Beyond GCP

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.

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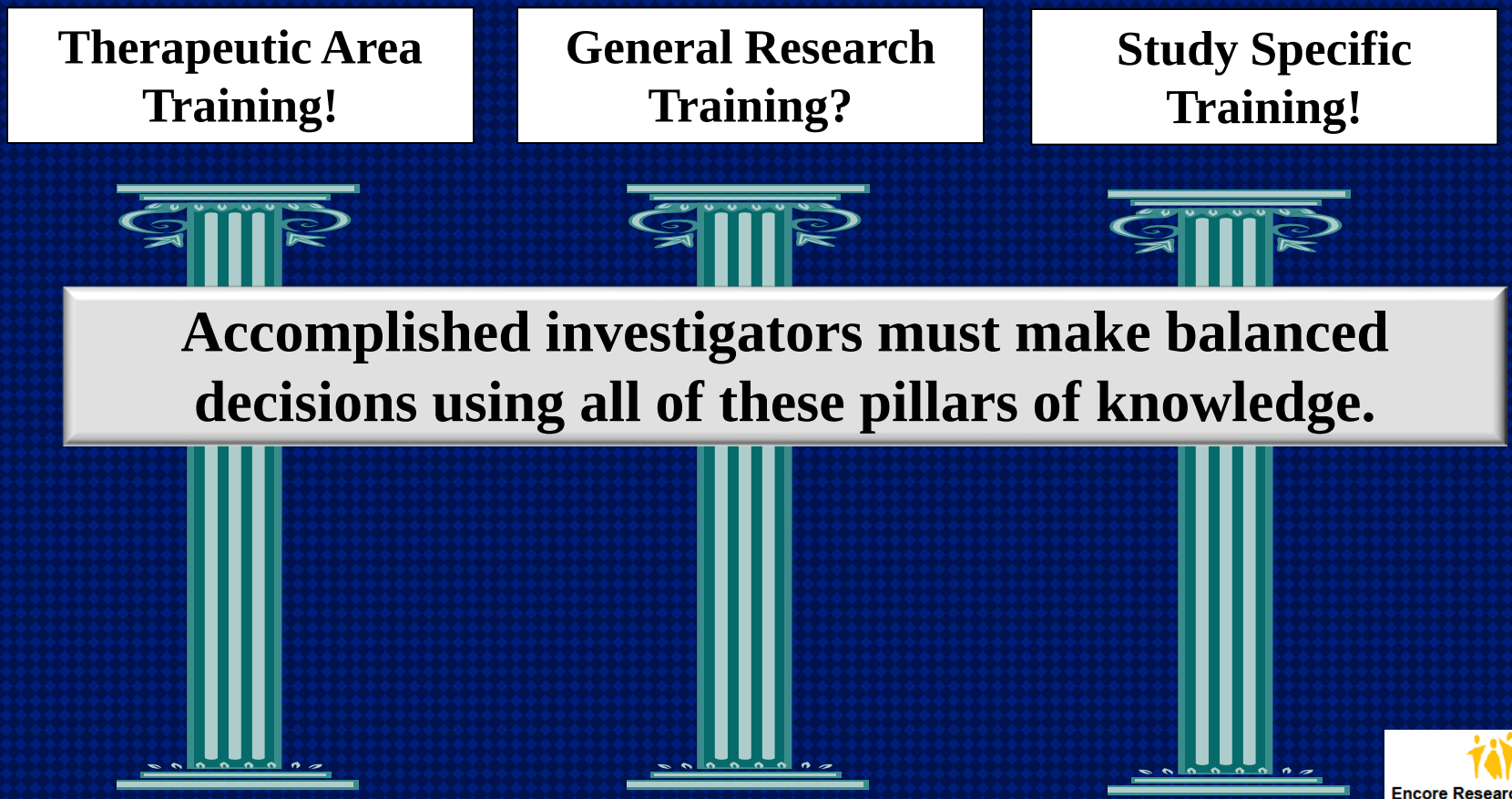
Training Physicians Require for Clinical Trial Preparedness

- 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)

Source: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

Three Pillars of Knowledge Support the Accomplished Investigators



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

APCR
Academy of Physicians in Clinical Research

APCR Consensus Statement

Statement of Clinical Investigator Competence

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Source: The Monitor, August 2011; Vol 25 (4):79-82

