DESIGN & ENDPOINT OF PHASE I / TRANSLATIONAL RESEARCH

MONDAY 7TH JULY 2014

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CLINICAL OPERATIONS MANAGER

Drug Development Office

100
DRUG DEVELOPMENT AND OPERATIONAL STAFF

2
DRUG MANUFACTURE FACILITIES

9
CDP DEALS COMPLETED TO DATE

NEW AGENTS IN CLINICAL TRIALS
120

1
FOCUS

13
FIRST-IN-CLASS DRUGS

50
FIRST-IN-MAN TRIALS

DRUGS ON MARKET
6

TOP 5
LARGEST PHASE 1 CANCER PORTFOLIO

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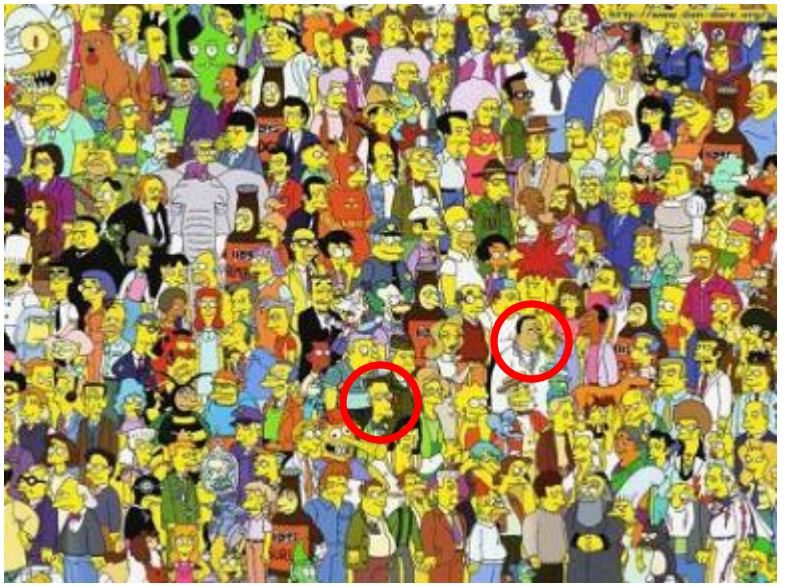
Today's Topics:

- Introduction to Clinical Development
- Requirements Necessary to Develop an Early Phase Protocol & Overview of Patient Safety
- Dose Escalation Schemes
- Trial Set Up
- Sum Up



Introduction to Clinical Development

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Re-Cap of Drug Discovery & Development:
Classical View

Basic Science

Discovery

Preclinical

Establish the safety and efficacy of new drugs in patients

— First time in man —

Safety, tolerability, PK, Dose? → Phase I

This stage checks that the treatment is safe and finds the best dose to use.
(6 - 30 volunteers)

Early signals for clinical efficacy (proof of concept) → Phase II

This stage tests how well a test or treatment works.
(20 -150 volunteers)

Large randomised trials comparing with current treatments → Phase III

This stage compares the new treatment with the current treatment.
Large-scale trials
(100s or 1000s volunteers)

— Marketing Authorisation & Product Launch —

Generation of further safety data or to demonstrate efficacy in new indications → Phase IV

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Requirements Necessary to Develop an Early Phase Study Design

Key Definitions 1/3

Objective

Describes what you want the study to investigate

Example

To evaluate the safety and tolerability of CB7630 administered orally continuously in a once-daily regimen in post-menopausal women with advanced breast malignancy.

Endpoint

An indicator measured in a patient or biological sample to assess safety, efficacy or other objective in a trial

Determining causality of each adverse event to CB7630 and grading severity according to NCI CTCAE Version 4.02.

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Key Definitions 2/3

Biomarker

A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.

Can also be a biological molecule being examined to see if the anti-cancer treatment is having a biological effect.

Pharmacokinetics

Study of how drugs are handled within the body, including absorption, distribution, metabolism and excretion.

Drug concentration in the body over time, how drugs cross cell membranes, effects of long-term administration, drug-drug interactions etc.

