Calling Your Own Shots:

*The Ins & Outs of Investigator-Initiated Trials (Studies, Research)*

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SHARe Advisory Board Member
Associate Director of Clinical Research & Professor
University of South Alabama Health
• **Goals**
  – Understand models of IIRs
  – Opportunities and challenges
  – Share personal experiences

• **Personal experiences**
  – Clinician scientists in eye/vision (JN) and obgyn (RR)
  – JN: mix of Device/Drug (regulatory), IIR, and NIH/NEI
    • Other than collaborating with CCC, I don’t do Phase 1 research

• **Discussion, not a lecture**
  – We welcome others’ experiences, input, counsel and advice
Why Investigator-Initiated Research (IIR)?

• Improves general scientific knowledge (academic)
  – Support product strategy (industry)
• Answer your own questions (rather than being handed a protocol to implement)
  – Builds your/institutional reputation and rankings
• Diversifies sponsored research portfolio
• Improves patient health/well-being
• May support new use/indication
Other Considerations…

• Industry partnerships not without caveats…
  – Conflicts of interest
  – Pressure (direct or indirect) to avoid publishing negative results
  – Perceptions…industry research “undermines academic standards”
    • Institutions working to change that (entrepreneurial initiatives)

• Most situations can be managed (institutional system/processes)
IIR Considerations

• Types…
  – IIR, IIS, IIT
    • Traditional IND/IDE
    • Non-IND/IDE drug, biologic, device
    • Non-drug, biologic, device (e.g., chart review)
    • Pre-clinical
    • Non-human

• Parties involved and roles/responsibilities
• Challenges & opportunities
• Scope/criteria
• Review and selection process
Roles/Responsibilities

• Federal and state laws/regulations
• ICH guidelines
• Institutional policies
• Granting/contracting agency policies
• Contractual agreements (confidentiality/clinical trial agreements)
  – Spell out responsibilities (publication rights, IP, data ownership)
  – Spell out realistic timelines (for study AND milestones for invoicing)
• Regulatory bodies (e.g., IRB, FDA)
  – The protocol
  – Investigator SOPs
IIRs... What’s Being Funded?

- Association of Clinical Research Professionals (ACRP)
- 2015 Survey on Investigator Initiated Sponsored Research (IISR)
  - Respondents: “Predominantly ISSR Program Managers”
    - Products with marketing authorization approval (89%)
    - Outcomes research on patient outcomes only (68%)
    - Observational studies (66%)
    - Products with unapproved product indications (61%)
    - Investigational products requiring regulatory approval (IND/IDE) (57%)
    - In vitro studies (48%)
    - Outcomes research on pharmacoecnomics (45%)
Defining Sponsor?

Sponsor ≠ Funder

(industry funded = industry and institution/IIR sponsored)
Sponsor (Institutional) Responsibilities…

- Sponsor responsibilities (21 CFR 312.50)…
  - Select qualified investigators (trained, certified)
  - Provide investigators with resources to conduct the investigation
  - Ensure proper monitoring of the investigation
  - Ensure study is conducted in accordance with the general investigational plan
  - Maintain an effective IND (if applicable)
  - Ensure that regulatory bodies (and all participating investigators—MSS) and participants are promptly informed of significant new adverse effects or risks

Sponsor ≠ Funder
Collaborator Responsibilities

• Collaborator responsibilities…
  – Funding/financial support
  – Provision of product (drug, device)
  – Regulatory compliance
  – Some protocol development assistance

Sponsor ≠ Funder
IIR Process

• Company submission portals and review process.

• Scientific Review
  – OIG: Any remuneration from manufacturer provided to a purchaser that is expressly or impliedly related to a sale potentially implicates the anti-kickback statute.
  – To reduce risk, industry should insulate (firewall) research grants from sales and marketing influence.

