An Investigator's Perspective

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Firecrest Clinical

- **Established in 2001 – Ireland & USA**
- **Over 160 studies across 70 countries**
- **Experience across all therapeutic areas in Phase II, III and IV trials**
- ***Developed 'by Investigators for Investigators'***

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The Clinical Development Process 1

Under tight control of Sponsor:

Drug discovery
Non-clinical development
Phase 1
Phase 2 (maybe)

ballpark

$200 million

Ensured by:

Hiring policy

Training

Tight supervision

S.O.Ps

Performance review

Accountability

Firing policy

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The Clinical Development Process 2

The Sponsor Struggles to Control:

- Phase 2 (maybe)
- Phase 3
- Phase 4
- PMS

ballpark

$500 million

Problems in Control

Not Investigators' core business

- Motivation of Investigators
- Training of Investigators
- Supervision of sites
- *"Don't upset the K.O.L.s !"*
- Turnover of staff

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The Clinical Development Process

A Cynical View?

First, spend $200 million on carefully nurturing a new drug from its discovery through non-clinical development, then hand it over to a bunch of semi-amateurs **AND** struggle to try to ensure that it all works out.

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Objectives in the Clinical Trial Process

Decrease cycle times

Maintain (and preferably improve) quality

Ensure that trial results fairly reflect the drug's characteristics

Control costs

> *"Within the R&D process, clinical trials form the largest single cost center for new drug development."*

Global Information, Inc. 'Optimizing the Clinical Trial Process: Strategies to Reduce Costs and Increase Quality.'

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Challenges in the Clinical Trial Pathway

80% of clinical trials fail to finish on time.

Paraxel. Pharmaceutical R&D Statistical Sourcebook, 2001

25% of Informed Consents are inadequate or missing.

Bohaychuck W, Bell G. Conducting GCP Compliant Clinical Research, Wiley

Delays in attaining MA result in a cost to companies of as much as $1million a day in unrealised sales.

Kermani F, Findlay G (2000). The Pharmaceutical R&D Compendium.

Only 50% of successful Phase II trials meet their Phase III endpoints

Robert O'Neill, FDA, speaking at DIA EuroMeeting, Paris 2006

30% of Phase III trial failures are likely due to problems in execution

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The Classical Response

"We need to hold an Investigator Meeting"

Conservatively… $2000 per participant within the US !

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Polling Question

What is the most likely outcome of an IM held before trial commencement?

1. Attendees learn all they need to know about the trial?
2. Sponsor and CRO staff will network well with Investigators?
3. We get to visit interesting places?
4. Everyone's risk of DVT is increased?
5. It's a good use of time and resources?

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Why hold Investigator Meetings?

….. to educate all physicians and site staff on how to properly conduct a study in order to collect valid patient data in a safe, compliant, and efficient manner.

"GCP compliance and training issues top regulators' concerns"

M Mathieu The Global GCP Compliance Report 2006: US, EU, and Japan,

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What do Investigator Meetings achieve?

Positives

- Relationship building with investigators and site staff
- Networking between investigators
- Sharing of recruitment strategies
- Ticks the “training box”
- Marketing and corporate image benefits
- Reward for investigators’ staff
- Good times are had by all

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What do Investigator Meetings achieve?

Negatives

- Many investigators don't attend
- Those who do are travel-weary
- Many send short-contract staff instead (e.g. Residents / Fellows)
- Meetings are often held long before the study can commence
- Variable quality of presentation skills
- Competing attractions of locale (if held in Gloomsville, nobody will come)
- Enormously expensive and poor value for money.
- Few are actually trained at the end

