The Insider's Insights on Investigator Initiated Trials

Investigator initiated trials (IITs), also known as investigator initiated research, sponsor-investigator studies, investigator sponsored trials or external research programs, offer benefits for investigators, patients and pharmaceutical companies, but they also carry risk. Regulatory authorities have levied substantial fines on pharmaceutical companies for irregularities around the conduct of IITs. Investigators face challenges around regulatory requirements and following Good Clinical Practice (GCP), often due to lack of experience or training.

Here we explore how the benefits of IITs can be maximised while minimising the risks. An approach based on independent ethical and scientific assessments coupled with guidance from experienced industry professionals with medical and legal expertise ensures successful project delivery.

Before you start

- Use IITs to address innovative medical concepts with potential to advance medical knowledge or address novel questions around new indications and patient populations that might otherwise go unanswered.
- Establish a robust oversight infrastructure to maintain regulatory and ethical requirements.
- Instigate a clear and detailed formal agreements between partner organisations.
- Employ an effective and impartial review committee to consider the feasibility, scientific value and cost of the proposed research.

Prepare to succeed

- Well performed IITs offer benefits for investigators, pharmaceutical companies and, most importantly, patients.
- Build a detailed budget proposal and modify as the scope changes.
- Confirm that the investigating team have appropriate training and awareness of GCP and/or local regulatory requirements.
- Agree clear remuneration schedules.
- Register the research on an appropriate public information portal and plan your study's legacy via an appropriate publication strategy.

Key Insights

Investigators frequently seek support to conduct clinical trials as part of their medical research interests from pharmaceutical companies. The support being sought can range from the supply of a particular drug/device to financial assistance.

Well performed IITs offer benefits for investigators, pharmaceutical companies and, most importantly, patients [1, 2]. Often they address innovative medical concepts with the potential to advance medical knowledge or address novel questions around new indications and patient populations that might otherwise go unanswered. Some view IITs as having scientific value beyond industry sponsored trials as they are conceived independently of commercial interests [3, 4].

However, IITs carry risks for the sponsoring pharmaceutical companies. Several have faced substantial fines following inappropriate conduct of studies they have been associated with [4, 5]. Concern over the proper conduct and oversight of IITs has diminished the industry's appetite to get involved in such initiatives which risks losing potential benefits for patients. Poor trial conduct puts companies in jeopardy of breaching regulations. Similarly, not demonstrating a robust oversight may be viewed as an unethical incentive or reward for physicians that may support the pharma company's position. They also open pharmaceutical companies to accusations of undue influence on study design, perhaps 'shaping' studies in order to fill a gap in their development programme, or to deliver favourable data.

Investigators also face risk from their involvement in IITs. A lack of experience and training in study design and conduct, awareness of GCP and/or local regulatory requirements can lead them to censure [4]. Concerns have been expressed over the impact on patients safety [6]. Failure to appreciate the principles of IIT conduct, can result in an investigator feeling 'obligated' to deliver what might be considered favourable data or impact on a study participant's safety.

Possible pitfalls that can beset industry-funded IITs include [4]:

- Concerns over supplementing the clinical development programme
- Publication and data bias
- Funding bias, rewarding early adopters and high volume prescribers
- Over compensation
- Potential for insider trading
- Physician/investigator coercion
- Double billing where a subject's insurance company and the Sponsor are billed for the same service

Proposed IIT budgets should be appropriately costed and free of any suggestion of influence [5,7].

What is an Investigator Initiated Trial?

Pharmaceutical companies (that might for example be developing a new medicine) often get involved with investigator initiated trials (IITs). Projects are normally concepts proposed by an independent investigator and may be undertaken at any stage during development. They can involve small single centre studies or large multi-centre/multi-national programs.

> *"...Investigator Initiated Trials (IITs) have become a cornerstone of collaboration between the pharmaceutical industry and independent researchers representing individuals, academic institutions, and co-operative groups."*

They are intended to address specific scientific questions and unmet clinical needs that might otherwise be outside the scope of drug a development program – often limited to research required for a new treatment or device to gain regulatory approval.

Investigations often include, but are not limited to:

- Assessing an intervention, which may be a drug, device or procedure, in a real-world setting (i.e., at the point of care)
- Testing an intervention on a novel patient population
- Testing an intervention for a different indication
- Comparing the effects of an intervention with a similar product
- Testing an intervention in combination with other therapies

Under such circumstances, the investigator is responsible for securing funding to conduct investigations. The IIT can be funded in part or wholly by the pharmaceutical company developing a novel product or intervention; however, studies can also be funded by health agencies and charities.