Key Definitions 3/3

Pharmacodynamics

The interaction of drugs with cells i.e. the drug's effect on the physiology or pathology of the body and/or tumour.

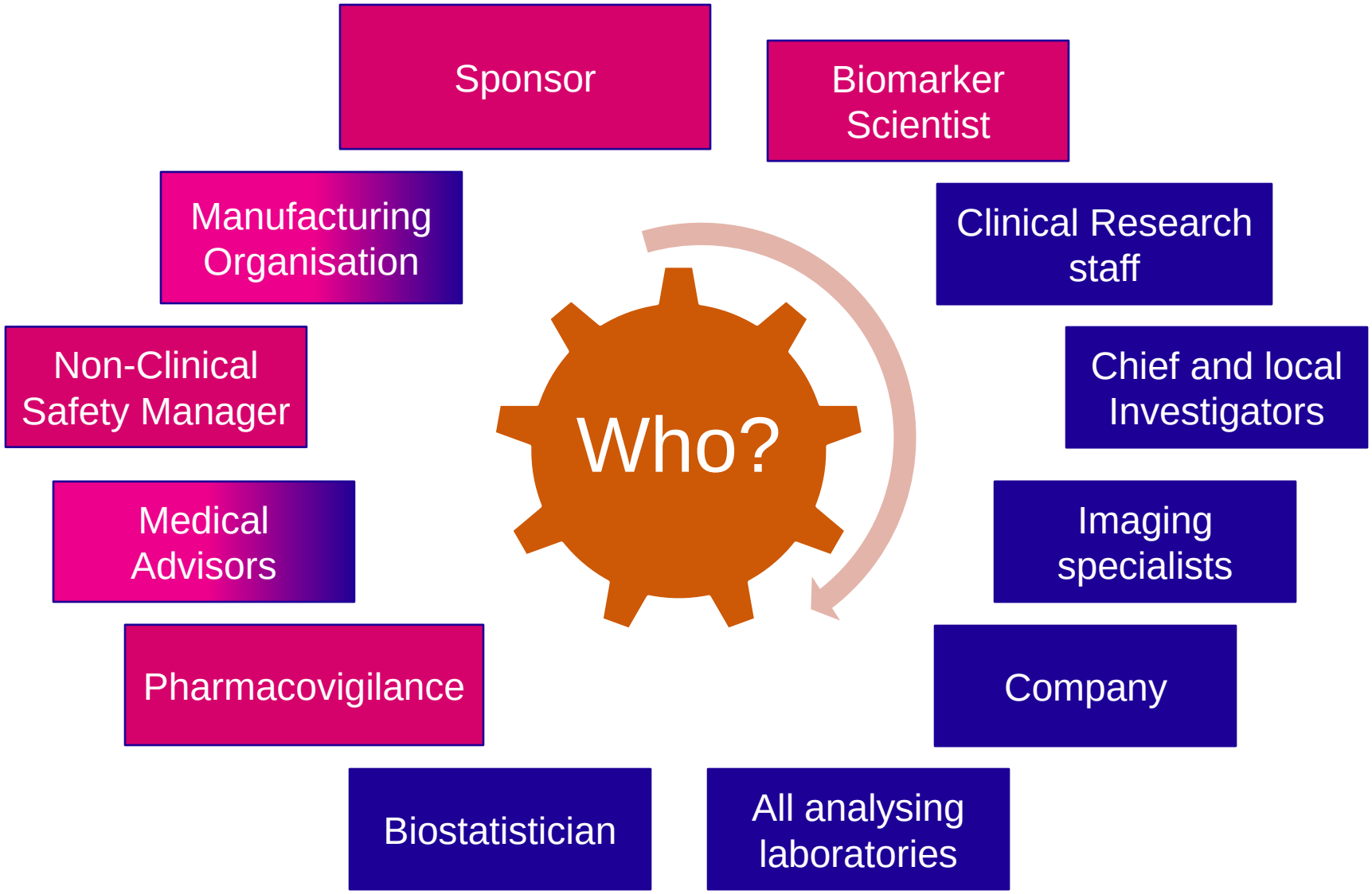
Binding of drugs to cells, their uptake, intracellular metabolism, effect on tumour signalling pathways etc.