Beyond GCP – Real World Learning
The Case of the Swollen Feet

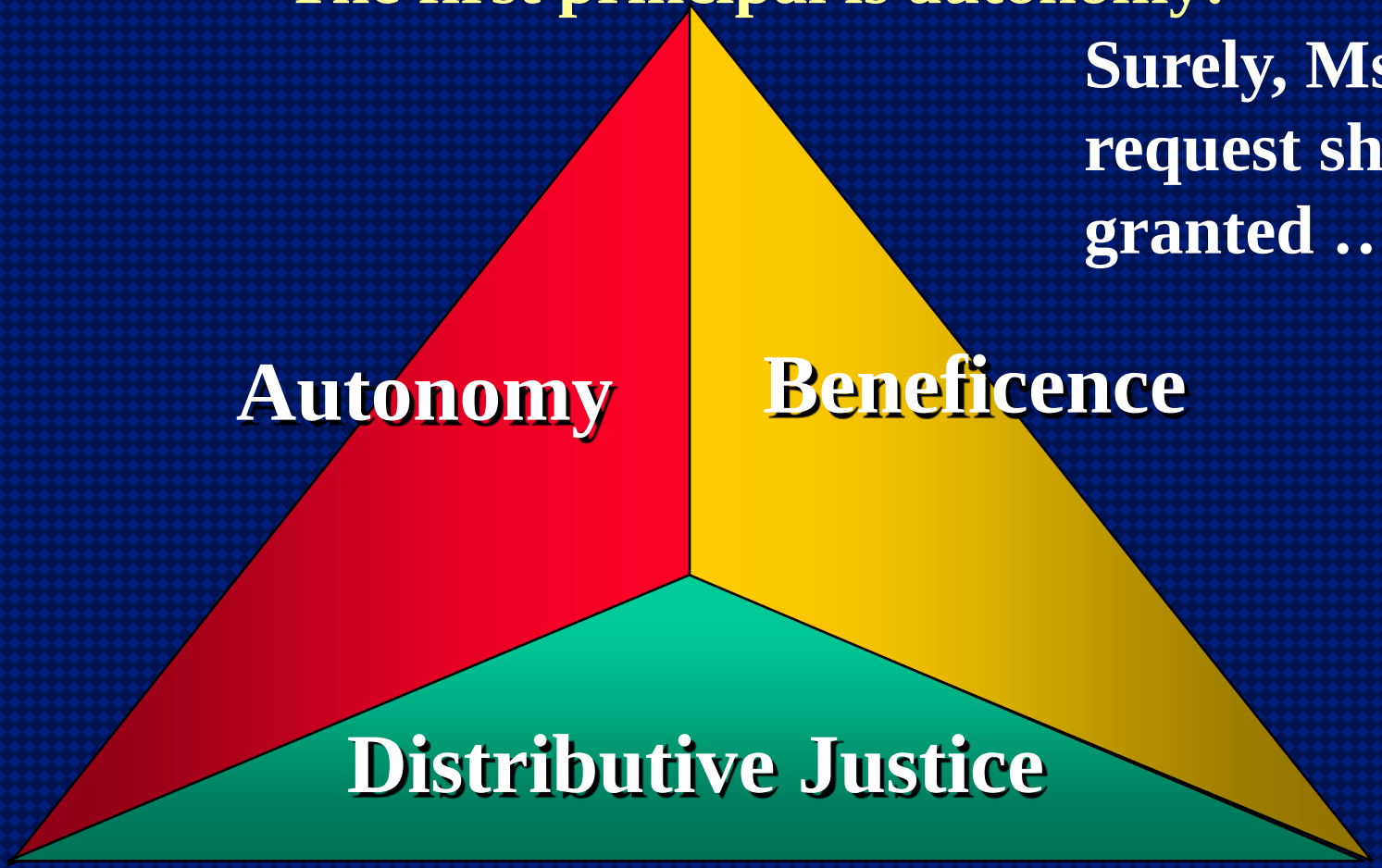
A research coordinator rushes into your office asking you to "close out" a subject participating in a hypertension program stating, "Ms. R. is upset and wants to withdraw consent from the study right away." "Her feet are swelling and she insists on taking a diuretic." Diuretics are prohibited medications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

The Case of the Swollen Feet
Additional Information

"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?

