- *Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations*
- *Protecting the rights, safety, and welfare of subjects under the investigator's care*
- *Controlling drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)*

Supervision of the Conduct of a Clinical Investigation

As stated above, investigators who conduct clinical investigations of drugs, including biological products, under 21 CFR Part 312, commit themselves to personally conduct or supervise the investigation. . .When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study."

Many centers use a centralized model for overseeing clinical trial staff, with physicians/PIs having little to no say in their hiring, training, and evaluation. This causes an impossible to reconcile misalignment between responsibility and authority. The physician/PI is responsible for the protocol conduct but has no authority over the staff who do the day-to-day work. Any errors are attributed to the physician/PI, even though those errors may be made by staff over whom he/she has no or very little influence.

In contrast to this centralized model, the MD Anderson early-phase department was built on a decentralized model,[7] in which each physician/PI manages their own team, including research coordinators, financial analysts, and regulatory/administrative staff. The physician/PI leader is also responsible for oversight of the finances of the team, with clinical trial revenue coming to the physician/PI, except for a relatively small "tax" (approximately 10% of revenues) taken by the department in order to provide adequate training and independent auditing (this "tax" is in addition to institutional overhead). The decentralized model allows hiring of staff who are a good fit with the individual physician leader's personality and special research interests, as well as with the other team members, and fosters camaraderie and stability. It also diminishes the "musical chairs" reallocation of coordinators that often occurs when a manager without responsibility for the trials makes decisions and assigns staff on a project-by-project basis, a situation that also does not enable a cohesive team environment. In the physician/PI-led model, each investigator decides which trials to take on, based on the scientific merits of the trial as well as the financial revenue and expenses of the team. Furthermore, the physician/PI/team leader decides whether sufficient staffing is available for new clinical trials based on their evaluation of the capacity of their research team and their current project load and also based on the income/expenses associated with their trials and whether or not their trial financial portfolio is adequate to support their team's salaries and other needs. Finally, the physician/PI is best suited to selecting trials based on their scientific merit.

People, People, People

People are the essence that make a phase I unit (and probably any unit) work. In the case of phase I units, where clinical trials are complex and patients are ill, the investment in people and their ongoing education is crucial. Neither faculty nor staff should be doing phase I as a "side hobby." Early-phase trials are complicated and critical, and require faculty and staff who have a dedicated focus on this effort. Faculty and staff should be compensated fairly for this high-level work and there should be ongoing education/training for all faculty

and staff for their lifetime in the unit to ensure that they are knowledgeable in the science, regulations, finances, and patient care aspects as appropriate (see also section "Ongoing education").

Ensure Regular Weekly Meetings to Foster Accountability and Follow-up

To ensure accountability and follow-up, there need to be at least three weekly meetings that the physician/PIs lead for their team: activation timeline meeting, administrative/regulatory meeting including with financials, and protocol review meetings that include review of accrual, toxicity, responses, and any protocol deviations.

In addition, there need to be three meetings that are departmental: faculty meeting, scientific grand rounds, and a molecular tumor board (treatment planning). Faculty meetings and scientific grand rounds can occur monthly, whereas molecular tumor board/treatment planning should occur at least weekly (with the addition of a just-in-time electronic molecular tumor board activated within 24 hours of request and closed within 72 hours, for patients who cannot wait).

During weekly activation timeline meetings, the entire team is present and the activation timeline for each protocol is reviewed. Having weekly meetings allows any bottlenecks to be addressed early. If administrative staff seem "stuck," the PI may need to intervene, speaking with the sponsor or clinical research organization staff. Simply the act of having these regular meetings helps ensure that the timeline team stays alert to activation traffic jams. During weekly administrative/financial meetings, the team's financial manager updates the physician/PI regarding the team's financial status, including revenue and expenditures for all studies. The physician/PI is thus able to make decisions about hiring additional staff and whether or not important but underfunded studies can be undertaken and subsidized. During weekly protocol meetings (should include physician/PI and team coordinators and managers), accrual, responses, toxicity, and deviations are reviewed in depth for all team protocols.

Monthly faculty meetings with the department chair permit the faculty and the chair to address cross-team concerns and strategic directions, as well as disseminate information. Monthly scientific grand rounds include presentation of all newly activated clinical trials to the entire department as well as response and toxicity of interest. Finally, weekly departmental molecular tumor boards/treatment planning meetings[14] permit the entire department to participate in planning a patient's treatment and updating relevant scientific information. Our extensive experience with molecular tumor boards indicates that the patient's physician should make the final decision about the patient's treatment, and the molecular tumor board discussion should be advisory. Furthermore, in addition to the weekly in-person/zoom molecular tumor board, a just-in-time electronic molecular tumor board should be instituted that permits immediate discussion of patients who cannot wait for the weekly molecular tumor board.

Ongoing Education

Formalized educational modules for regulatory compliance, as well as regarding the emerging science, and discussion of response and toxicity on protocols, is crucial. Education must be an iterative process, and all members of the phase I unit should be expected to attend the educational seminars throughout their employment lifetime to ensure keeping up-to-date in this fast-moving field. Furthermore, not all educational modules are available and we found it was necessary to create many modules in the first place and also to update them whenever it became apparent that there was a knowledge gap in one or more faculty or staff.

CONCLUSIONS

Drugs entering phase I trials in oncology are now increasingly science-based and of significant potential interest to patients with lethal cancers and to the entire oncology community. Building a world-class phase I unit is only possible if first principles are followed. Most important is putting the patient first in decision making, following the best science, and strong support from institutional leadership. Operational processes for best practices include aligning responsibility and authority (and hence instituting physician/PI-led teams because the FDA is clear that the PI is responsible for the protocol) and ensuring regular operational meetings between physician/PI and their team staff to foster accountability and team cohesion. Timelines to opening studies at many institutions are excessive and can often exceed 1 year. Frequently, these excessive timelines are due to multiple administrative (bureaucratic) processes; most of these processes do not add value and, even if they did, they cannot counterbalance the fact that patients with lethal diseases cannot wait. The goal should be opening clinical trials within 100 days of protocol receipt/finalization, and this can be accomplished only by performing processes in parallel, rather than in series. Furthermore, use of central IRBs should be considered (without internal institutional redundant review) so that multisite studies do not unnecessarily undergo multiple IRB reviews. Accrual optimization, especially in the phase I setting, requires multiple competing protocols (contrary to conventional wisdom), which increases the likelihood that a suitable patient will be eligible for the best-matched study. In the era of gene- and immune-targeted novel drugs, reflex NGS testing should occur on these patients' tumors so they can be quickly matched with the right drugs. Because phase I studies often accrue patients with multiple histologies and because expansion cohorts and tumor-

agnostic studies are increasingly important, phase I physicians should be those who are ready to see patients across the malignancy spectrum. Furthermore, faculty and staff for an early-phase unit should be fully focused on this work, and not doing it as a "side hobby." Patients should be prescreened before clinic for protocol eligibility, and the basic principle of the patient comes first must be followed—hence coordinators should wait for the patients, not vice versa. Finally, for phase I unit leaders and team members, education must be an iterative process for their lifetime with the unit, and encompass a wide variety of topics, from regulatory compliance to emerging science, response and toxicity review, and molecular tumor boards.

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