

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.
- 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)

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

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



APCR Consensus Statement

Statement of Clinical Investigator Competence

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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.

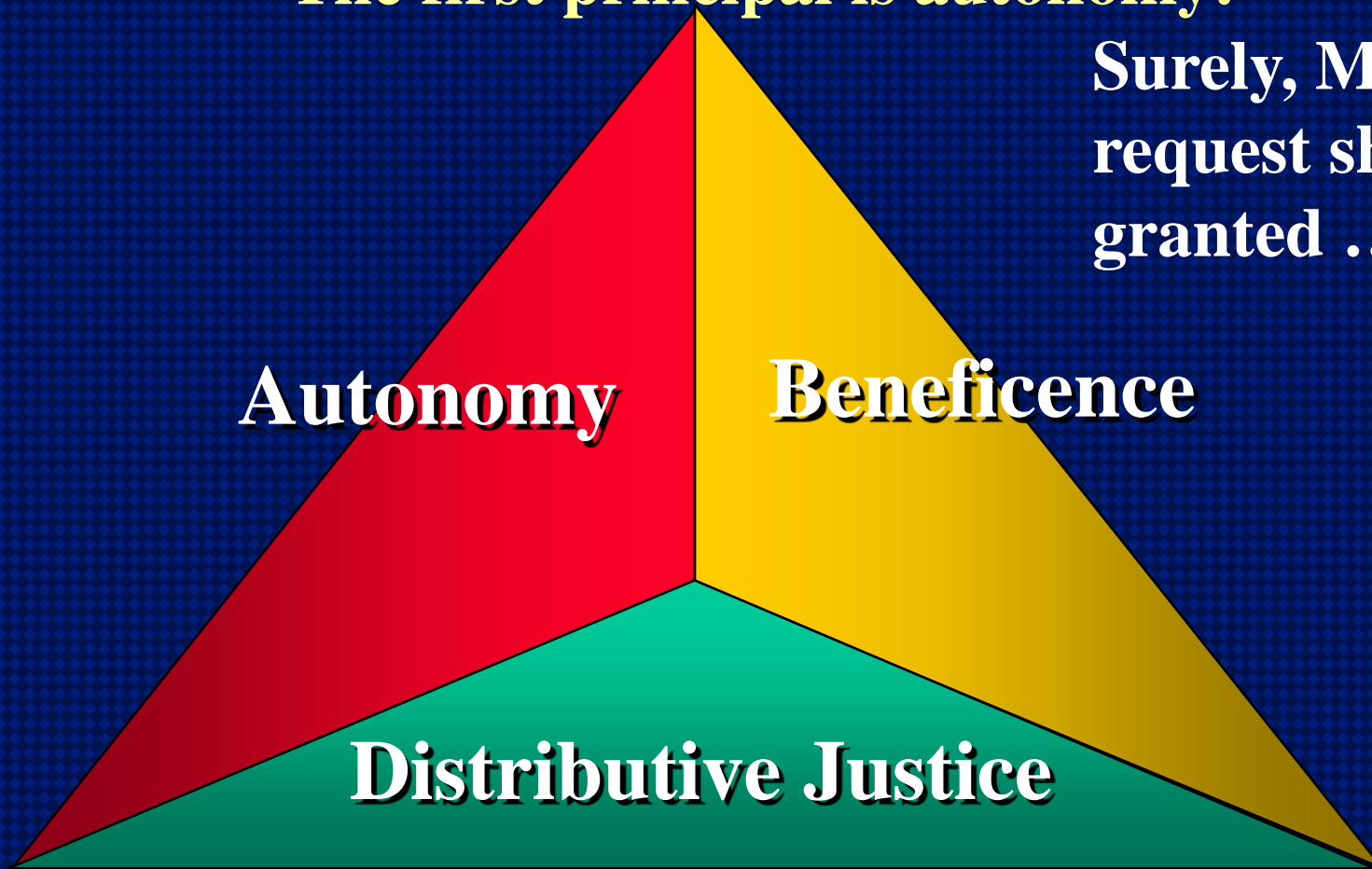
Does the investigator need to know anything more before honoring the patient’s request to withdraw from the study?



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

Active investigators get multiple emails about research training each week

The screenshot shows an email client interface with a search bar containing the word "training". Below the search bar, a message states: "Your search returned a large number of results. Narrow your search, or click here to view all results." The email list on the left includes several entries, with the selected email being from "cust.login@firecrestclinical.com" dated 6/25/2013, titled "Reminder: B1481015 Training Available on o...".