Clinical Trial Sponsor

The role of a sponsor in a clinical trial is to oversee the critical tasks and processes that make up the trial. A sponsor can be an organisation including government agencies, pharmaceutical companies, universities or academic institutions. Alternatively, sponsors can be a private individual. Sponsor tasks include:

- Designing the study
- Insuring investigators are qualified and have the right training
- Taking responsibility for the concept, management and reporting of the IIT
- Safety monitoring and that clinical conduct complies with Good Clinical Practice and other relevant regulations
- Trial monitoring to ensure it is conducted as documented in the protocol
- Maintaining thorough records and updating the regulatory authorities and ethics committees of any safety concerns [8]
- Ensuring the data and results are reported appropriately (published) – something often poorly achieved [8,9]

> *"...The pharmaceutical industry seeks to improve patient care through support of scientific advances in medicine. As part of this commitment, IIT programs support innovative clinical and basic science studies that address important medical and scientific questions related to compounds and therapeutic areas of mutual interest."*

Project Oversight

Collaboration among industry, government, and medicine in the pursuit of clinical research is critical to driving scientific progress, particularly as industry increasingly replaces government as the primary source of research funding. However, the compensation methodologies employed by industry, as well as other financial relationships between industry and physicians, create potential conflicts of interest that possibly jeopardize the rights and well- being of research participants as well as the integrity of research results [7].

While the landscape of clinical research has changed dramatically – the number of trials has increased, industry funds a larger proportion of research, and more research now occurs in physicians' private offices – federal policy on recruitment and enrolment, and conflicts of interest in research more generally, has not changed substantially.

Independent functioning and decision making are the primary benefit of engaging an external review committee. It ensures that applications are assessed based on the scientific merit of the proposal. A further benefit is that it is less possible for the company providing the sponsorship to 'shape' the trial, providing an additional level of impartiality. An independent committee can also follow-up on study delivery, adherence to agreed timelines and ensure the the study findings are reported appropriately.

The function of the external committee is similar to internal committees often used by larger pharmaceutical companies and aim to to ensure:

- Sound scientific rationale and value
- Trial design meets the objectives
- Patient safety
- Operational feasibility and fair market value
- Compliance with ethics and regulations

The Department of Health and Human Services in the United States (68 Fed. Reg. 23731 [May 5, 2003]) recommended that sponsor companies establish external and independent review committee to assess the suitability of IIT proposals [10].

Investigator Initiated Trial Funding

Investigators/sponsors can apply for financial support from pharmaceutical companies. Many pharmaceutical companies have established formal application processes (such as an online portal or web pages) whereby potential investigators can submit their interest. Submission usually involves providing brief details of your project concept or outline that details its aims and objectives, along with a summary of the support that is being requested. The pharmaceutical company reviews the application through a local or central internal committee that decides on whether to support the application and what level of support to offer [11]. The internal committee might respond to the applicant with comments and clarifications before making any decision. The internal review committee will determine whether the project aligns with the company's strategic objectives.

Where a case proposed by an independent researcher is considered to have strategic and scientific merit, an investigator will be expected to provide a full proposal, essentially a more detailed version of the concept, that would be expected to include an itemised budget, time line and detailed protocol.

The review committee should formally assess the proposal in terms of:

- Confirmation of scientific merit
- Research design
- Proposed budget
- Ethical considerations
- Credentials and experience of the investigator/team

The committee would be expected to document its considerations in determining whether or not to fund the research.