REF: OIG Compliance Program Guidance for Pharma Manufacturers—68 FR 23736
ACRP 2015 Survey on Investigator Initiate Sponsored Research (IISR)

- 93% of industry respondents have formal review process
- Reviews ranged 46-90 days
- 5 Reviewer Types (median)
  - Regulatory affairs/legal
  - Clinical
  - Biostatistics
  - IISR management
  - Safety/medical affair
- >50% of respondents indicated >50% chance of funding
“Studies with scientific and medical merit developed and sponsored by an independent investigator or academic sponsor. An IIT may be a clinical or non-clinical study conducted without the participation of Novartis, for which the IIT sponsor requests Novartis to provide either funding, drug product or both.”

Requirements (feasibility) to conduct a clinical study

Below are the key requirements that will need to be fulfilled in order for Novartis and consider supporting your study. Should you have any questions on these requirements, please contact your Novartis Medical Science Liaison (MSL) or local Medical contact.

Investigator qualifications – all of the following must be met:
- Current valid license to practice medicine*
- Recent clinical research experience within the previous 3 years*
- Good clinical practice (GCP) training within the previous 3 years*
- The investigator’s curriculum vitae would be obtained to ensure that the investigator is suitably qualified and able to conduct the required evaluation and analysis.

*Only applicable for interventional studies

Study Criteria – the proposed study should be:
- For a legitimate research purpose – scientific merit, which complements the Novartis-generated research
- To better understand the risk/benefit profile of the compound
- Address an unmet medical need
- Aligned with the Novartis compound scientific/development strategy – strategic fit

Resources – the investigator must have the right infrastructure in place and capability to conduct the study proposed.

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IIT application process

An overview of the application process required for submission of a proposal is shown below.

- Investigator submits notification of interest to Novartis.
- Novartis provides study concept sheet form and qualification form if the proposal is aligned with the overall development plan of the study drug.
- Investigator completes and submits the study concept sheet and qualification forms, including proof of qualifications and high level budget.
- Novartis evaluates the study concept sheet and qualification forms.
- Novartis notifies investigator that study concept is of interest or not of interest.
- Investigator submits full protocol.
- Review by Novartis.
- Investigator notified of non-approval of protocol or approval of protocol.
- Investigator notified of approval of protocol or non-approval.
- Novartis prepares IIT agreement.
- Investigator notifies investigator's institution that agreement is ready for review.
- Investigator notifies investigator's institution of completion of regulatory requirements (e.g., local ethics approval, registry in a public database).
- Investigator.

Letter of Intent/Proof of Concept

Full Protocol/Complete Budget

Contracting/Regulatory/IRB
Overview of the IIT process

Receipt of funding/study drug

IIT budgets submitted to Novartis will be subject to a Fair Market Value (FMV) assessment against an externally benchmarked database prior to approval.

The purpose of IIT funds are only to further the scientific research and knowledge within a particular therapeutic area. IIT funds cannot be provided to just gain experience with a study drug or treatment protocol.

It is also important to note that IIT support may not be given to pay for the recipient's ordinary operating expenses (i.e. expenses of activities that the recipient is already required to perform or customarily performs) or support research that has already occurred. Following the initiation of a study, funding will be released as key milestones are achieved, in accordance with the payment schedule noted in the IIT Agreement. The mandatory key milestones will include:

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Percentage of funding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Execution of IIT Agreement, Ethics Committee (EC)/Health Authority (HA) approval and First Patient First Visit (FPPV)*</td>
<td>10</td>
</tr>
<tr>
<td>Provision of final Third Party Study Report (TPSR) to Novartis</td>
<td>10</td>
</tr>
<tr>
<td>Submission for publication or provision of publication to Novartis</td>
<td>10</td>
</tr>
</tbody>
</table>

*50% can be paid on execution of the IIT Agreement.

Please note that all other milestones will depend upon the study design and the schedule noted in the IIT Agreement and could include milestones based on recruitment.