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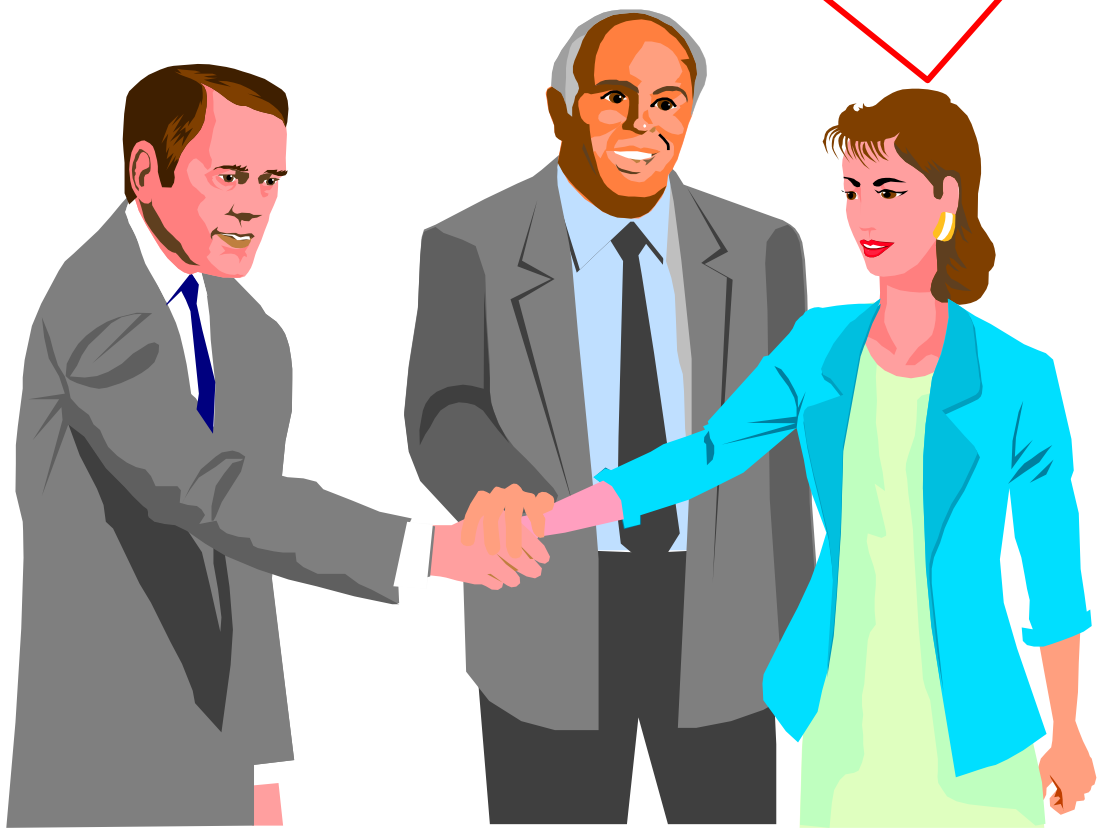
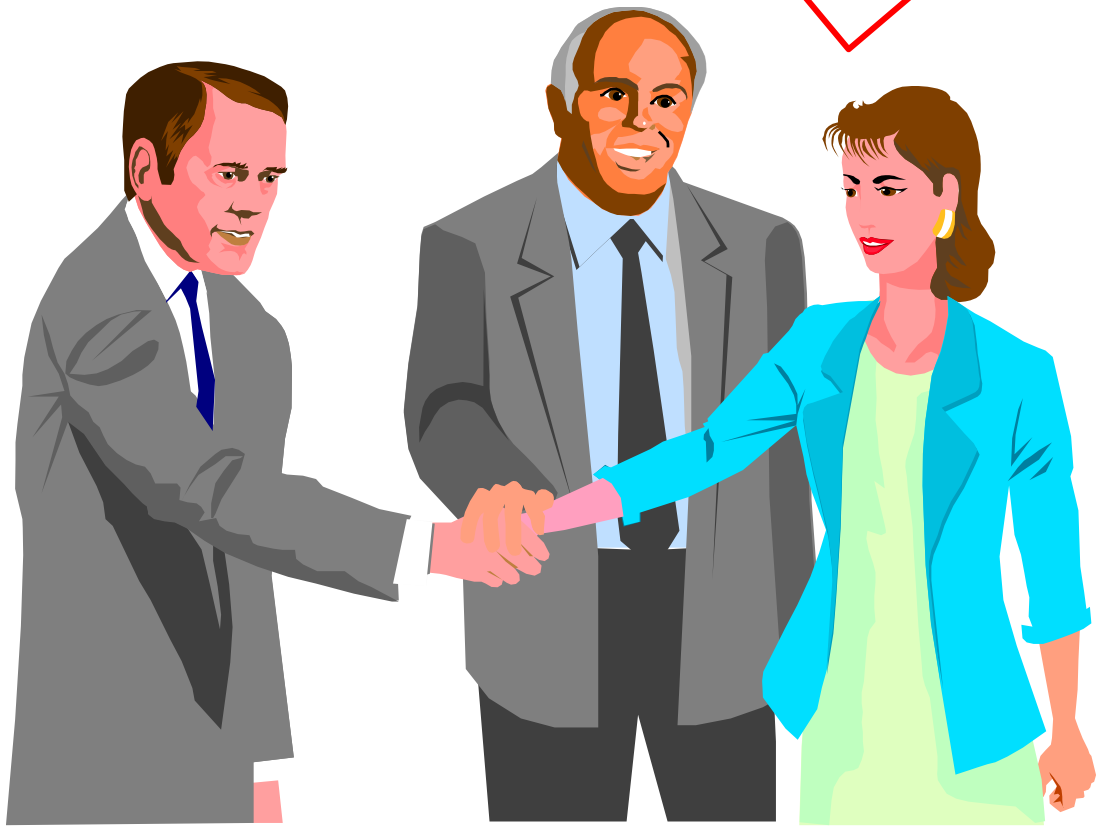
Thanks for inviting me to the Investigator Meeting.

