Perspectives on “GCP” and Clinical Research Training of Physicians

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Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.
Investigator Training Hypotheses

1) Understanding **Good Clinical Practices (GCP)** is an essential element of investigator competency, but it represents only one of several fundamental areas of knowledge of effective investigators.

2) GCP training in its current form adds a burden that dissuades physicians from participating in research and distracts investigators from meaningful study oversight.

3) GCP training in its current form doesn’t address the real world challenges that investigators face on a daily basis.
Training Physicians Require for Clinical Trial Preparedness

- FDA requires that “qualified scientists” conduct clinical trials. FDA has also issued guidance to sponsors and investigators about training.
- In fact, there are three “pillars” of knowledge that an accomplished investigator must master:
  - Therapeutic area expertise (e.g. cardiology or dermatology)
  - General research knowledge (methods, principles, regulations and nuances of clinical research)
  - Study specific information (what’s in a protocol)

Three Pillars of Knowledge Support the Accomplished Investigators

Therapeutic Area Training!

General Research Training?

Study Specific Training!

Accomplished investigators must make balanced decisions using all of these pillars of knowledge.
Task Force Addressed Elements of General Research Training for Investigators

- Ethics / Subject’s Rights
- Patient Care
- Scientific Methods
- Regulatory Compliance
- Leadership / Site Management

Consensus statement:
http://www.acrpnet.org/PDF/apcr_consensus_statement.pdf
Task Force Addressed Elements of General Research Training for Investigators

Statement of Clinical Investigator Competence

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A research coordinator rushes into your office asking you to “close out” a subject participating in a hypertension program stating, “Ms. R. is upset and wants to withdraw consent from the study right away.” “Her feet are swelling and she insists on taking a diuretic.” Diuretics are prohibited medications in the study.

Does the investigator need to know anything more before honoring the patient’s request to withdraw from the study?
The Belmont Report

The first principal is autonomy!

Surely, Ms R’s request should be granted .......

... or should it?

A competent investigator wants to know more!
“Ms. R.” is a 61 y.o. white female known to you with a several year history of uncomplicated hypertension. Prior to study enrollment 6 weeks earlier, the patient was on hydrochlorothiazide / triamterene.

Blood pressure was 142/96 at the time of study enrollment. The subject was taken off her baseline medication and randomized into a double blind study comparing an angiotensin receptor blocker / calcium blocker combination with either agent alone.
The Swollen Feet - Examination

On examine the patient appears pleasant and looks well. Blood pressure = 120/78. You note trace to mild pedal edema, left greater than right. Ms. R. corrects you, “The swelling is worse when I’m on my feet all day.” Physical exam is otherwise benign. The primary endpoint of the study is blood pressure after 8 weeks. Subjects can then receive open label therapy with the combination drug. Diuretics could be added to open label therapy after 1 month.

Question - Would you now immediately withdraw the patient from the study in light of her demand to the coordinator?
You explain to the patient that her blood pressure improved on study meds and that her data would be unusable if she were to withdraw before 8 weeks.

You also reassure Ms R that the edema isn’t a serious medical problem. You mention the option of starting a diuretic during open label treatment in a few weeks & emphasize strategies for reducing pedal edema.

After your conversation, the patient is agreeable when asked if she is willing to complete the blinded study and randomize into the open label phase in 2 weeks. Nonetheless, she drops 2 months later during open label therapy due to persistent edema.
The Swollen Feet - Outcome

In this scenario the investigator applied knowledge of:

- The Protocol
- Statistical Analysis
- Patient Care
- Pharmacology

As a net result of investigator competence, a patient contributed to the primary data analysis and generated information relevant to her ongoing clinical care. GCP issue of adverse event reporting was secondary.
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Problems with Current GCP Training

- Contemporary “GCP training” has become a dysfunctional process applied by each sponsor without site or investigator input that:
  - Doesn’t consider investigator experiences or even certifications in many cases;
  - Creates the hassle of obtaining one time and often unreliable Internet log-on credentials;
  - Slows down study start-up;
  - Discourages sub-investigators.
GCP training doesn’t distinguish between casual and dedicated sites

<table>
<thead>
<tr>
<th>Mean number of</th>
<th>All Sites (N = 1, 126)</th>
<th>Most Experienced (N=257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigators</td>
<td>1.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Study Coordinators</td>
<td>0.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Other Staff</td>
<td>0.2</td>
<td>2.9</td>
</tr>
<tr>
<td>Number of Patients Enrolled Annually</td>
<td>13.2</td>
<td>220.4</td>
</tr>
<tr>
<td>Number of Study Grants Awarded Annually</td>
<td>1.7</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Source: Centerwatch, 2012; Tufts CSDD
Dear Dr. Michael Jay Koren,

You have previously been provided access to the B1481015 study portal which was created for the B1481015 study to ensure compliance to regulatory requirements.

We have noticed that you haven’t yet completed DILI training module. It is recommended that you log onto the Study Portal to complete this training module. On completion of this module, a certificate will be recorded.

You can access this portal, hosted by Firecrest, with the details below:

Firecrest Portal URL: http://www.firecrestclinical.com/pfizer
Your Firecrest Username: mkoren@encoredocs.com
Can you help me decipher what this email means?

**Typical training email with no sponsor, study or contextual information**

This is an auto-generated email, please do not reply to this email.

User name: michael koren
User's email address: mkoren@encoredocs.com
Date and time of training completion: 12-Jun-2013 09:38
Version of OCRDC training: v4.6

Please retain this notification as proof of training completion for your study file.

A Helpdesk representative will be sending you via email your OCRDC UserID and temporary password within 1 hour.

Should you have any questions about gaining access to OCRDC please feel free to contact the Helpdesk.

• US dial: 1 888 426 8801
• Outside the US dial: 001 888 426 8801

ICON plc made the following annotations.

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Typical “on line” GCP question

An investigator has the responsibility to report which of the following to the sponsor:

1) Adverse events within 24 hours;
2) Serious adverse events within 24 hours;
3) Adverse events related to the test article;
4) All the of above;
5) None of the above.
You learn that an elderly male in an outpatient Alzheimer’s dementia study was recently admitted to a local hospital with agitation and epigastric pain. A monitor reviews the records you requested and then questions you about “exertional dyspnea”, an abnormal ECG, troponin = 8.5 ng/ml and ALT = 70 IU/L.

- Monitor recommends 6 AEs: “agitation,” “epigastric pain,” “dyspnea,” “abnormal ECG,” “elevated troponin,” and “hepatitis.”
- Is there a simpler solution?
Conclusions

• Current GCP training is burdensome, redundantly applied by multiple sponsors and doesn’t address actual investigator needs.
• Physician time may be better spent getting experiential investigator training, observing and communicating with patients, and problem solving the multiple ethical and logistical dilemmas intrinsic to contemporary clinical research.
Thanks for your attention!
AE Assessment:
Apply the Power of Observation

Yes, I did have my mammogram today—Why do you ask?
"If you remember, I did mention possible side-effects."
Some things can only be understood through experience!

Our Philosophy:

For practicing physicians, sharing experiences with seasoned investigators is the best approach to clinical research training.