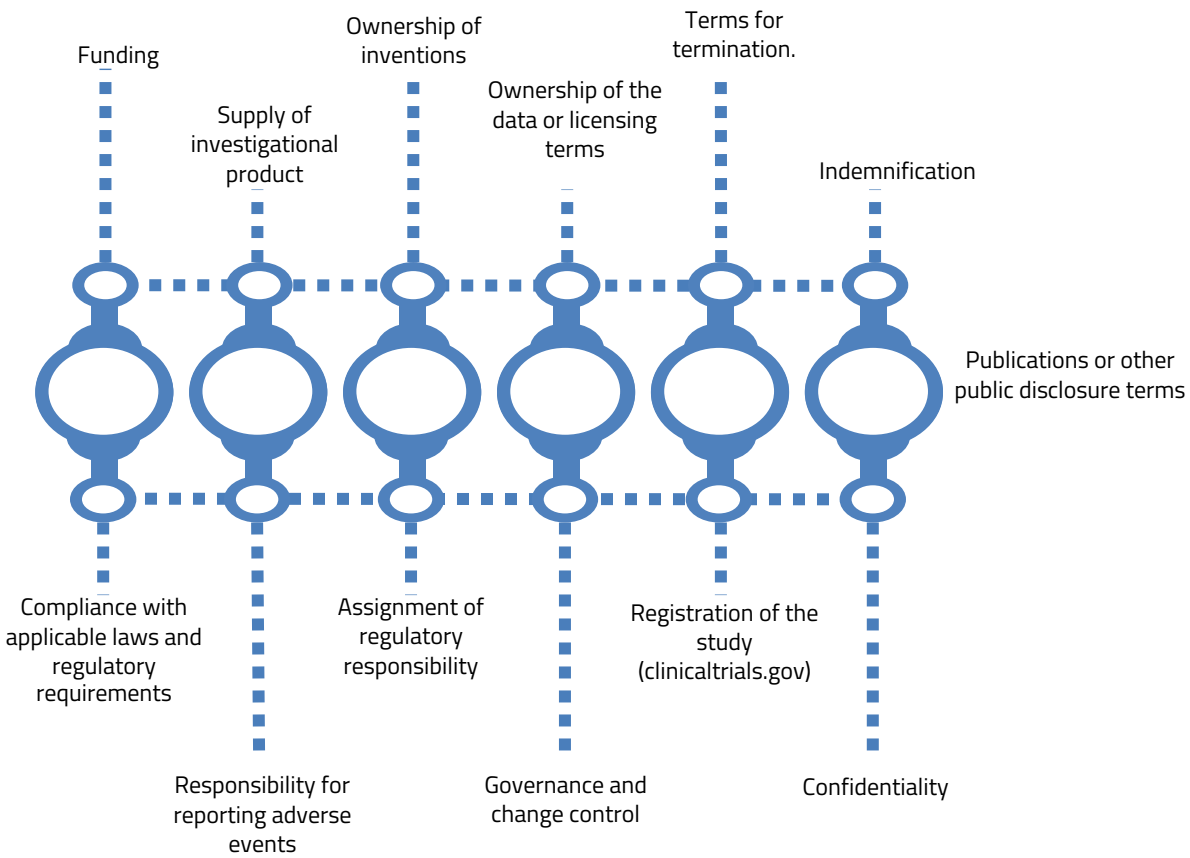
Research Agreements

It is critical that any IIT is governed by a robust agreement. Non-commercial sponsors should pay attention to the contract framework and try to improve the legal agreements with the funder, so that responsibility/liability issues are shared, with key aspects clarified (see below). To achieve this, non-commercial organisations aiming to act as a trial sponsor should invest in developing legal, administrative and management skills [10].

> *"...Many pharmaceutical companies will monitor the IIT investigators' compliance and adherence to their contractual obligations, such as the disclosure of IIT findings, agreed upon milestones, and safety information reporting. As regulatory bodies may ask for safety and efficacy findings from IITs for New Drug Applications, it is imperative that IITs be conducted with the highest standards of scientific rigor."*

This allows them to negotiate fair and meaningful contracts for other key-activities in clinical research, such as the supply of investigational products, the transfer and sharing of trials' data and samples, and the policy insurance contract(s) [11]. To help cope with this, it is suggested that the WHO/ and ICH/GCP Guidelines model contract templates or standard checklists, with clauses for "reasonable flexibility", included as annexes, are considered as starting negotiating positions with external funding agencies. The same applies to templates and guidance for negotiation with other research counterparts, e.g. insurance policies, data and material transfer agreements etc.

In the research agreement, the parties must clearly address critical components such as:

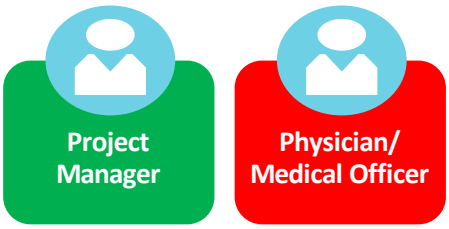


Building an Effective and Independent Committee

A committee should include a chairperson or coordinator, a project manager, an experienced medical officer, a statistician and a legal representative (see External Review Committee Considerations).