The Swollen Feet - Outcome

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

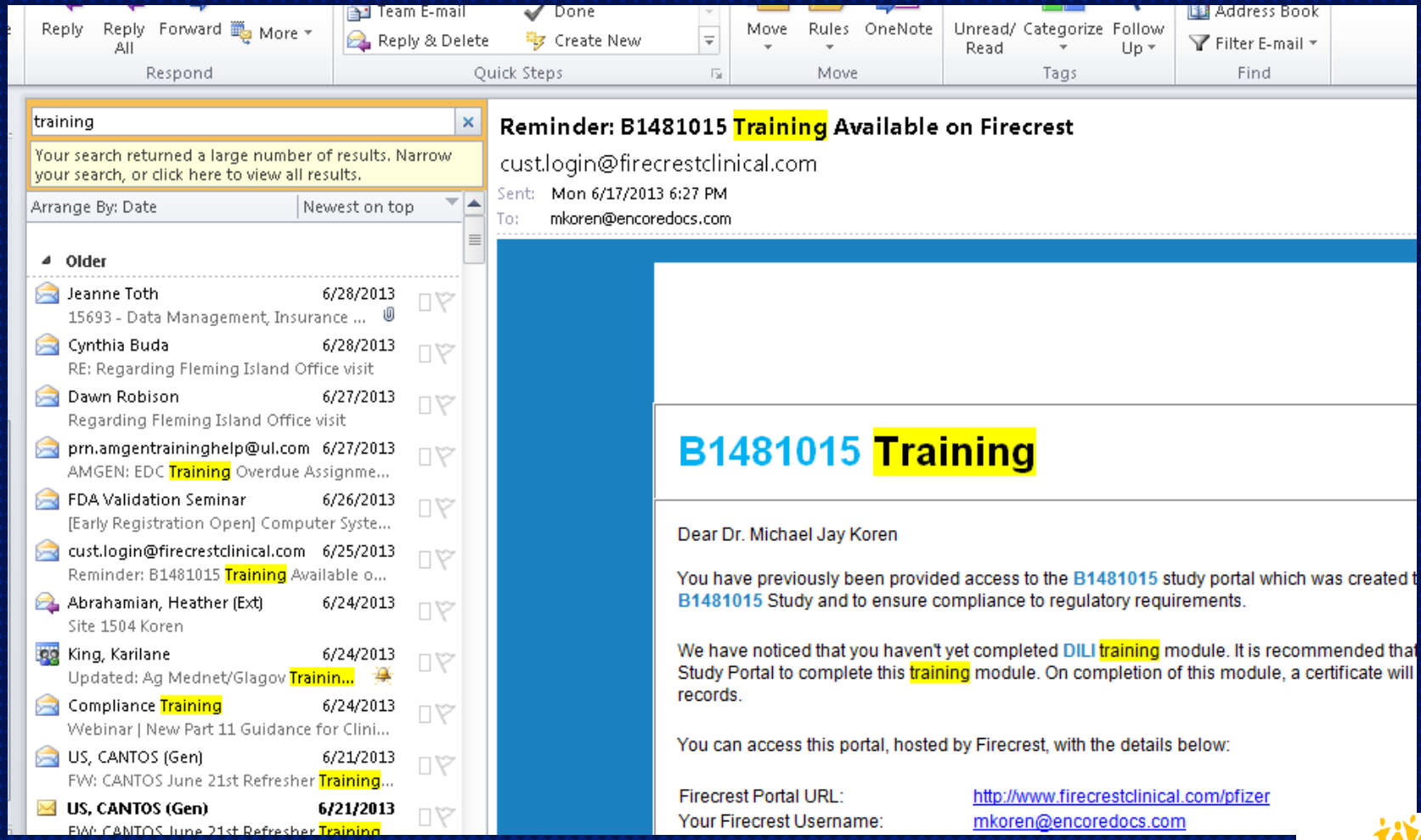
- Contemporary "GCP training" has become a dysfunctional process applied by each sponsor without site or investigator input that:
  - Doesn't consider investigator experiences or even certifications in many cases;
  - Creates the hassle of obtaining one time and often unreliable Internet log-on credentials;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