Budget...
FMV assessment
Must be justified
Not ordinary
Milestone driven

Funding...
IRB approval
Executed CTA
Budgets—Investigator Reminders

• Budget must be representative of **FULL** study costs.
  – Startup Fees (both institutional AND your study team)
    • Protocol development
    • Regulatory/compliance filings/clinicaltrials.gov (your responsibility)
    • CRF generation
    • Training/study initiation
  – Personnel
    • Clinical, administrative, coordination, data/statistical
  – Procedures
  – Supplies
  – Recruitment (traditional, media, digital)
  – Monitoring/audits/closeout visits
  – Data storage
  – Facilities and administration (indirect) costs
### Key responsibilities of Novartis and the Investigator

<table>
<thead>
<tr>
<th>Responsibilities</th>
<th>Novartis</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of the Research Protocol</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Review of the Research Protocol</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Distribution of updated, approved product information</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Submission of dossier to IRB/EC at study start and annual renewal</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Submission of dossier to local HA</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Registry of IT in a public database, such as <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a></td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Implementation and monitoring of clinical research (including data monitoring)</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Contracting with third-party vendors (clinical research organizations, medical writing, Pharmacokinetic (PK) or other analyses, patient insurance, statistical, courier, etc.) and the management and oversight of any other participating sites or contractors</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Conduction of research (patient inclusion, exams conduction, etc.)</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Ensure that the IRB/EC/local HA approved protocol is adequately followed (in accordance with GCP, applicable guidelines and local and international standards)</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Submission of protocol amendments</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Review of protocol amendments</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Maintaining clinical records of the study and assurance of the veracity of collected data and other attributions related to GCP</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Reporting of safety data to the manufacturer of the study drug as required, based on the study type</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Perform AE reconciliation, as required based on study type</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Reporting of safety data to HAs, as appropriate</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Analysis of study data, prepare interim and final study reports and forward them to Novartis</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Submit draft publications to Novartis prior to submission to a scientific congress or journal</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Independently publish the clinical trial results</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Report study results to HAs, as required according to local regulations</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
MULTISITE IIR STUDIES
14-member **REGIONAL** consortium launched by the CCTS to build on the strength of our Partner Network to develop transformational research network in multisite studies for the Deep South.

https://www.uab.edu/ccts/partnerships/share
**SHARE and/or TIN Opportunities**

<table>
<thead>
<tr>
<th>Multi-Site Studies Considered</th>
<th>Observation &amp; Experimental Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic diversity</td>
<td>Clinical Trials</td>
</tr>
<tr>
<td>Demographic Variety</td>
<td>Natural History &amp; Cohort Studies</td>
</tr>
<tr>
<td>Large Sample Sizes</td>
<td>Cases / Controls</td>
</tr>
<tr>
<td>Rare Disease</td>
<td>Sample Collection Protocols</td>
</tr>
<tr>
<td>Source of Funding</td>
<td>Federal, Industry, Foundation</td>
</tr>
</tbody>
</table>
SHARE and TIN: Resources Available

- Single IRB (SMART) assistance
- Common contracting
- Protocol Assistance: Methodology/design/biostats (BERD)
- PI and Resource Identification
- Recruitment/enrollment/retention (traditional and electronic)
  - Community engagement studio
How does SHARE work?

- Fact Sheet about project is submitted to POC (FH) by PI’s office
- Circulated to and considered by Partners
- Interested Partners propose a site PI to SHARE administrator who connects sites with Lead PI team
- SHARE can assist with:
  - Single IRB through SMART IRB
    - Each institution has its’ own processes and procedures for accepting responsibility or ceding review
  - Contract Templates
  - Staff Training
Using the Trial Innovation Network to Plan Your Trial

HUB POC/TIN Liaison Team

1. **Submit Study Proposal**
   - Apply to the TIN now for a personalized assessment of what the Network can offer.

2. **Contact Investigator**
   - Assigned TIC/RIC contacts the investigator to assess priorities.

3. **Conduct Consultation**
   - In collaboration with the investigator, the assigned TIC/RIC conducts the initial consultation.