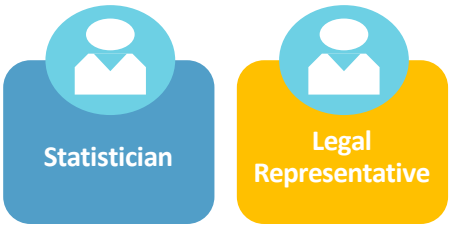
The chairperson/coordinator serves as the point of contact for both the pharmaceutical company and the investigator. Their role involves compiling the required documentation and sharing it with committee members. Reports by the committee members on their assessment of a submission should be made during the course of a specific 'hearing'. The chairperson is responsible for both setting an agenda for and chairing the meeting. Following the meeting, the Chair is also responsible for notifying both the pharmaceutical company and the investigator of the decision and providing any feedback.

The project manager considers the validity and practicality of the scientific investigation. They must have experience in the management of clinical trials in order to determine whether the proposed trial is achievable and whether the proposed budget and timelines are realistic.



The medical officer/physician uses their clinical trial experience to assess proposals for their scientific validity and to determine whether the proposed approach is suitable to address the scientific question. They are also responsible for assessing safety issues and determining whether the potential benefits out-weigh any potential risks.

The statistician's role is to evaluate the study's analysis plan and to ensure proper data reporting.



The legal representative is responsible for ensuring that any proposal meets the appropriate rules and regulations. They should have experience of working within the clinical trial landscape.

Assuming an IIT is approved, the chairperson/coordinator is responsible for ensuring that key milestones are being met and that all results are published as per GCP requirements.

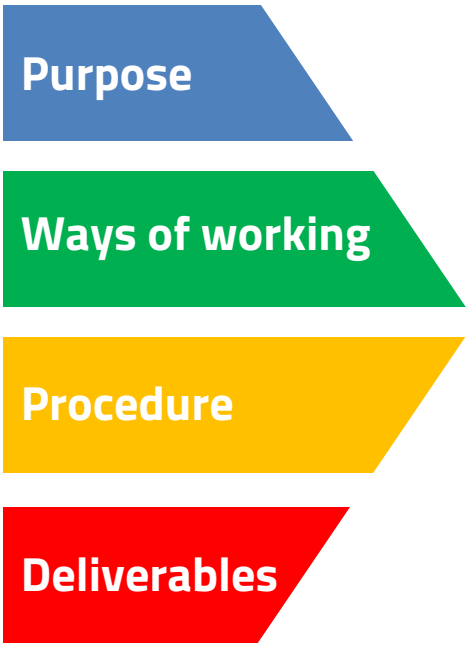
External Review Committee Considerations

- The scientific question being addressed; confirming the proposals validity and that any data generated would complement the existing scientific/medical body of evidence
- That the investigation has a robust design incorporating ethical and safety considerations
- Investigators commitment to finding dissemination in a transparent and timely fashion
- The research will be delivered independent of sponsoring company influence. Scientific discussion with the investigator is limited to aiding them to achieve their original objective
- The intellectual property contained within the proposed work will remain with the investigator
- Established sponsor company mechanisms to ensure investigation funding (either in part or in full and provide agreed support i.e., where appropriate drug or device)
- The scope of the research is well defined and understood by all participating parties
- That proposals are reviewed by an appropriate committee with the required competencies to critically review all aspects of the proposal
- Go/no go decisions are based on not just scientific merit but also budgets, feasibility and ethical considerations
- Management of the trial remains the responsibility of the investigator (and the pharmaceutical company) not the review committee
- Payment schedules are agreed by both parties and include timelines and key milestones
- The investigator agrees to timely registration of the trial and reporting of the results (as outlined by GCP). The responsibility of reporting is outlined in any final agreement
- Consultation and agreement with any partner company, including clinical research organisations, are not within the remit of the review committee

The Independent Committee Charter

Usually, companies have the interest to fund these studies as part of post-marketing research that could help them prove the efficacy and/or safety of their medication or device. Their expectations are to prove that their medication or device provides good results, that it is safe, to acquire an idea for potential new indications, or upgrade the features of the medical device. However, as the actual name says these studies should be initiated by investigators, and not solicited by companies. The companies should not be involved in any data analysis nor should it limit publication of the research if it does not speak in favour of their product/device.

An external, independent and impartial committee, such as the Niche Investigator Initiated Trials Review Committee (NIITRC), can review IIT applications free of pharmaceutical company influence and the company can use this as evidence of their IIT approval being transparent and ethical.



Purpose

To thoroughly evaluate IIT proposals by assessing the projects design, scientific validity, safety, feasibility and budget as well as compliance with ethics and local regulations.