GCP training doesn't distinguish between casual and dedicated sites

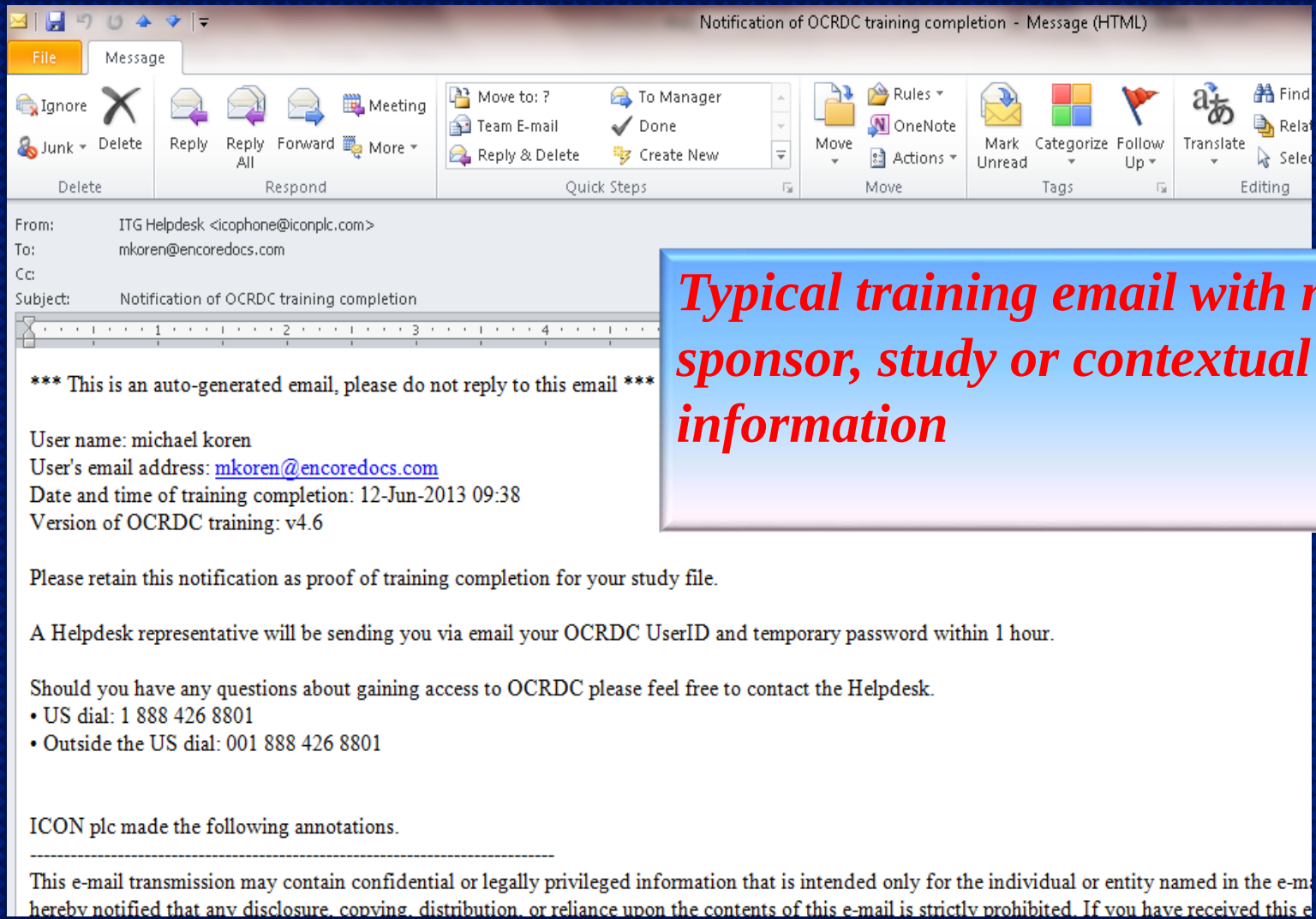
Mean number of	All Sites (N = 1, 126)	Most Experienced (N=257)
Principal Investigators	1.4	6.6
Study Coordinators	0.8	3.7
Other Staff	0.2	2.9
Number of Patients Enrolled Annually	13.2	220.4
Number of Study Grants Awarded Annually	1.7	6.3

Source: Centerwatch, 2012; Tufts CSDD

Active investigators get multiple emails about research training each week



Can you help me decipher what this email means?