4. **Pre-Application Project**
   - Investigators may wish to have one of the TICs act as the data coordination center / clinical coordinating center and utilize all TIN resources for their study. In this situation, the TIC will be included in the grant application to an individual NIH Institute or Center (IC).

5. **Complete Comprehensive Consultation**

6. **Approve Discrete Resources**
   - Resource requests will be prioritized based on resource availability and funding status.

7. **Funded Project**

Questions? Contact your Frannie Horn at (205) - 934-3980. Learn more at trialinnovationnetwork.org

Illustrated timeline is approximate and may be subject to change based on the responsiveness and needs of the research team and current number of active proposals.

- **Hear from us within 5 business days.**
- **~5 days**
- **~30 days**
- **~180 days**
The key to successfully engage the SHARe and TIN?

Early Identification
of proposals, applications, project ideas!

Contact Frannie Horn at the CCTS

fhorn@uab.edu – 934-3980

https://www.trialinnovationnetwork.org

https://www.uab.edu/ccts/partnerships/share
The IDEA!

Well formulated idea that improves knowledge in a industry category AND moves your science forward...

Create WIN-WINs

Be entrepreneurial

Know the business (what does industry need), MSL

Leverage your lab’s strengths
IIRs: Leveraging Strengths

- Principal lacrimal gland
- Meibomian glands
- Conjunctiva: Transparent membrane which lines the inside of the eyelids
- Free margin of the eyelids: Where are the eyelashes
- Lacrimal film
- Cornea
- Lacrimal Gland
- Meibomian Glands
- Mucus Layer
- Aqueous Layer
- Lipid Layer
- Tear Film
IIRs: Leveraging Strengths

Figure 3: The platform integrating the OCT and the TDF subsystems. Left, the physical setup of the system with hardware components labeled. Right, a diagram indicating the light paths of the two subsystems and their subcomponents.
Figure 4: Co-registration image of TDF (a) and OCT (b) of the precorneal tear film (PCTF) *in vivo*. The dashed line in (a) indicates the position of the OCT B-scan of in (b). The average thickness of tear film and lipid layer is measured to be 2.8 µm and 85 nm respectively.
EXPERIENCE
Failures

Company Change

- New agent
- Small biotech
- 3x over 4 yrs
- End Celgene
- Cut program

KNOW the landscape
Failures

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Leadership Change
- New HH-inh
- Preclinical data
- Top 3 company
- New R&D
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Competing Approval
- New LMWH
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KNOW the landscape

Negative Study
- New CSC-inh
- Preclinical data
- Diff tumor site
- Negative study
- Cut program
- Company closed

KNOW the landscape
Successes
Know the landscape

- How to adjust to rapid changes
- Control what we can control
- Importance of relationships
- Important to be consistent
- UNDER promise & OVER deliver
Successes

Know the landscape
Successes

Know the landscape

- Personalized engineered vaccine autologous tumor cells
- Dual targeted:
  (a) rhGM-CSF enhanced antigen presentation
  (b) shRNA-furin inhibits immunosuppression via TGFbeta
- Originally sarcoma
- Mutual friends / colleagues
- Ovarian cancer rationale

KNOW the landscape
Successes

Know the landscape

ELISPOT (+) = 6 mos
ELISPOT (-) = 4 mos
P = 0.04

ELISPOT (+) = Median not reached
ELISPOT (-) = 4 mos
P = 0.008
Successes

Know the landscape

- Vaccine tolerated well no DLT
- Promising efficacy of ORR and survival
- ELISPOT predictive biomarker
  (a) T-cell activation via quantitative measure of mononuclear gamma-IFN
  (b) predicts response
  (c) Corresponds to lines of prior therapies

Plans:
(a) 2 future studies
(b) Specific biomarker

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Phase 1 Vigil in OVCA
Successes

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- Plans:
  (a) 2 future studies
  (b) Specific biomarker