Procedure

Independent IIT committees have regular (monthly) sessions to discuss projects and assess submissions. A hearing date for the committees consideration of a proposals is set (within approx. 2 weeks of submission). The chair/coordinator distributes the proposal and supporting materials. A decision and feedback are provided within 2 working days of the hearing.

Ways of Working

Committee decisions are established based on core member voting following group discussion. Positive outcomes require a majority vote.

Deliverables

An evaluation of the proposed IIT including the provision of a go/no go decision in a timely manner, feedback on the committees considerations and to ensure successful partnership between the pharmaceutical company and the investigator.

How do you formulate a research question?

After identifying a gap in our current knowledge, we start the research process by formulating questions. These questions typically come from problems involving diagnosis, aetiology, prognosis, and treatment or prevention of diseases during routine patient encounters in clinical practice.

They are usually derived from a complex thinking process accumulated from available knowledge and a careful analysis of the health problem by the researchers. The research questions may also arise when new diagnostic tests or new treatments become available to compare with what we already have.

How is intellectual property managed?

In broad terms, the investigator owns the intellectual property to any research that is done. In the case of IITs, most pharmaceutical companies will detail ownership of the data generated in the contract that outlines the level and degree of support. It is recommended that this is reviewed carefully by the investigator and their affiliated educational/clinical institute.

An Interview with our Chief Medical Officer

Q **Why do pharmaceutical companies fund IITs?**

A The predominant reason for funding these trials is to increase the overall usefulness of the drug or device. These studies will usually focus on an unmet need, such as using the drug for a similar but new indication or testing it in a specific population such as the elderly, people who smoke or patients with another disease in combination with the one the trial drug is treating (e.g., asthma or Alzheimer's). This ultimately has the effect of increasing the number of people who could be treated successfully with the drug.

"...investigator-led trials should collect radically simpler data than industry-sponsored trials"

The risk with internal committees

The primary problem with using internal committee(s) for approval of IITs is their lack of independence and impartiality. This exposes the pharmaceutical companies to potential accusations of approving IITs for reasons other than scientific merit [10].

Q **What are the benefits of IITs for patients?**

A The benefit to patients in general is the testing of a drug for efficacy and safety in a new population or for a new indication; therefore, making that drug available to more patients who could benefit from it. The benefit to a specific patient could be that they have access to a drug that might treat their illness which they otherwise may not have had access.

Q **How would having an independent review committee positively impact IITs and the wider scientific/medical community?**

A Having an independent review committee allows the approval process to occur without any suggestion of bias. This means the IIT will only be approved if it has a genuine benefit to the scientific/medical community and meets an unmet need. The presence of an experienced medical officer will also be able to provide feedback without shaping the study to ensure the investigator is able to achieve their aims. Ultimately, these types of investigations allow advancements in drug development which may have otherwise been overlooked, or not actively pursued by the pharmaceutical company.

Investigator-led clinical trials have particular merit in the field of oncology, offering the potential to generate much of the evidence upon which the treatment of cancer patients is decided.

And finally...

Whether a new drug is sufficiently safe and effective for clinical use takes careful review. It requires meticulous assessment of the trial design of the pivotal regulatory studies, their conduct, data and analysis. However, additional post-approval evidence on novel drugs or devices continues to provide a better understanding of the effectiveness and safety of competing interventions in 'real life'. Investigator-led clinical trials allow for the assessment of patients and settings not necessarily covered by the initial approval package, leading to potential extensions of indications and refinement of the drug usage in patient subgroups. Even for newly approved drugs, many questions of clinical interest typically remain unanswered at the time of approval, including the duration of therapy, dose or schedule modifications that may lead to improvements in benefit/risk ratios, combinations of the new drug with existing regimens, etc.

Equally, repurposing of existing drugs, whose safety and efficacy profile is well documented in other indications, is often less complicated in investigator-led trials compared to those run by pharmaceutical companies who might have a product that ceases to be financially attractive towards the end of its life-cycle. In addition, large, simple trials that address questions of major public health importance have been advocated for decades as one of the pillars of evidence-based medicine [13].

In order to maximize the benefits with conducting IITs, it is important that the information obtained is disseminated to inform healthcare decision makers and physicians on the benefits or risks associated with the experimental intervention. It is important to publish data, whether positive or negative. Making these data available for inclusion in systematic reviews and meta-analyses to ensure that the decisions made are correct – leaving out studies can lead to erroneous conclusions. Study registries and prospective study registrations can help make data available publicly and help in supporting healthcare decisions as well as further research.