The selected email content is as follows:

Reminder: B1481015 Training Available on Firecrest
cust.login@firecrestclinical.com
Sent: Mon 6/17/2013 6:27 PM
To: mkoren@encoredocs.com

B1481015 Training

Dear Dr. Michael Jay Koren

You have previously been provided access to the **B1481015** study portal which was created to support the **B1481015** Study and to ensure compliance to regulatory requirements.

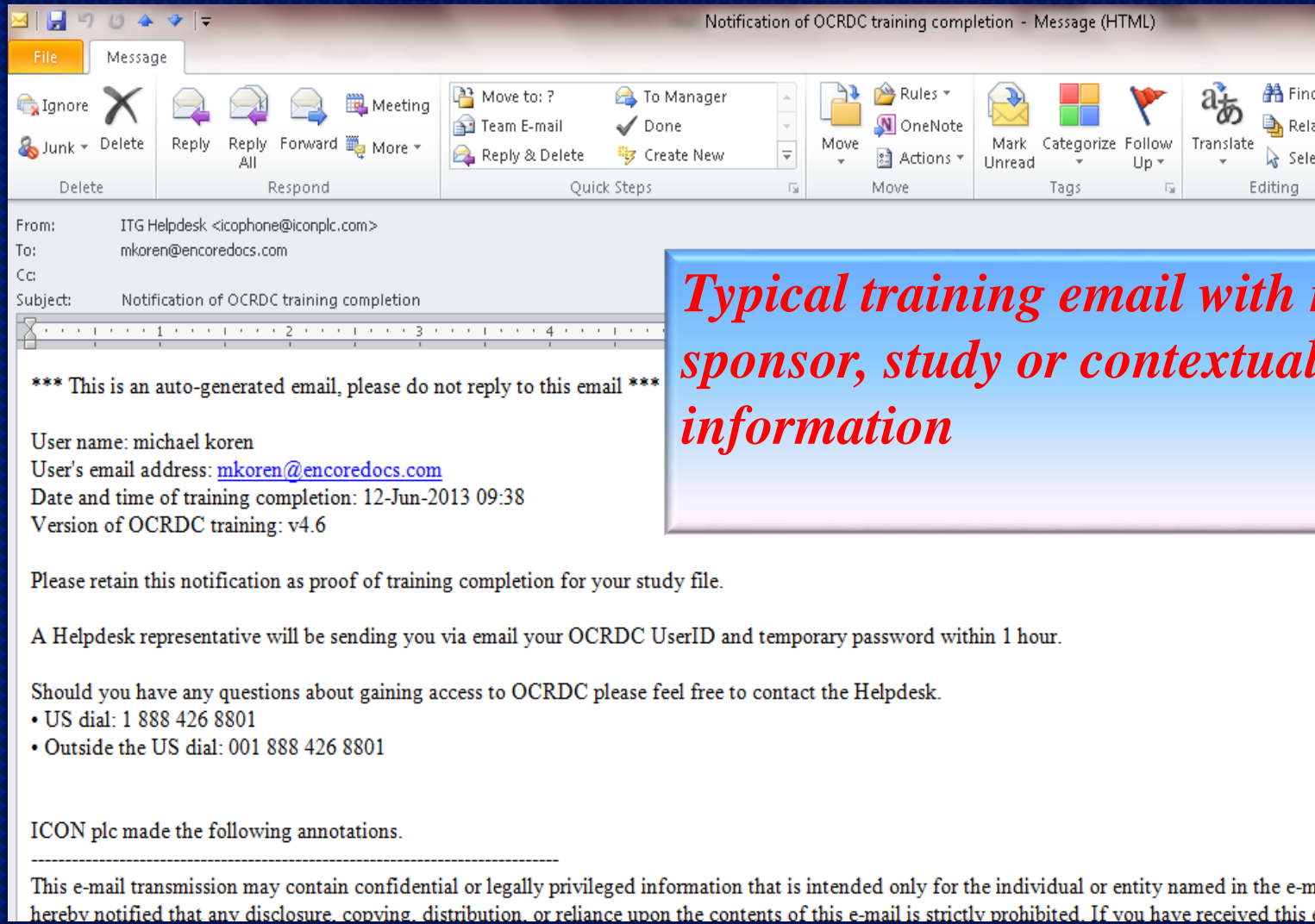
We have noticed that you haven't yet completed **DILI training** module. It is recommended that you access the **B1481015** Study Portal to complete this **training** module. On completion of this module, a certificate will be generated for your records.

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?