Phase 1 Vigil in OVCA

Cabo + Pembo in Cervical Cancer

- Cabozantinib oral TKI
  - MET, VEGFR2
  - RET, KIT, AXL, & FLT (cervical cancer)
  - Preclinical data supports
  - Pitched Cabo + Pembrolizumab
    - KNOW THE LANDSCAPE
  - Company wanted monotherapy
  - Pembro received indication for 2nd line
  - Now proceeding with Cabo+Pembro
  - CCTS SHARE
How to Optimize Success & Minimize Failure

Helpful Hints

Relationships

- Both Pharma & colleagues
- Stay in touch (qtr meetings)
- Take charge (small institution)
- Administrative assistant
- Trust takes time
- Be persistent
- UNDER promise OVER deliver
How to Optimize Success & Minimize Failure

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Elbow Grease

- Professional meetings (ASCO)
- Speaker bureau
- Ad boards (idea exchange)
- Pitch idea to all in field
  - PARP inhibitor companies
- Control what you can control
  - IRB turnaround
  - Grants/Contracts
- Be nimble
How to Optimize Success & Minimize Failure

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  - Grants/Contracts
  - Be nimble

**Elbow Grease**

**Good Ideas**

- All trials are compromises
- Fit goals of company
- Fit business plan of company
- Be open to suggestion(s)
- Expect change
- Keep chopping wood
How to Optimize Success & Minimize Failure

Helpful Hints
Questions & Discussion

Center for Clinical and Translational Science (CCTS)
Stay Connected

www.uab.edu/ccts
205-934-7442
ccts@uab.edu
PCAMS – 1924 7th Ave South
@cctsnetwork
Search YouTube: cctsnetwork

Science through Synergy
The objective of our Investigator-Sponsored Trial (IST) program is to provide support for clinical research that advances medical and scientific knowledge about our products or disease states of interest, and to enhance patient care. Letters of Intent are accepted on an ongoing basis via our online portal.

The regional MSL will present the proposal to the Investigator-Sponsored Trial Review Committee (ISTRC). If accepted, a full protocol and budget is requested within 90 days, which will be reviewed by the ISTRC. Following ISTRC approval, regulatory and contracting activities may begin.
We work closely with Sponsor-Investigators to provide support for their clinical research, but **wish to remind applicants that our role in ISTs is limited.** We are available as a resource to assist Sponsor-Investigators throughout the development and implementation of their IST.

We have found that the most successful ISTs are conducted by experienced clinicians who understand their responsibilities as a Sponsor-Investigator and enter the process with realistic expectations.
Seattle Genetics
Sponsor-Investigator Responsibilities

- Design and conduct of the study protocol
- Regulatory authority (such as FDA) approvals/IND filings
- Safety reporting and updates to regulatory authorities and Seattle Genetics
- IRB obligations
- Investigational drug management
- Collaborating site selection and management
- Budgeting and milestone invoicing
- Protocol and informed consent form maintenance
- Trial registration on www.clinicaltrials.gov
- Correlative study conduct including vendor contracting (if needed)
- Data collection and analysis
- Monthly updates to Seattle Genetics regarding enrollment and safety
- Timely updates regarding protocol changes. Changes to target enrollment and/or budget will require a contract revision.
- Publication planning including Seattle Genetics review as outlined in contract
- Overall compliance with Good Clinical Practice (GCP) guidelines
• Provision of study drug and safety reporting information for inclusion in study protocol
• Provision of IND cross reference letter for inclusion in the Sponsor-Investigator’s regulatory filing
• Timely review of protocol amendments, budget revisions and publications
• Granting permission to vendors to use specimen assays for specific ISTs
• Distribution of new IND safety letters and/or Investigator Brochures to Sponsor-Investigators
• Drug shipment to the primary sites and collaborating sites with IRB approval
• Payment of invoices submitted by the Sponsor-Investigator at the completion of each milestone defined in the research agreement