I never thought I'd enjoy the Louvre so much!



I hope you feel that our Investigator Meeting was a success!

Я ничего не понял



Many Investigators don't attend Meetings

Why investigators don't attend meetings:

- 35% are too busy with clinical practice
- 20% don't like travelling
- 15% believe they already understand the protocol
- 8% believe all meetings are the same

CR Focus **14,** No 10, Dec 2003

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When I attend an Investigator Meeting

I am polite enough to attend all the sessions

I may acquire some interesting insights into the pharmacology of the drug

I get to know some of the study staff (*except the overall P.I. who is too important*)

I keep getting calls on my cell phone from the Hospital

I suffer ‘death by PowerPoint’ and struggle to stay awake.

I stay up too late talking to friends in the bar the first night

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When I attend an Investigator Meeting

I wait another four months afterwards to get my site initiated

By then I have forgotten most of the things I was taught at the meeting, especially all the logistics stuff.

But, I was marked “Present” and I am assumed to be trained.

And I was nice to my hosts when I wrote the evaluation form.

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Before your trial commences….

Ask yourself…

- What do site staff really know about the study?
- Do they understand the protocol?
- For how long will they remember it?
- How many members of the study site team know and understand the protocol?
- Do all study staff (site, CRAs, Sponsor's team) have the same baseline knowledge?
- How will they avoid confusing it with the other studies being simultaneously done in the site?

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Now…let me see…

What do we do in this visit…

In that trial …

?????

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Variance Kills Power Calculations

?

Waist Circumference

?

Royalty-free clipart from ClipArtOf.com

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Variance Kills Power Calculations

How do I do that 6-minute walk test again?

How do I do the cognitive function tests?

What draw tubes do the bloods go into?

What are the centrifuge settings for the Biobank specimens?

Where do I get the ‘dry ice’?

How do I calculate the RECIST status?

What treatment option should I now follow based on RECIST?

And be the same as ALL the other 200 sites in the study

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Mistakes are Expensive

Cost of Data Queries in 5800 patient stat in trial

Number per Page of CRF	= 0.5
Number per visit (6 CRF pages)	= 3
Number per patient per year (4 visits)	= 12
Number per patient per trial (3 year)	= 36
Number per trial (1000 patients)	= 36,000
Cost to correct each query	= $ 190
Total Cost	**= $ 7,000,000**

Personal data: B.M.Buckley: PROSPER Study 2003

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It's not just the Investigators and Site Staff about whom there may be training Issues….

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Not just Investigators and Site Staff ?

Survey of Monitors' Competence in an Oncology Trial

- 35% of Monitors are managing 3 or more other Oncology Studies
- 40% of Monitors are managing 3 or more other Non-Oncology Studies
- 16% of Monitors in one G8 country had never worked in an oncology study
- RECIST was a problem for the majority of Monitors
- One of the 5 CRO Leads had left the study within 3 months
- High monitor turnover - up to 35% within 9 months

Source: Firecrest Surveys; 2007.

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What can we do?