Notification of OCRDC training completion - Message (HTML)

From: ITG Helpdesk <icophone@iconplc.com>
To: mkoren@encoredocs.com
Cc:
Subject: Notification of OCRDC training completion

*** 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.

This e-mail transmission may contain confidential or legally privileged information that is intended only for the individual or entity named in the e-mail. If you are not the named individual or entity, you are hereby notified that any disclosure, copying, distribution, or reliance upon the contents of this e-mail is strictly prohibited. If you have received this e-mail in error, please notify the sender immediately.

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.**



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.**



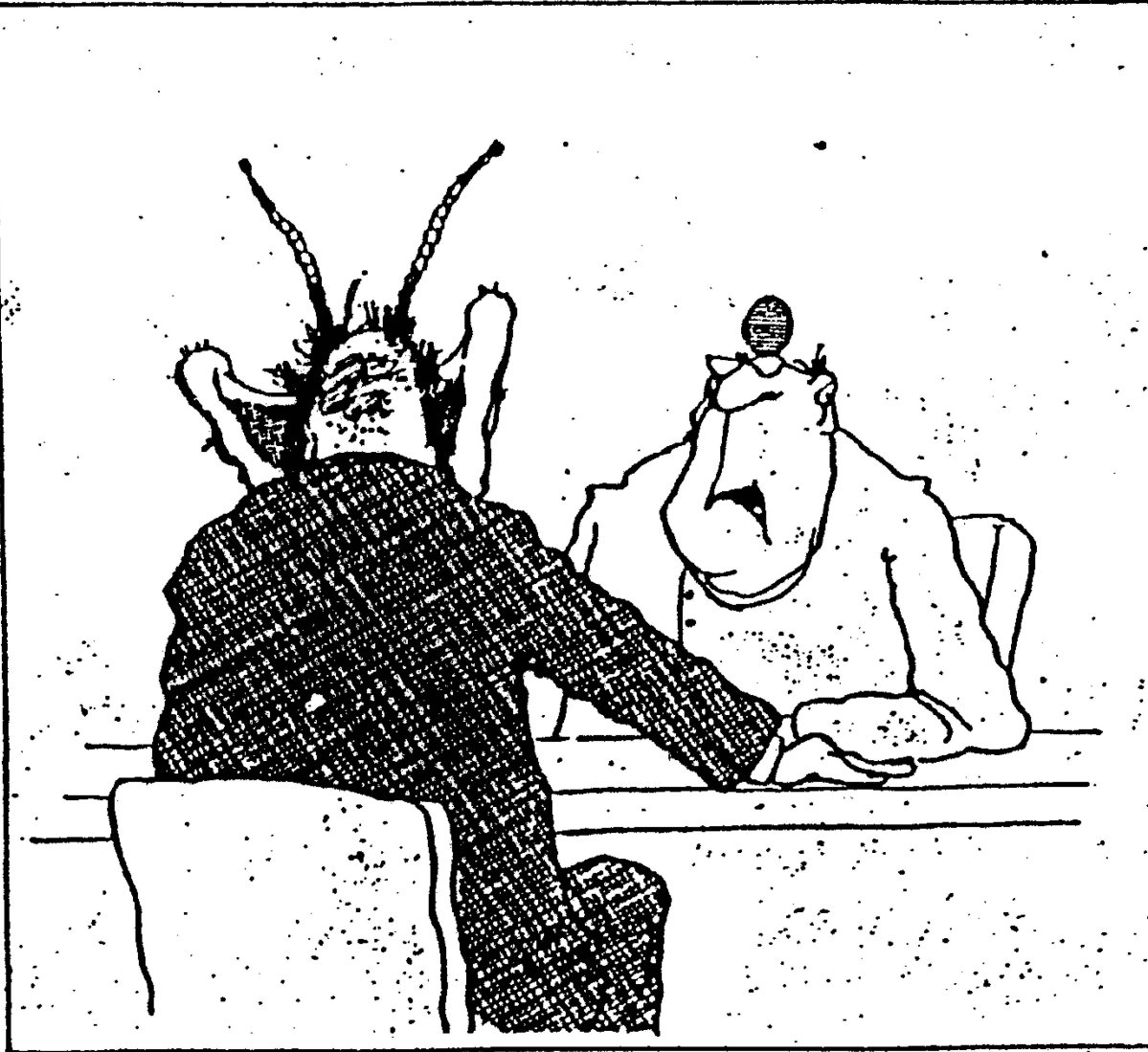
Thanks for your attention!



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!

Wii Childbirth



Our Philosophy:

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