Typical training email with no sponsor, study or contextual information

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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.**

Beyond GCP

Adverse Event Classification Real World Example

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?**

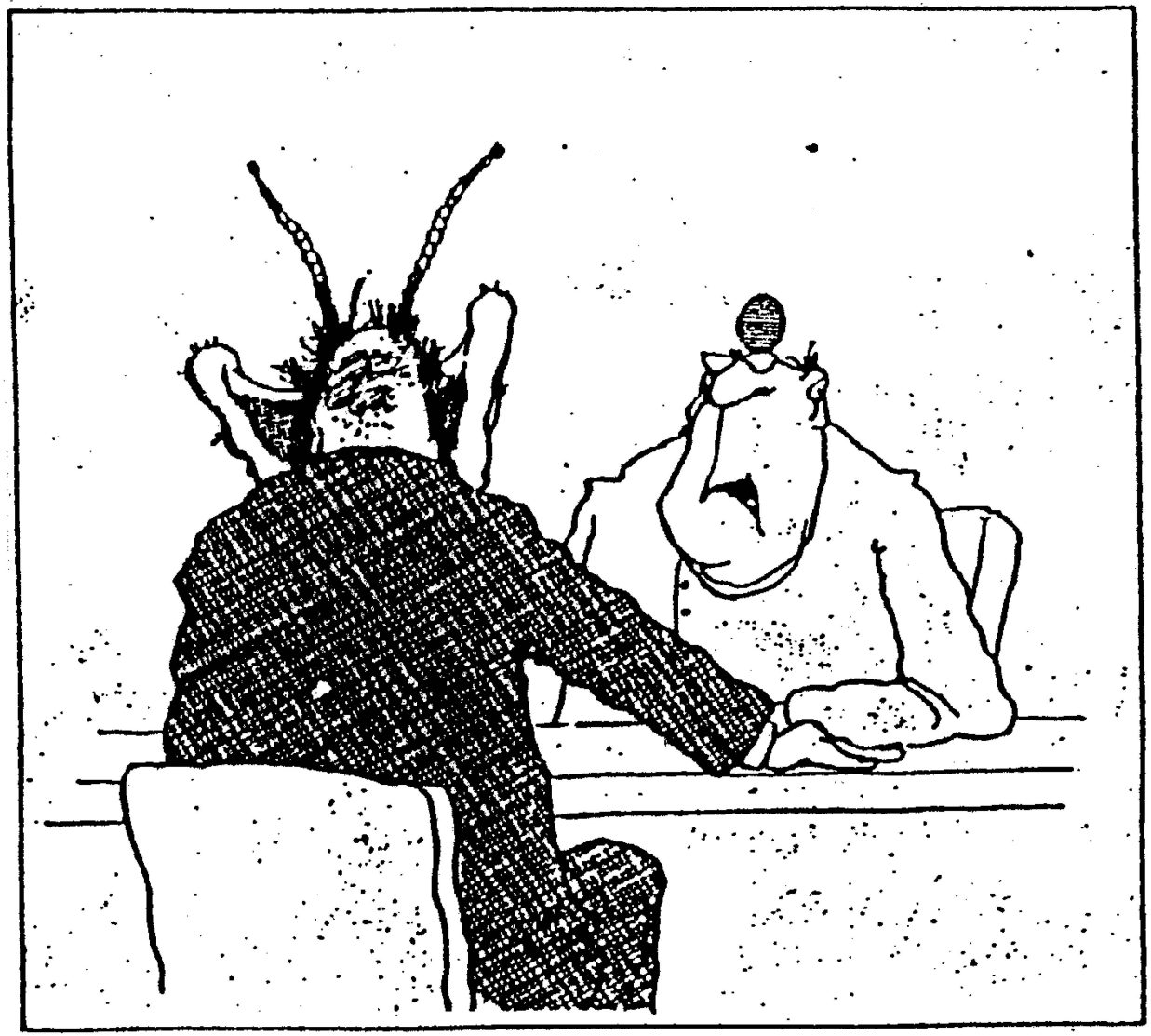
Conclusions

- 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!