We often use PD biomarkers.

Toxicity

The degree to which a substance is poisonous.

Normally species specific and dose dependent.



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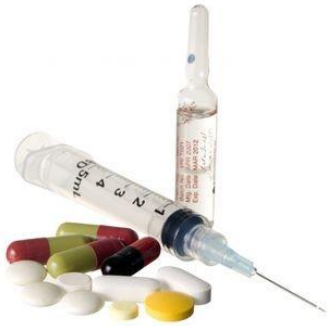
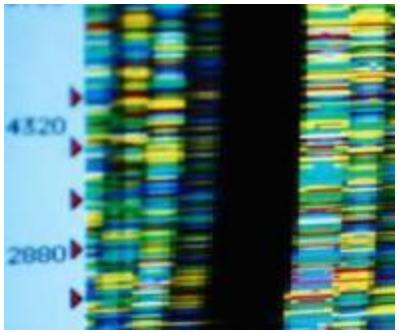
Data informing the Trial Design

Safety risk: Results of pre-clinical toxicology & pharmacology studies

Mechanism of action of the drug – results of pre-clinical pharmacology studies

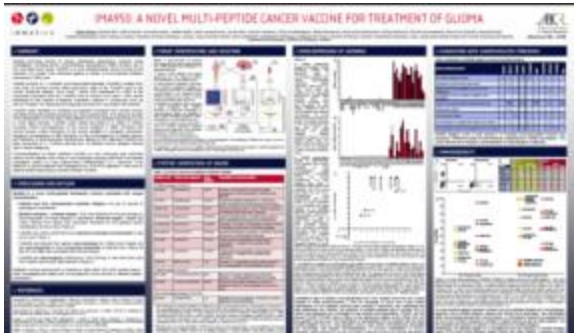


Drug formulation options, amount of drug available



What can we measure? Available and possible proof of principle biomarkers.