Training needs to be:

- Protocol-directed
- Comprehensive
- Targeted at individual needs and deficiencies
- Individually paced
- Entertaining
- Brief 1
- Available trial-long for established as well as for new trial staff

1 Shakespeare W et al. Danish J Psychopathol. (1586) 200,156-8 .

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What can we do?

Training needs to be :

- Monitored
- Evaluated
- Capable of providing certified competence as an outcome
- Responsive to staff needs as identified by measuring effectiveness
- For all study staff (site staff, monitors, Sponsor's clinical team etc.)
- Compulsory

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Compulsory training?

Companies are often afraid to alienate or overburden investigators,

BUT

would you undertake the pre-clinical development of the compound using only untrained staff over whom you had little control?

Investigator non-compliance complaints are increasing rapidly.

Our experience is that linking start-up payment with completion of training both works and is acceptable to investigators.

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How can we do it?

e-Learning based (obvious)

BUT

How good are commonly provided solutions:

- PowerPoints® on line?
- Web-casts?
- Webex-type lessons?
- Teleconferencing?

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How can we do it?

To compete successfully for my time,

you need to provide a solution which is:

- structured
- integrated
- effective
- efficient
- engaging

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Can it be done?

Highly structured and integrated solution needs:

- Validated instructional design: “Tell, show, ask, do”
- Engaging, highly interactive presentations
- Just-in-time availability of training
- Tailored to individual needs
- Localized to language and culture of site

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Can it be done?

Highly structured and integrated solution needs:

- Consistent message across study sites
- Consistent message throughout trial despite staff turnover
- Evaluation and certification capability
- Informative to Sponsor about site competence & enthusiasm
- Capable of guiding Sponsor remedial action
- Corrective instructions easily communicated during the trial

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Can you make a difference?

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Show me the results…..

Study type: Cardiovascular

- 15,000 patients across 1,000+ sites
- Global Study

Remit:

- Address data issues – Firecrest was only intervention

Results:

- 52% reduction in number of data queries
- Time to clean data reduced from 75 days to 35 days

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Show me the results…..

Study type: Auto-immune Disorder

- Phase II - 50 site study
- 8 patient visits (incl Screening)

Remit:

- Protocol-specific training and site support tools

Results:

- Top 10 performing sites used Firecrest an average of 8.1 times per patient
- Top 10 performing sites had an average of 54% less protocol deviations per patient

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Show me the results…..

Study type: Oncology

- Phase III - 140 site study
- Global

Remit:

- RECIST training and calculator tool

Results:

- Reduction in Tumour Response calculation errors by 71%

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How can you do it?

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Before your trial commences…

Ask yourself…

- What do site staff really know about the study and how long will they remember?
- How many members of the study site team know and understand the protocol?
- Do all study staff (site, CRAs, Sponsor's team) have the same baseline knowledge?
- How will they avoid confusing it with the other studies being simultaneously done in the site?

INFORMATION is not INSTRUCTION!