FDA Guidance

The May 2015 FDA draft guidance entitled "Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators Guidance for Industry" is written to guide the individual investigators doing studies on marketed drugs or drugs with an existing IND for a different indication [14]. The FDA provides guidance on the IND submission and review process as well as makes the key point that in these IITs, the investigators must handle the responsibilities of both the Sponsor (21CFR312 Part D) and the Investigator (21CFR312.60). The draft guidance is an excellent review for investigators interested in conducting IITs. Another resource is the FDA Investigator-Initiated Investigational New Drug (IND) Applications website [15].

How can Niche help?

There is no doubting the potential benefits that can be delivered by IITs when they are conducted correctly. However, despite the pressure on clinicians to get involved in research, teaching of the skills and understanding to conduct clinical trials is still largely neglected. Inexperienced physicians and teams are often left struggling to build understanding from the relatively poor materials available in the scientific literature and more commercially orientated publications [16]. Many published reports and books that claim to instruct readers about IIT conduct are expensive and/or locked behind paywalls [17]. Equally, valued content about IITs is often padded out with the more general requirements for any normal clinical trial.

Here we have focused on the challenges at hand, providing a summary from our own experience of the key considerations for those thinking of conducting an IIT and a ready source of further reading. Don't just take our word for it – check out some of the successful projects we have completed, such as the MRC funded RASP-UK industry partnership (www.RASP-UK.org) and the Horizon 2020 MID-Frail initiative (www.midfrail-study.org). Please contact us if you would like further support bringing your planned project to fruition.

References

1. Tyndall, A. Why do we need noncommercial, investigator-initiated clinical trials? Nat Rev Rheumatol 2008;4:354–355
2. Arbit HM. Investigator-initiated research. J Clin Res Best Prac 2008;4: -6
3. Breault JL, Knafl E. Pitfalls and Safeguards in Industry-Funded Research. Ochsner J. 2020;20:104-110
4. Finger RP, et al. Basic principles, planning and implementation of non-commercial clinical trials. Ophthalmologe. 2011;108:25-32
5. Bekelman JE, et al. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA 2003;289:454–465
6. Olivieri NF. Patients' health or company profits? The commercialisation of academic research. Sci Eng Ethics 2003;9:29–41
7. Koch VG. Conflicts of Interest in Clinical Trial Recruitment & Enrollment: A Call for Increased Oversight. Center for Health & Pharmaceutical Law & Policy, Newark, NJ: 2009
8. Patwardhan S, et al. Quality and completeness of data documentation in an investigator-initiated trial versus an industry-sponsored trial. Indian J Med Ethics. 2014;11:19-24.
9. Landewé RB, et al. Can we improve the performance and reporting of investigator-initiated clinical trials? Rheumatoid arthritis as an example. Ann Rheum Dis. 2014;73:1755-60.
10. OIG Compliance Program Guidance for Pharmaceutical Manufacturers. Office of Inspector General. Federal Register/Vol. 68, No. 86/Monday, May 5: 2003
11. Ravinetto R, et al. Sponsorship in non-commercial clinical trials: definitions, challenges and the role of Good Clinical Practices guidelines. BMC Int Health Hum Rights 2015;15: 34
12. Marais D. Where there is no lawyer: Guidance for fairer contract negotiation in collaborative research partnerships. Council in Health Research for Development (COHRED) 2013. Geneva & Pietermaritzburg. Last accessed on 19/9/22 at http://www.cohred.org/wp-content/uploads/2012/04/Fair-Research-Contracting-Guidance-Booklet-e-version.pdf
13. Yusuf S, et al. Why do we need some large, simple randomized trials? Stat Med 1984;3:409–422
14. Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators Guidance for Industry. Center for Drug Evaluation and Research Center for Biologics Evaluation and Research, FDA-2015-D-1484
15. Investigator-Initiated Investigational New Drug (IND) Applications. https://www.fda.gov/drugs/investigational-new-drug-ind-application/investigator-initiated-investigational-new-drug-ind-applications
16. Review of "Guide for Investigator Initiated Trials." J Clin Res Best Prac 2011; 7: 1-4
17. Review of "Guide for Investigator Initiated Trial Management." J Clin Res Best Prac 2012; 8: 1-4

Next Steps

We created this Insider's Insight into investigator initiated trials to share a few helpful points and learnings that we have gained over the years. If you are interested we would be happy to share more of our experience with you and discuss how you can get the most out of your research.

I hope that you found our guide useful. If you would like to discuss support for any of our upcoming initiatives please contact me using the email address below:

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