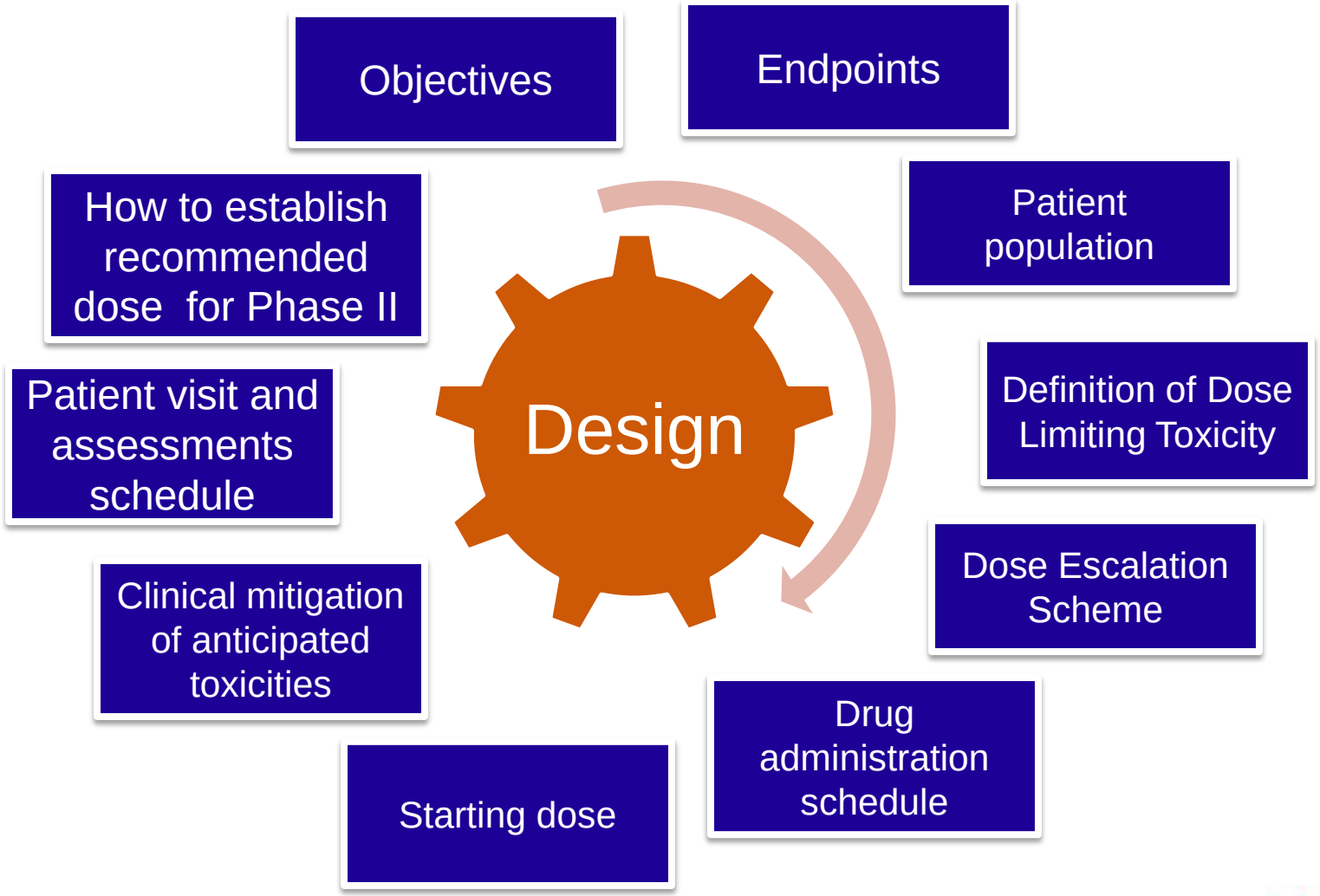
Future path for drug development



Clinical safety information – other trials or similar marketed compounds

Intended patient population

Key aspects of the study design



How does patient safety determine the study design?

Anticipated toxicities.....

- ✓ Preclinical toxicology studies
- ✓ Previous clinical studies of similar agents
- ✓ Class effects