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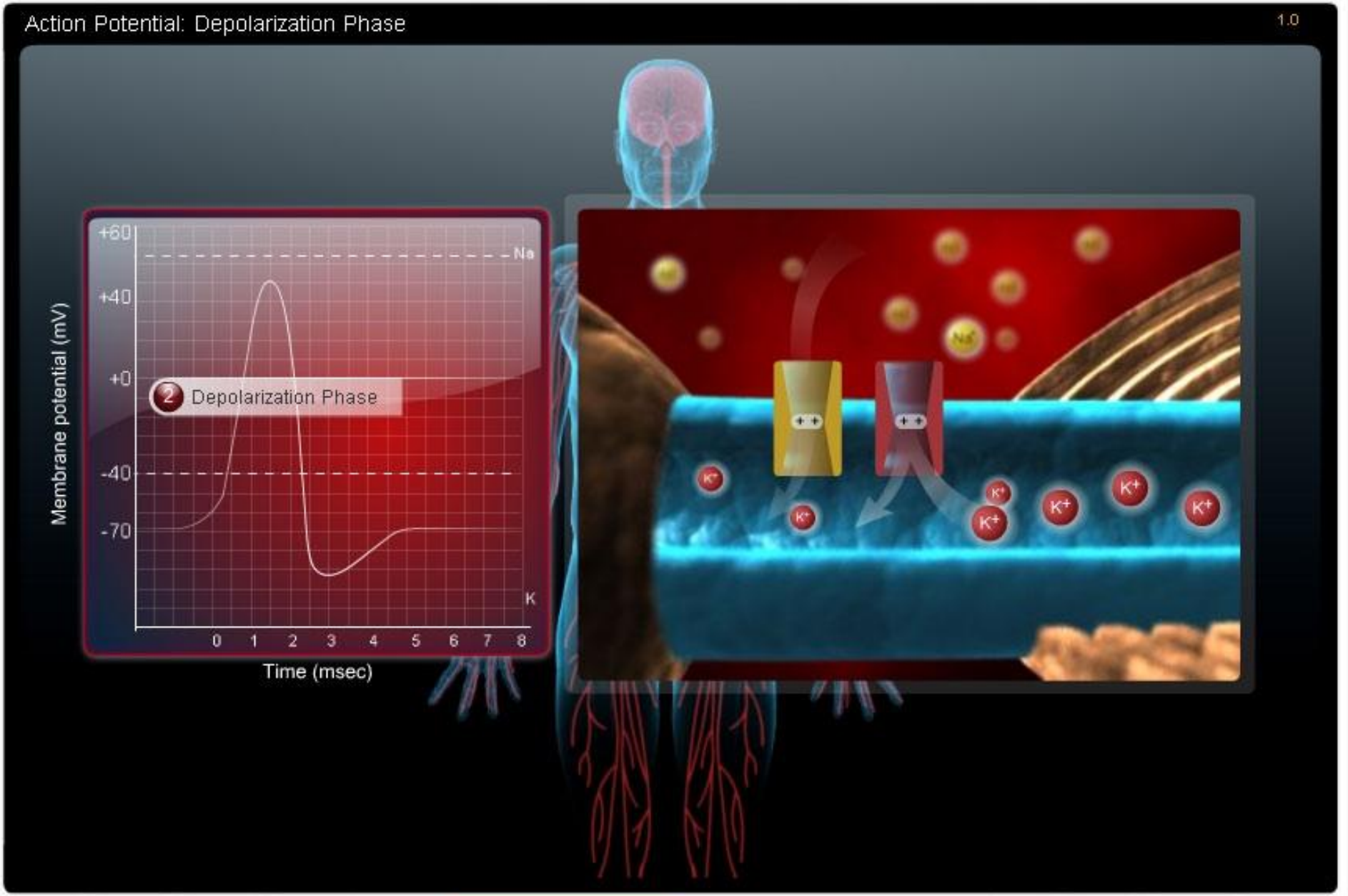
Action Potential: Depolarization Phase
1.0
+60
+40
+0
-40
-70
Na
K
2 Depolarization Phase
Membrane potential (mV)
0 1 2 3 4 5 6 7 8
Time (msec)
Na+
K+

Drug Pathway

1.0

Diamond

Certificate of Completion

Diamond Study

This is to certify that:

Damien Wilmot

Study Site Reference number:

Temporary Site

Successfully completed the following module(s):

Name of Module	Version	Date of Completion
GCP and Study Management	2.0.49	24-Mar-2010

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Remember what sites need to know and when they need to know it!

1. **What have I got to do at this visit?**
2. **How do I do it?**
3. **Where do I report it?**

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Study Visits | Procedures | Withdrawal | FAQs | Toxicities | Calculators | IVRS

- Visit 1
- Visit 2
- Visit 3
- Visit 4
- Visit 5
- Visit 6
- Visit 7
- Visit 8
- Visit 9
- Visit 10
- Visit End of Treatment
- Visit Follow-Up