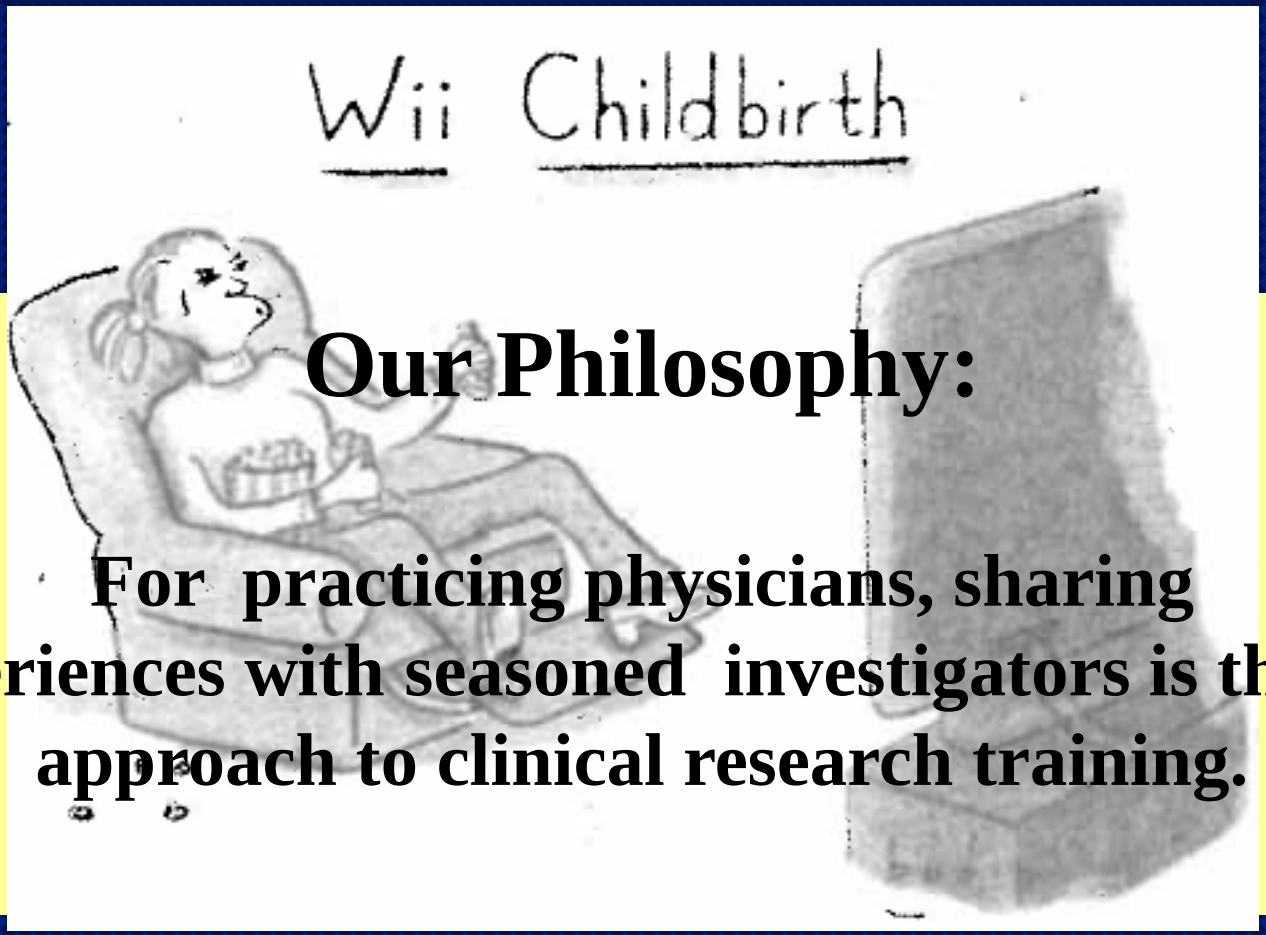
AE Assessment:
Apply the Power of Observation

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.