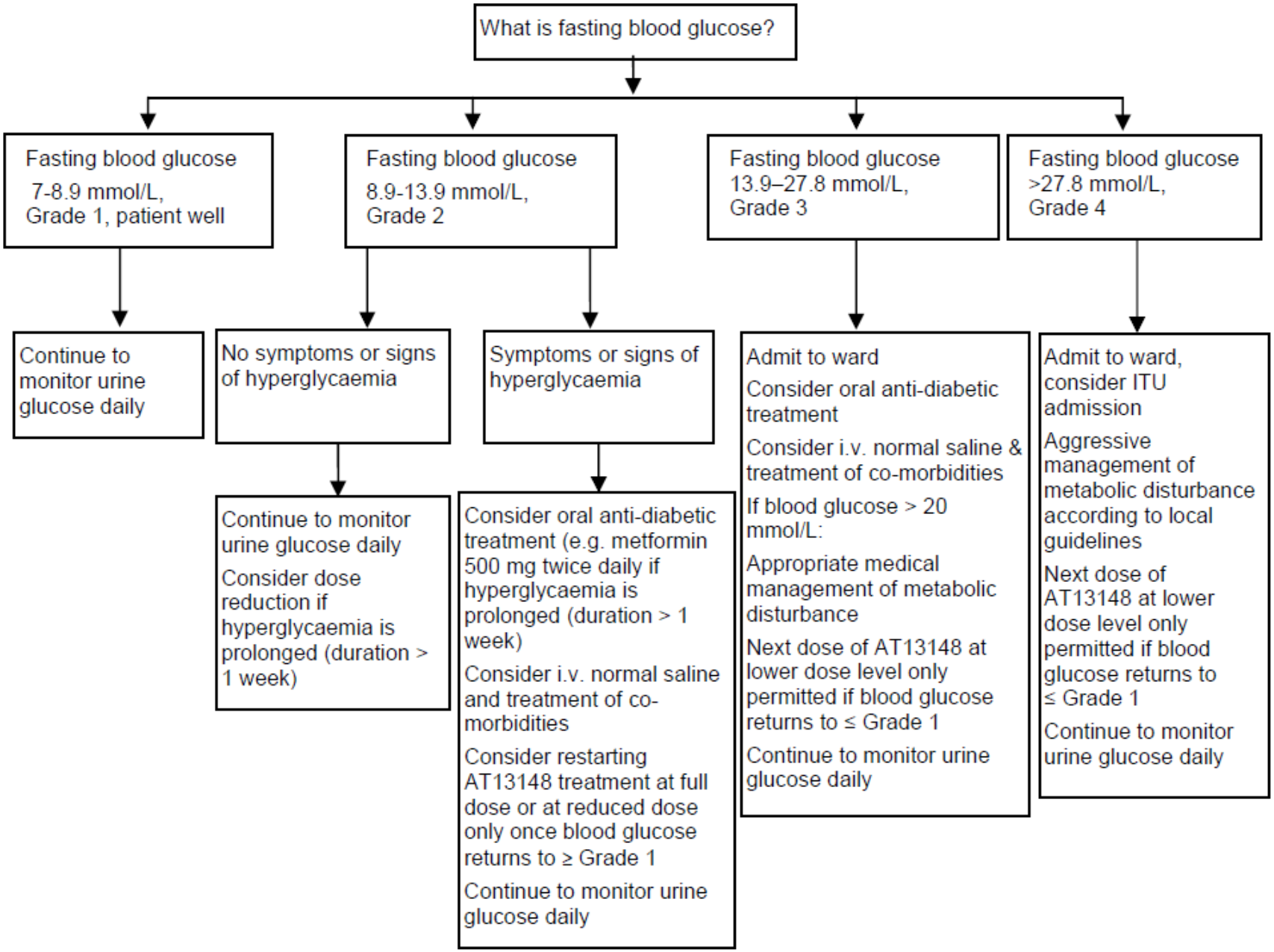
.....inform safety monitoring design

- ✓ Early warning signs
- ✓ Home monitoring between clinic visits e.g. BP or heart monitor
- ✓ Extra precautions
- ✓ Patients are informed of anticipated side effects

How does patient safety determine the study design?

.....Clinical management of toxicity

- ✓ Action to take with study drug
- ✓ Introduction of pre-medication
- ✓ Local management vs Protocol mandated



How does patient safety determine the study design?

.....which patients should be excluded to protect their safety

- Minimum level of function in key organ systems

  e.g. Mitigation again hyperglycaemia (glucose ≤ 7 mmol/L)

- Concurrent conditions

  Concurrent hypotension defined as a baseline supine blood pressure (BP) systolic < 90 mmHg.

- Contraindicated medications and other IMPs

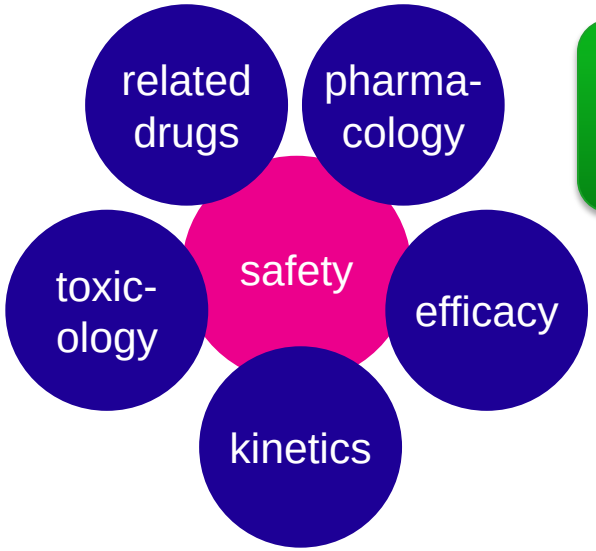
Which patients do we need to include to explore the objectives?

- Primary diagnosis and current status of their cancer
- Previous treatment
- Life expectancy
- Current medical condition

Dose Escalation Schemes

Initial part of a first in human trial that determines the safe or biologically active dose

How do we Define a Safe Starting Dose?