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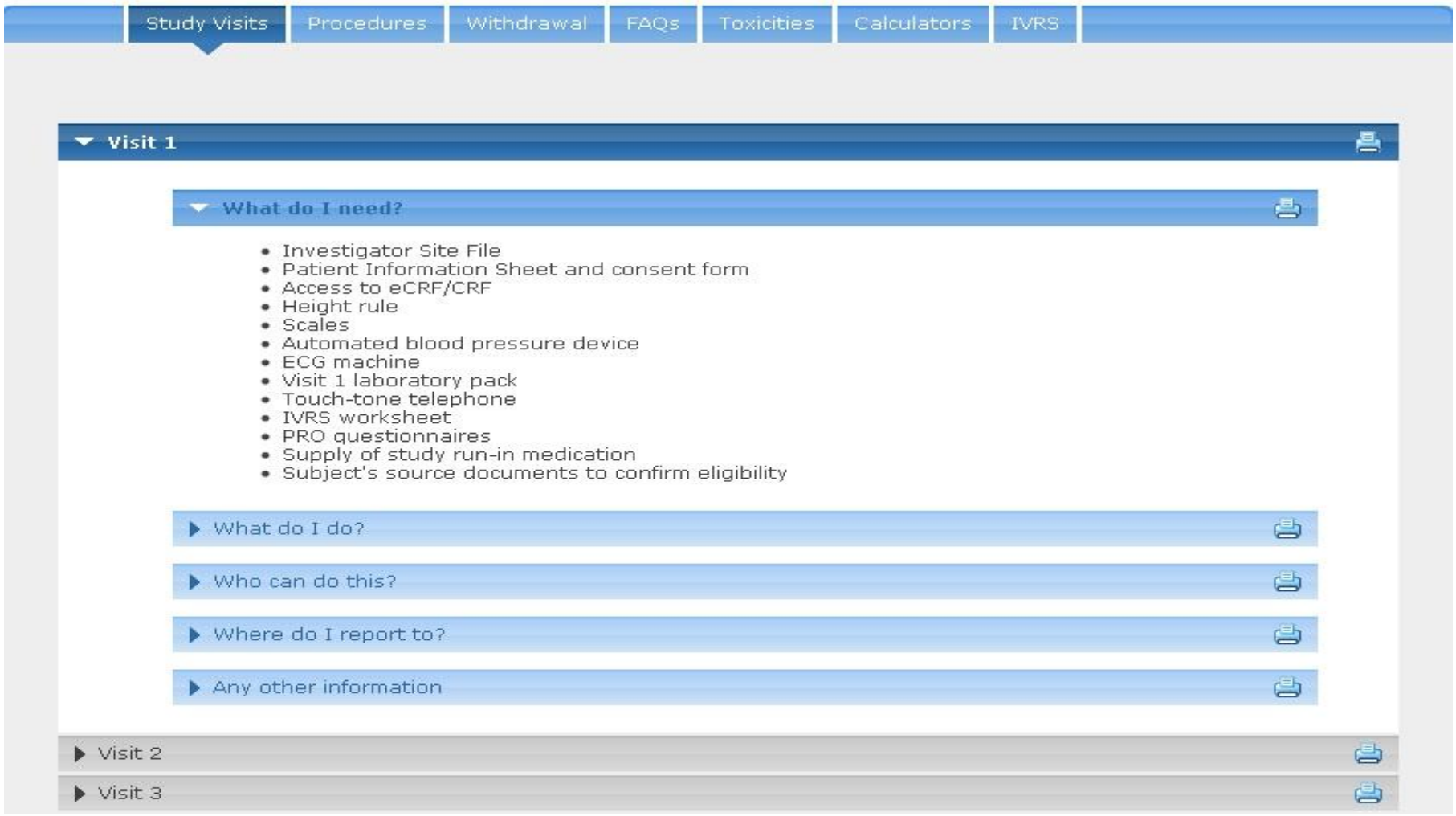

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Study Visits | Procedures | Withdrawal | FAQs | Toxicities | Calculators | IVRS

- Adverse Events
- Randomisation
- Concomitant Medication
- Demography
- ECG
- Eligibility Criteria
- Informed Consent
- Laboratory Assessments
- Medical History
- Physical Examination
- Patient-Reported Outcomes
- Vital Signs
- RECIST 1.1

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Laboratory Assessments

Biochemistry

Collect the following biochemistry and liver function tests sample at all visits:

- Blood urea nitrogen (BUN), creatinine, glucose, potassium, chloride, total CO^2, calcium, sodium, albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, direct bilirubin, and total bilirubin.

Complete the requisition forms and process the samples.

Biochemistry - How to Obtain and Prepare the Samples

Haematology

Haematology - How to Obtain and Prepare the Samples

Urinalysis

Urinalysis - How to Obtain and Prepare the Samples

1. Collect blood sample

1 2 3 4 5 6 7 8

1.0.3

Collect a blood sample into an 8.5-ml, orange-top, SST tube.

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