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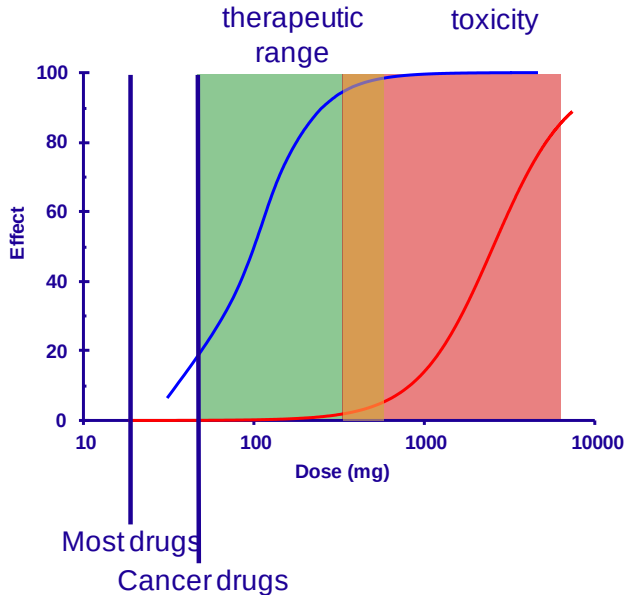
Holistic Approach

Scientifically justified starting dose

Pharmacologically active but safe



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What do we Escalate Dose Toward?

Maximum Tolerated Dose driven by safety OR

Biologically Effective Dose driven by biomarker OR

Something else?

Questions:

- Biomarker measurable in ALL patients?
  - Technique validated to a sufficient level to inform future development or clinical decisions?
  - Tumour or surrogate?
- What are the Manufacturing feasibility/commercialisation limits?
- Maximum response or clinical benefit?

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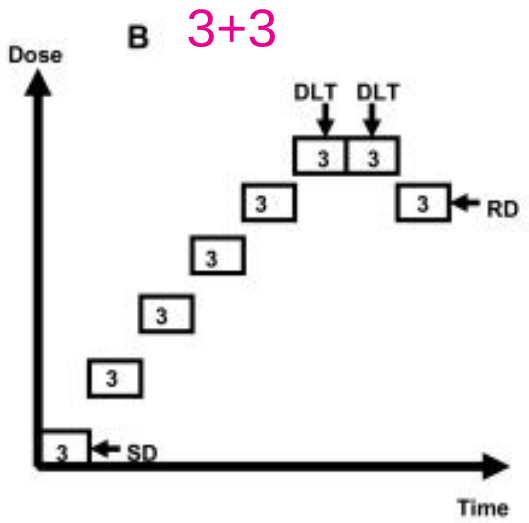
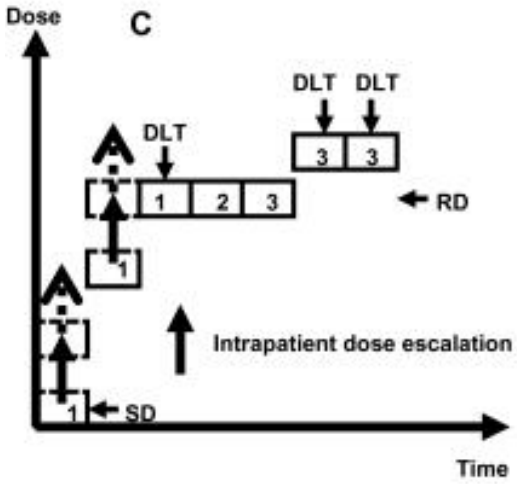
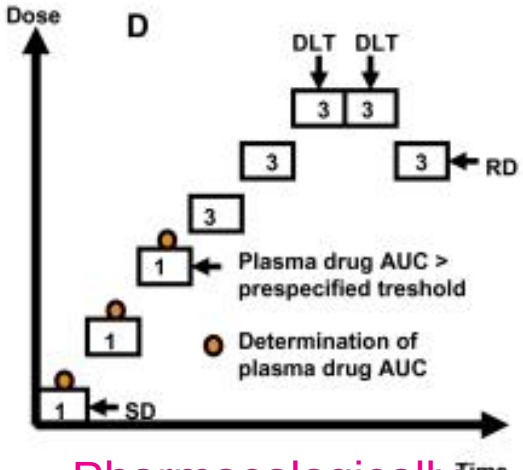
Dose Escalation: Which Type?

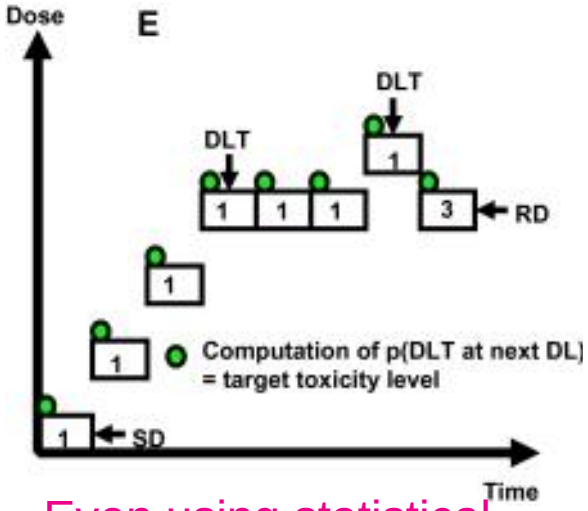




Accelerated titration



Pharmacologically guided



Even using statistical modelling!

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A dose escalation phase is not always appropriate in an early Phase trial!

When is a Dose Escalation Phase NOT Appropriate?: Therapeutic Vaccines

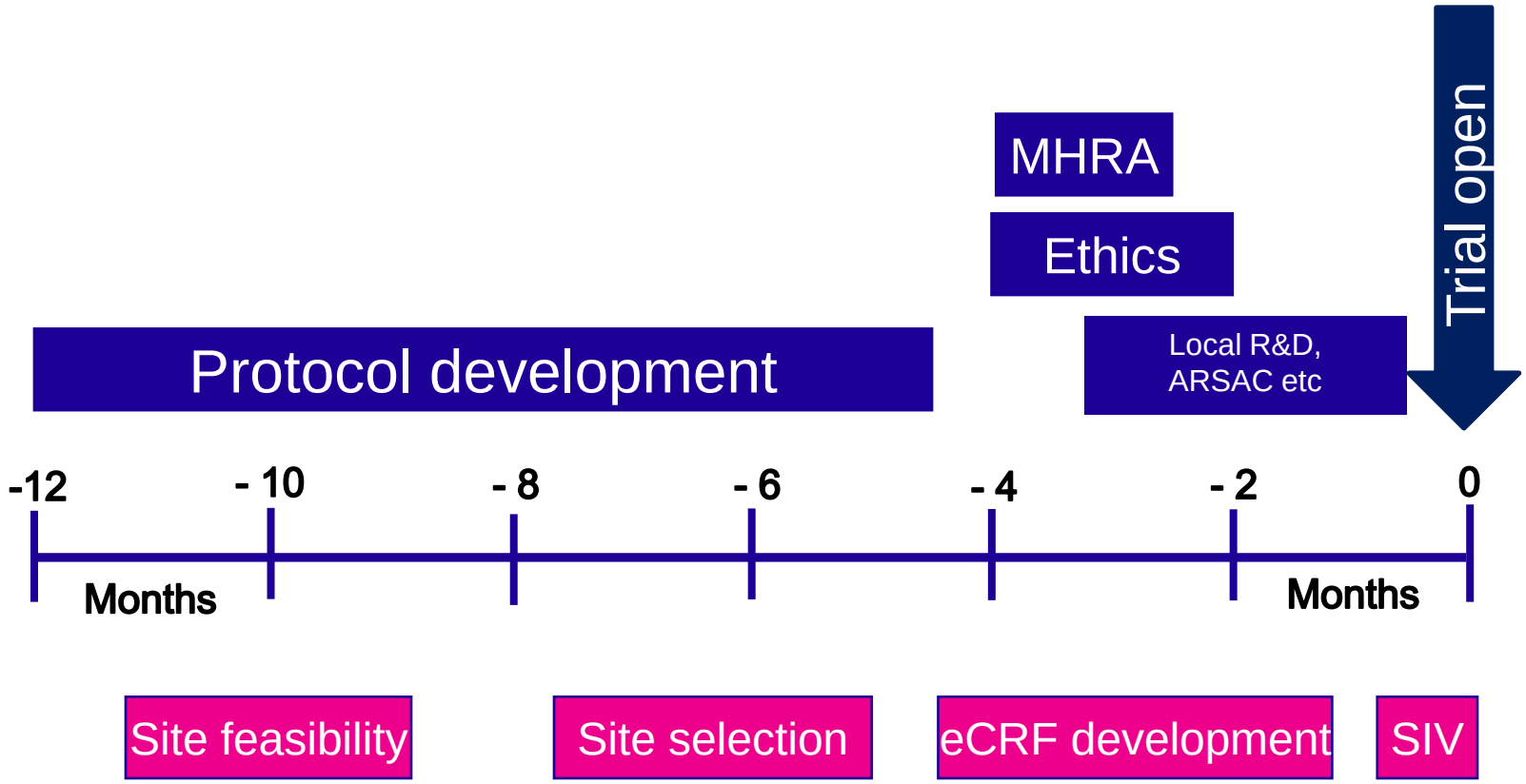
Example:

- Vaccines are not directly cytotoxic; escalation to MTD inappropriate
- Dose setting for further trials not based on safety data
- Pharmacokinetics of locally injected vaccines not meaningful for many products
- In addition: terminally ill patients with compromised immune systems probably not suited for determining immunogenicity of candidate vaccines

Trial Set-up

The who, what & why?

Trial Set-up



What makes a great site?

- Specialist in type of cancer
- Patient access
- Infrastructure
- Clinical trials experience
- Approval times

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The Sponsor

ARSAC

Approvals

Regulatory Authority

MHRA

Ethics Committee

IRAS

INTEGRATED RESEARCH APPLICATION SYSTEM

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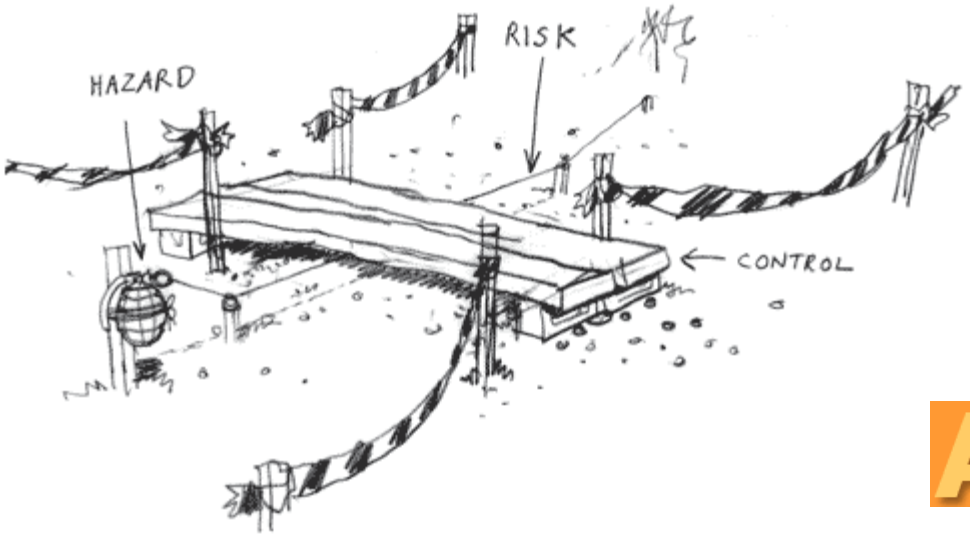
The Site

IRAS
INTEGRATED RESEARCH APPLICATION SYSTEM

NHS



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The Rules

- 1996 ICH GCP Guidelines (E6) ‘Principles of Good Clinical Practice
- 2001 EU Clinical Trials Directive
- 2004 The Medicines for Human Use (clinical trial) regulations
- 2004 – 2012 Amendments, Guidance, Q&A , Reflection papers
- 2012 MHRA Grey Guide
- 2014 New EU Clinical Trials Regulation

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Questions?